

Flexible Bayesian Regression Models for Quantifying Complex Interactions in Exposure Mixture Studies

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Abstract

In our modern world, we are constantly exposed to toxins, permeating our bodies through our food, skin, and lungs. Studies of environmental hazards have typically focused on identifying the health effects of single exposures. However, humans are invariably exposed to whole mixtures of exposures, and analyses of their joint effects can provide more accurate estimates of true health risk. The study of mixtures presents unique statistical challenges, though. This thesis explores the theory of emerging Bayesian regression techniques for quantifying the health risks of mixtures of pollutants. We use simulation studies to assess how modern statistical methods can detect interactions between multiple pollutants, and between pollutants and sociodemographic factors. We are keenly interested in combating habits of thought that associate outcomes with single, isolated causes, and progressing toward a study of health that acknowledges the relationality of our bodies to the environment and to each other.

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Chapter 1 Introduction

Rapid industrial development has created conditions of cumulative chronic toxicity which pose an acute risk to the wellbeing of humans and our living environment. In fact, it has been estimated that, globally, human activity releases chemicals at a rate of 220 billion tons per annum (Cribb, 2016). These staggering levels of pollution have led scholars to formally declare that humanity has surpassed the safe operating space of the planetary boundary for novel entities (Persson et al., 2022). As a result, exposure to low levels of pollutants has become an inevitable peril of daily life (Naidu et al., 2021; Vineis, 2018). In this new era of pervasive toxicity, understanding the nature and severity of health effects associated with chemical exposures is especially timely.

For this, we turn to epidemiological studies. The broad field of preventive epidemiology involves the identification of potentially modifiable risk factors that contribute to the burden of disease within human populations. Environmental epidemiology, in particular, considers the effect of environmental exposures — chemical or otherwise. However, studies concerning chemical pollutants in environmental epidemiology have historically focused on elucidating the effect and mechanisms of exposures to a single pollutant. In reality, humans are invariably exposed to numerous complex exposure mixtures which together contribute to the progression of adverse health outcomes. Therefore, risk assessments of single pollutants likely fail to capture the true consequences of these complex exposures (Heys, Shore, Pereira, Jones, & Mar-

tin, 2016). Assessing mixtures of chemicals can also have more direct implications for public health interventions. The United States Environmental Protection Agency (U.S. EPA) currently passes regulations for individual pollutants. In practice, though, regulation occurs by controlling the source of pollution, which is responsible for the production of a whole mixture of chemicals with specific joint effects on human health. As a result, the National Academies of Science (NAS) has advocated for a multipollutant regulatory approach, which is likely to be more protective of human health (NAS et al., 2017).

There are clear practical motivations for studies that examine the health effects of exposure to co-occurring mixtures of chemicals, hereafter referred to as exposure mixtures. However, expanding the focus of analysis from one exposure to multiple exposures introduces unique statistical challenges (Dominici, Peng, Barr, & Bell, 2010). In addition to a common issue of small effect sizes and small sample sizes present in most exposure analyses, multiple exposure analyses must also contend with high-dimensionality, collinearity, non-linear effects, and non-additive interactions (Yu et al., 2022). In particular, data with numerous pollutants, or predictors, require exponentially greater levels of complexity and time cost in analysis. Collinearity between exposures is common when analyzing pollutants from a single source and can lead to unstable estimates in a generalized linear model if left unaccounted for. Finally, exposures can have both non-linear single effects and non-additive interaction effects, which are difficult to capture unless explicitly specified in the model.

The classic multiple linear regression framework often fails to capture the true effects in this setting. In the past few years, a wide variety of statistical methods have been developed to overcome these challenges (see reviews, Gibson et al., 2019; Yu et al., 2022), which have been accompanied by a host of comparative simulation studies for general mixture scenarios (e.g., Hoskovec, Benka-Coker, Severson, Magza-

men, & Wilson, 2021; Lazarevic, Knibbs, Sly, & Barnett, 2020; Pesenti et al., 2023). However, to our knowledge, there has yet to be a simulation study which provides conclusive guidance about the ability of recently developed methods to conduct inference on non-additive interactions between exposures when the nature and effect sizes of these interactions vary. Moreover, there is no guidance in the literature on assessing interactions between covariates and exposures in exposure mixtures, including the potential of stratified models for detecting such interactions.

The goal of this thesis is to fill this gap in the literature by exploring the theory and performance of Bayesian regression techniques for quantifying complex interactions between multiple environmental exposures and related covariates. Specifically, we will compare two recently developed models for estimating the health effects of exposure mixtures: Bayesian Kernel Machine Regression (BKMR) (Bobb et al., 2015) and Bayesian Semiparametric Regression (BSR) (Antonelli et al., 2020).

In an age where anthropogenic actions have radically reshaped the earth, humanistic inquiry can offer critical insights into how we navigate and comprehend the hazards of our rapidly changing environment. We begin in Chapter 2 by contextualizing this thesis with a brief overview of cultural and social understandings of toxicity. Chapter 3 explains the motivation for studying interactions and provides background on the theory of Bayesian methods for analyzing exposure mixtures. Chapter 4 assesses the performance of these methods using a simulation study, based on a dataset with information on the relationship between prenatal exposure to heavy metals and gestational weight. We conclude with a discussion of the implications of this work for the future study of complex interactions in exposure mixture studies.

Chapter 2 Humanistic Perspective

In this section, we briefly introduce ideas from science and technology studies, which track habits of thought that have fundamentally shaped the ways in which we think about and study toxicity. Our goal, here, is to contextualize exposure mixture studies — the motivation for this thesis — within larger regimes of knowledge production. We aim to recognize the limitations in current norms of understanding toxicity, in order to progress toward a study of health that better reflects the complex realities of communities who bear the burdens of toxic exposure.

Modern scientific thinking encourages the onlooker to see objects in the world as distinct entities. For instance, when we talk about chemicals, we tend to talk about them as disconnected molecules: lead, mercury, per- and polyfluoroalkyl substances, etc. Clouds of pollution are conceived through their individual components, each of which becomes separated from its surroundings through the lenses of our imaginations (Myers, 2015). It is easy to accept this ontology as inevitable — how else should one view chemicals? Yet, its origins can actually be located in the history of chemistry. The Industrial Revolution turned chemistry into a hugely profitable field, leading practitioners to become keenly interested in how structural representations of chemicals could be most useful for industrial and corporate technoscientific disciplines (Bensaude-Vincent & Stengers, 1996). Reducing chemical mixtures amidst complex environments down into discrete molecules made the quantification of their effects simpler — certain side effects or relations could be masked or hidden in technical

reports. Such reports were then used by industrial lobbyists as evidence for reducing or withholding environmental regulations (Murphy, 2017).

These lines of thinking have filtered out of industry and into scientific studies of environmental health, which have historically been permeated by a focus on studying single chemicals. The end goal has often been to obtain mechanistic explanations of their modes of toxicity. By isolating attention to a single chemical entity within a purely biological framework, one can simplify the problem; but, in so doing, one also captures only a narrow sliver of the complex social and physical realities of exposure (Murphy, 2004). This is not to dismiss such studies or their contributions when, in fact, they are necessary for understanding the mechanisms of exposure. Rather, we hope to acknowledge that there exist additional possibilities for the study of exposures when we shift perspective away from isolated molecules and into chemical relations.

We start by recognizing that an object cannot exist without also taking on relations to other beings — existence implies relationality. [*finish writing this section*]

- relationality: entities cannot be understood without considering their *relationality* to other surrounding entities
 - relationality disrupts the notion of bounded objects
 - motivation for chemical mixtures: chemicals themselves are not independent from surrounding chemicals
 - motivation for chemical mixtures in the context of social epidemiology: the effects of chemicals are modulated by structural/social conditions
- relationality also disrupts Cartesian split between body and mind
 - racial hierarchy positions certain groups closer to the bounds of the corporal body, while other groups have transcended these bounds and are defined by their intellect (i.e., the mind)

- result → some bodies are seen as inherently more susceptible to chemical exposure, more “porous”
- leads to damage centered research which, while well-intentioned, inadvertently de-humanizes marginalized groups
- remedy: relationality leads into concept of alterlife, modern life is inseparable from alteration due to chemical exposure

Within the context of exposure studies, we link this concept to practices in social epidemiology, which posit that one’s health is embodied within structural and social conditions (Krieger, 2001, 2011).

It is important to explore radical modes of living that make our increasingly toxic world more habitable (Nguyen, 2020; Shapiro, 2015). This task does not fall purely to science — other forms of knowledge are crucial for navigating the chemical hazards of our everyday life. The responsibility of science, though, is to become aware of how such hazards are lived and experienced, in order to better inform our understanding of exposure. We argue that the methods for exposure mixture studies examined in this thesis take us one step closer to this goal. In particular, exposure mixtures account for the realities of chemicals that co-occur with other chemicals. Moreover, testing for interactions between chemicals acknowledges that the relationality of these molecules with each other might affect their modes of action. Finally, we consider potential interactions between sociodemographic covariates and chemical exposures, a previously understudied form of interaction in exposure mixture studies. In so doing, we recognize that the effects of chemical exposure can be modulated by complex and unequal social conditions.

Chemicals — despite being inanimate objects — are not fully separable from the societal context in which they exist. They become entangled in bodies that are entangled in complex social relations.

Still, there is more work to do. We make a multitude of assumptions when reducing human livelihoods to numbers and then magnifying those numbers with models. For instance, the race variable that we use attempts to capture the full lived experience of racism within five categories. We set the response variable in our simulations as some numerical health outcome, which assumes that healthfulness and wellbeing can be represented by a one-dimensional variable. And there are certainly other factors that we have missed. So, we hope that this is the start of a conversation that continues to contend with how scientific studies of exposure can help us better make sense of our new toxic realities.

Chapter 3 Bayesian Regression Methods

3.1 Motivation

We are interested in using Bayesian regression techniques to characterize the nature of non-additive interactions in exposure mixture studies. We begin by reviewing definitions for what constitutes an interaction and why interactions are relevant from both a public health and biological viewpoint.

3.1.1 Interactions from a statistical perspective

First, we define additivity and non-additivity in the traditional statistical paradigm (Siemiatycki & Thomas, 1981). Suppose we have two variables x_1 and x_2 , and we want to consider their effect on some outcome of interest. If specifying [effect due to x_1 and x_2] = [effect due to x_1] + [effect due to x_2] can adequately capture this relationship, then we say that x_1 and x_2 each have an **additive effect** on the outcome and that there is no interaction between them. On the other hand, if there is variability in the outcome that can be captured by an additional term equal to some function of x_1 and x_2 , we say that there is a **non-additive interaction** between x_1 and x_2 . In this case, [effect due to x_1 and x_2] = [effect due to x_1] + [effect due to x_2] + [effect due to $f(x_1, x_2)$], where f is a non-zero function.

For our sake, when we refer to “interaction,” we mean any non-additive interaction. We consider such non-additive interactions to be complex, meaning that they are

difficult to detect. To see why, let us consider running a linear regression for Y on x_1 and x_2 . The theoretical model would be defined as

$$Y = \beta_0 + \beta_1 x_1 + \beta_2 x_2 + \beta_{12} f(x_1, x_2) + \varepsilon,$$

where the β 's represent the effect sizes, and ε has a normal distribution with mean 0 and variance equal to the residual variance. We can see that the form of the interaction must be explicitly specified in the formulation of the model. Most commonly, a multiplicative interaction is assessed, where $f(x_1, x_2) = x_1 * x_2$. However, a non-additive interaction can take on many different forms, the true nature of which is difficult to determine analytically.

We used a two-predictor case above, but interactions can also exist between more variables (i.e., two-way by $f(x_1, x_2)$, three-way by $f(x_1, x_2, x_3)$, etc.). So, if we wanted to assess all possible interactions, the number to consider quickly becomes intractable in high-dimensional settings. For instance, consider modelling 10 predictors in the above linear regression setting. In order to be assessed, each interaction must be explicitly specified as a new term in the model. Even if we only considered one form for each interaction, including all possible two-way interactions would involve adding $\binom{10}{2} = 45$ additional terms to the model, and all possible three-way interactions would add $\binom{10}{3} = 120$ additional terms.

It is important also to acknowledge, here, that there is a limit to how many variables can be included in an interaction before it becomes incomprehensible to most humans. For instance, Halford, Baker, McCredden, & Bain (2005) suggest that there is a steep decline in interpretability from three- to four-way interactions, and that five-way interactions are only interpreted correctly at chance level. Hence, for practical purposes, we will limit our exploration to two- and three-way interactions.

3.1.2 Mechanistic and public health relevance

Thus far, we have discussed interactions within a statistical paradigm. However, in addition to being an interesting estimation challenge, non-additive interactions are also relevant in exposure mixture studies from both a mechanistic and public health point of view.

From a mechanistic perspective, a non-additive statistical interaction between two chemical exposures suggests that these compounds may be functionally interacting with each other. Theoretical models propose that such interactions can be classified as either synergistic or antagonistic (Heys et al., 2016; Plackett & Hewlett, 1952). In a synergistic interaction, the joint effects of a mixture exceed the independent effects of each component. This usually occurs if a chemical induces an enzyme involved with the activation of a second chemical or if a chemical inhibits an enzyme that would have otherwise degraded a second chemical. For example, it has been shown that organophosphates slow the degradation of pyrethroids by inhibiting detoxifying enzymes — these two classes of chemicals are often found together in commercial insecticide mixtures (Hernández et al., 2013).

On the other hand, in an antagonistic interaction, the joint effects of a mixture are less than their independent effects. This can occur either through competition at the target site of an enzyme or through direct chemical reactions with each other. In general, synergistic interactions are more concerning in risk assessments, as they lead to underestimation of the true toxicity of a mixture.

It should be noted, though, that while statistical interactions may provide some insight into how exposure mixtures are related to health, they cannot confirm their underlying biology (Tyler J. VanderWeele & Knol, 2014). If the goal is to assess a meaningful biological interaction, then the discovery of a statistical interaction should

be followed up by a functional study.

Now, from a public health perspective, we might be interested in how exposure mixtures interact with other covariates, or, in other words, how social and health factors might mediate the relationship between a health outcome and chemical exposures (Tyler J. VanderWeele & Knol, 2014). In our case, we can include these additional covariates in the exposure mixture model, where, statistically, they would contribute to the model in the same manner as another chemical exposure: a predictor. A statistical interaction in our model between a covariate and an exposure would indicate that the *magnitude* of the effect of reducing the level of an exposure might differ across various levels of the covariate. This finding could be relevant to public health policy makers, as the potential benefit of regulating a pollutant might differ across groups. For instance, it has been suggested that nutritional intake may modify susceptibility to chemical exposures (e.g., Kannan, Misra, Dvonch, & Krishnakumar, 2006; Kordas, Lönnerdal, & Stoltzfus, 2007).

In many cases, we might assess a covariate related to health inequity, such as socioeconomic status. We provide a cautionary comment, here, that an interaction term should not be the *sole* measure used to measure a health disparity (Ward et al., 2019). In this case, we should first consider the independent, additive association between the covariate and levels of exposure or rates of a health outcome, in order to contextualize the meaning of a potential interaction term.

3.2 Bayesian kernel machine regression (BKMR)

In this section, we introduce the theory of BKMR. First, we define the notation that we will be using for kernel machine regression:

- X_m is an exposure in the exposure matrix \mathbf{X} with $m = 1, \dots, M$

- \mathbf{x}_i is a vector of values for a single observation in \mathbf{X} with $i = 1, \dots, n$
- x_{im} is the i th observation of X_m
- \mathbf{z}_i is a vector of covariates for a single observation in the matrix \mathbf{Z} , which contains a set of covariates, with $i = 1, \dots, n$
- Y_i is an observation of \mathbf{Y} , measuring the health outcome in this case
- $h(\cdot)$ is the flexible function relating \mathbf{x} to \mathbf{Y}
- k is the kernel function, the Gaussian in this case
- \mathbf{K} is the $n \times n$ kernel matrix, with (i, j) th element $k(\mathbf{x}_i, \mathbf{x}_j)$
- ρ is the parameter which controls smoothness, associated with the kernel function
- τ is the parameter multiplied by the kernel matrix to relate \mathbf{K} to h
- $\boldsymbol{\beta}_{\mathbf{z}}$ is a vector of the weights on the covariates, and
- $\varepsilon_i \stackrel{\text{iid}}{\sim} N(0, \sigma^2)$ are the residuals of the response.

And, we define the notation that we will be using specific to BKMR:

- $r_m = 1/\rho_m$ is an augmented variable in \mathbf{r} in the kernel matrix, controlling smoothness of the exposure-response relationship
- δ_m is an indicator variable in $\boldsymbol{\delta}$ which represents inclusion of the corresponding exposure in the model
- \mathcal{S}_g is a group of partitioned predictors with $g = 1, \dots, G$
- $\{\delta_m | \mathbf{x}_m \in \mathcal{S}_g\}$ is an indicator variable in $\boldsymbol{\delta}_{\mathcal{S}_g}$ which represents inclusion of a parameter in group g in the model
- π is the prior probability of inclusion of a predictor in the model, and
- $\lambda \equiv \tau\sigma^{-2}$ is used as a convenient way to define the prior on τ .

3.2.1 Kernel machine regression

We begin by introducing kernel machine regression, with attention to its specific implementation in BKMR. First proposed by Nadaraya (1964) and Watson (1964), kernel machine regression is a nonparametric regression technique that can be used to capture non-linear effects and non-additive interactions. In this introduction, we follow the presentation of kernel machine regression provided by Bobb et al. (2015).

To contextualize this method, we start at the typical linear regression setting,

$$Y_i = \mathbf{x}_i^\top \boldsymbol{\beta}_{\mathbf{x}} + \mathbf{z}_i^\top \boldsymbol{\beta}_{\mathbf{z}} + \varepsilon_i,$$

where Y_i measures a health outcome at a given point, $\mathbf{x}_i = [x_{i1}, \dots, x_{iM}]$ is a vector of M exposures, \mathbf{z}_i is a vector of covariates, $\boldsymbol{\beta}_{\mathbf{x}}$ and $\boldsymbol{\beta}_{\mathbf{z}}$ are vectors of weights for the exposures and covariates, respectively, and ε_i is a random variable from $\varepsilon \stackrel{\text{iid}}{\sim} N(0, \sigma^2)$. We can see that this function assumes that there is a linear relationship between the exposure and the response, and that the combined effects of multiple exposures are additive.

Kernel machine regression defines this relationship using a flexible function $h : \mathbb{R}^M \rightarrow \mathbb{R}$, where

$$Y_i = h(\mathbf{x}_i) + \mathbf{z}_i^\top \boldsymbol{\beta}_{\mathbf{z}} + \varepsilon_i.$$

Here, $h(\cdot)$ is represented by the function $k(\cdot, \cdot)$, a kernel. The kernel controls the covariance, or the similarity, between values of $h(\mathbf{x})$ and as such ensures that points near each other on the prediction surface will have similar values — or, in other words, that the prediction surface will be smooth. In the case of kernel machine regression, we define a positive definite kernel where $k : \mathbb{R}^M \times \mathbb{R}^M \rightarrow \mathbb{R}$. Note also that covariates

are assumed to have a linear, additive effect on the response.

There are many choices of functions for k . BKMR uses the Gaussian kernel, also known as the radial basis function or, sometimes, the squared exponential kernel. The Gaussian kernel is defined as

$$k(\mathbf{x}, \mathbf{x}') = \exp\left\{-\frac{\|\mathbf{x} - \mathbf{x}'\|^2}{\rho}\right\},$$

where $\|\mathbf{x} - \mathbf{x}'\|^2 = \sum_{m=1}^M (x_m - x'_m)^2$ for a set of exposure values \mathbf{x} and the exposure values of another subject \mathbf{x}' , and ρ is a tuning parameter that controls the relationship between the correlation between two points and their distance. Greater values of ρ will enforce more dependence between points and make the resulting function smoother. h is related to k by a multiplicative constant τ , a tuning parameter which controls the vertical scale of h .

Now that we have defined h and k , we can think about how to characterize the relationship between our response and exposures. Kernel machine regression is a nonparametric technique because it does not specify a functional form for this relationship. Hence, we will think about estimating the response at a particular query point. Operationally, Müller (1987) demonstrated that kernel machine regression uses a weighted average of all the observations in the dataset to estimate the response, defined as

$$\bar{Y} = \frac{\sum_{i=1}^n w_i Y_i}{\sum_{i=1}^n w_i},$$

with some set of weights $\{w_i\}_{i=1}^n$. Intuitively, we want to weight the observations that are closer to the query point more heavily. Using the Gaussian kernel as a weight allows us to achieve this. Replacing the weight with the Gaussian kernel, we get

$$\bar{Y} = \frac{\sum_{i=1}^n k(\mathbf{x}, \mathbf{x}_i) Y_i}{\sum_{i=1}^n k(\mathbf{x}, \mathbf{x}_i)}.$$

As we move through the predictor space, we can think of the prediction as a continuous moving average of local points in the dataset. The correlation between two values of h is defined as

$$\text{cor}(h_i, h_j) = \exp\left\{-\frac{||\mathbf{x}_i - \mathbf{x}_j||^2}{\rho}\right\},$$

which allows us to see that values of h near each other will have a higher correlation and thus similar values. This is also why the resulting function is smooth.

3.2.2 Connection to mixed models

It is useful to make connections between this definition of kernel machine regression and mixed models. Liu, Lin, & Ghosh (2007) demonstrated this by representing $h(\mathbf{x})$ as following a Gaussian process probability distribution,

$$h(\mathbf{x}) \sim \mathcal{GP}(\mathbf{0}, \tau k(\mathbf{x}, \mathbf{x}')),$$

with covariance function k , where \mathbf{x} is a vector of the exposure values, and \mathbf{x}' contains the exposure values of another subject. A Gaussian process is a collection of random variables, of which any finite number follow a multivariate normal distribution (Schulz, Speekenbrink, & Krause, 2018). Here, we assume that the expected value of the h function with input \mathbf{x} is $\mathbf{0}$. We use k for the covariance function, which represents the dependence between the function values with inputs \mathbf{x} and \mathbf{x}' : $k(\mathbf{x}, \mathbf{x}') = \mathbb{E}[(h(\mathbf{x}) - \mathbf{0})(h(\mathbf{x}') - \mathbf{0})]$.

Now, we can represent h as a collection of variables from a Gaussian process. h follows a multivariate normal distribution,

$$h(\mathbf{x}) \sim N(\mathbf{0}, \tau \mathbf{K}),$$

where $h(\mathbf{x}) = [h(\mathbf{x}_1), h(\mathbf{x}_2), \dots, h(\mathbf{x}_n)]^\top$ and \mathbf{K} is the kernel matrix. The kernel matrix is an $n \times n$ matrix with (i, j) th element $k(\mathbf{x}_i, \mathbf{x}_j)$. Now, returning back to the regression view, we can think of each Y_i as following the distribution,

$$Y_i \stackrel{\text{ind}}{\sim} N(h(\mathbf{x}_i) + \mathbf{z}_i^\top \boldsymbol{\beta}_{\mathbf{z}}, \sigma^2) \text{ for } i = 1, \dots, n,$$

where σ^2 comes from the variance of the residuals. Here, h can be interpreted as a random effect.

3.2.3 Toy example

In the following section, we illustrate kernel machine regression with a simulated toy example.

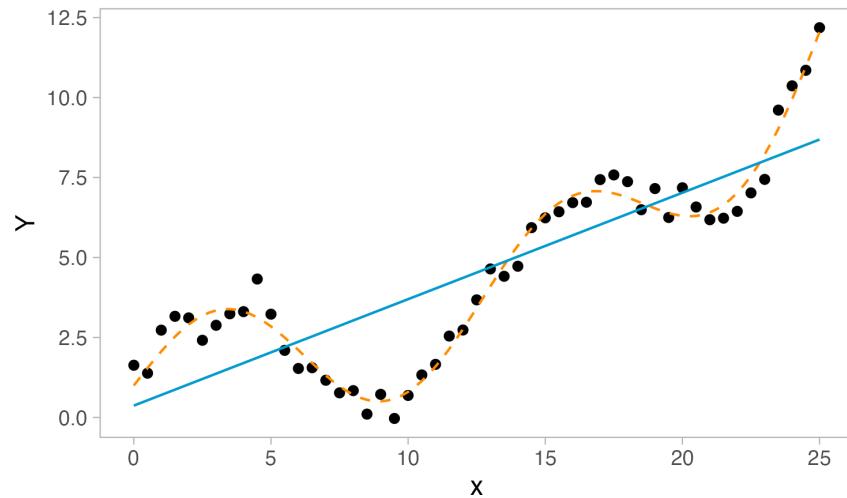


Figure 3.1: Non-linear data with a true relationship (orange) and a fitted linear regression (blue).

Consider the following case where we want to model the relationship between a

single predictor and a response variable. Suppose the true relationship between x and Y is defined $Y = e^{\frac{x}{10}} + 2 \sin(\frac{x}{2})$. We simulate 51 equally spaced observations of x from 0 to 25, with error $\varepsilon_i \stackrel{\text{iid}}{\sim} N(0, 0.25)$.

Figure 3.1 illustrates the shape of our simulated non-linear data and the fit proposed by a simple linear regression. We can observe that the linear regression fails to capture the true non-linear relationship. In this case, this would lead to an underestimation of the true association between x and Y . Now, we will try to capture this relationship using kernel machine regression.

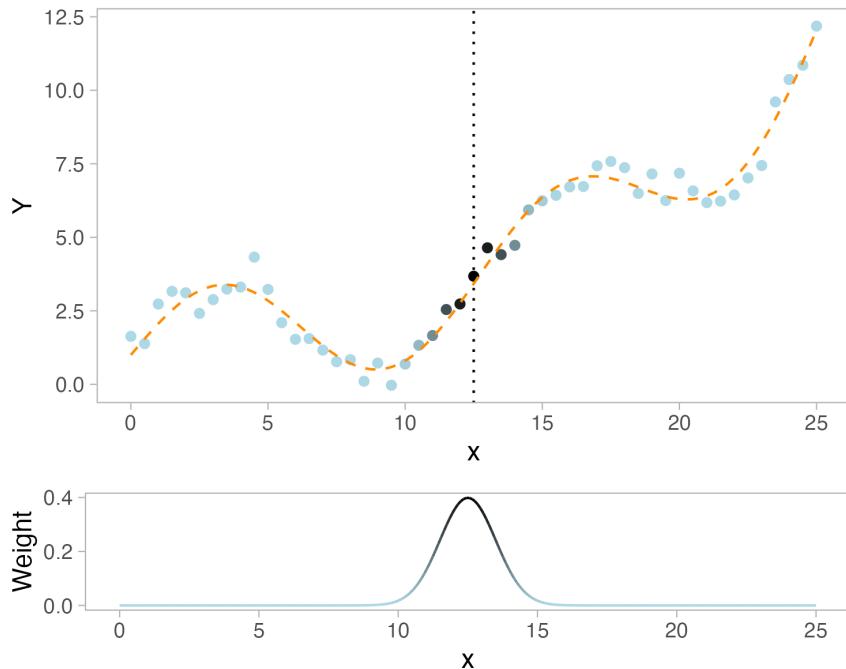


Figure 3.2: A query point of 12.5 and the weights of neighboring observations based on a Gaussian kernel

To visualize how kernel machine regression works as a moving weighted average, we can consider a query point of 12.5. Figure 3.2 identifies the query point and assigns corresponding weights to the neighboring points based on a normal distribution, which shares the same density as the Gaussian kernel. In this case, we will specify $\rho = 2$,

which is synonymous with assigning the weights using a normal distribution with $\sigma^2 = 1$. We can see how an appropriate estimate for $h(12.5)$ can be obtained by taking a weighted average of the Y 's, with those observations nearby weighted the most heavily.

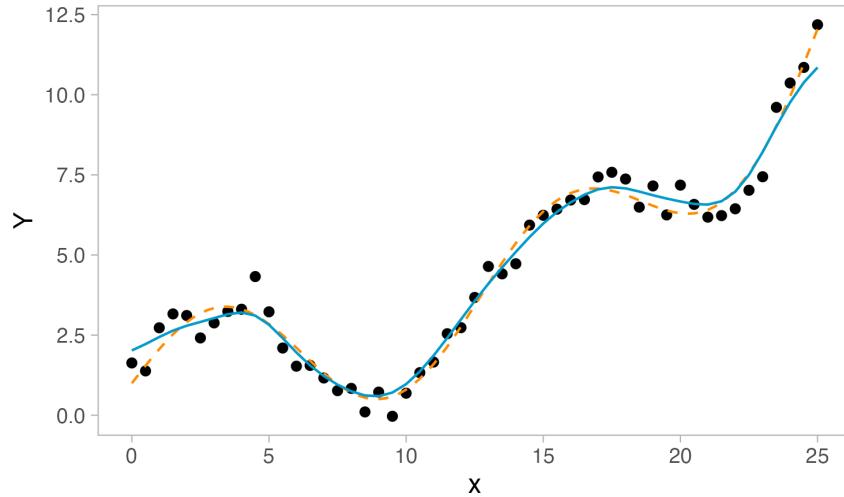


Figure 3.3: Fitted kernel machine regression (blue) with $\rho = 2$ compared to the true relationship (orange).

Now, we fit a kernel machine regression on this data with $\rho = 2$ using the `stats` package in R. We can see in Figure 3.3 that kernel machine regression captures the complex non-linear relationship between Y and x and closely follows the true relationship. We do note, though, that the estimation is less precise at the tails, where there is less information provided by local observations. We can also use this example to consider the effect of various values of ρ on the smoothness of the h function.

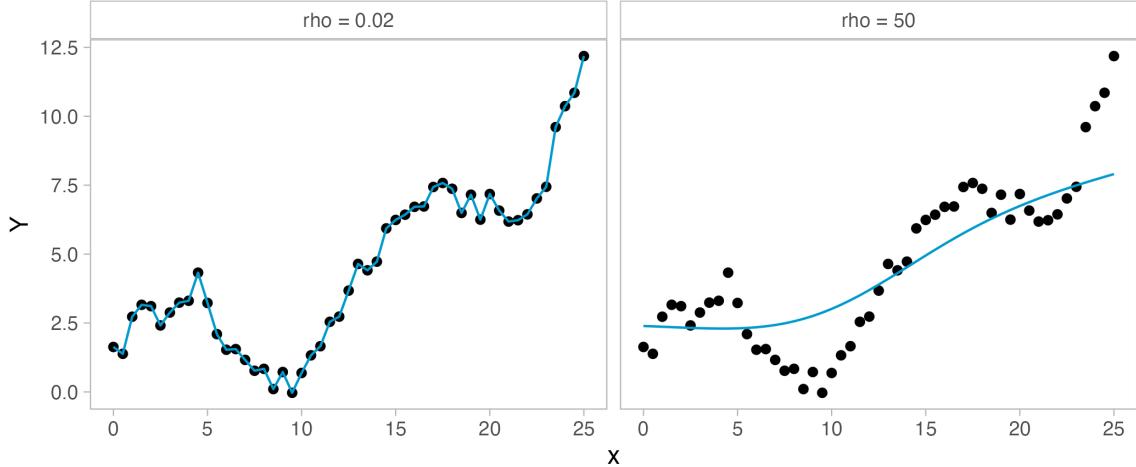


Figure 3.4: Fitted kernel machine regression with $\rho = 0.02$ (under-smoothed) and $\rho = 50$ (oversmoothed).

Figure 3.4 demonstrates the effect of relatively smaller and larger values of ρ on h . Decreasing the value of ρ allows kernel machine regression to overfit to the noise in the data by relaxing the dependence of neighboring values of h to each other. On the other hand, increasing the value of ρ enforces more dependence in h and as such results in an underfit estimation. Hence, the choice of ρ has a strong effect on the performance of kernel machine regression.

3.2.4 Variable selection

Now that we have defined kernel machine regression, we can extend it to the Bayesian paradigm. Bobb et al. (2015) showed that the Bayesian approach can outperform frequentist kernel machine regression because simultaneous variable selection and estimation can better capture the exposure-response relationship. In this section, we discuss the two methods for Bayesian variable selection in BKMR: hierarchical variable selection and component-wise variable selection (Bobb et al., 2015).

In order to perform variable selection, we define a parameter that puts a weight on each exposure. Each weight controls the degree to which its associated exposure

contributes to the model. In component-wise selection, we do this by augmenting the kernel function as

$$k(\mathbf{x}, \mathbf{x}' | \mathbf{r}) = \exp \left\{ - \sum_{m=1}^M r_m (x_m - x'_m)^2 \right\},$$

where $\mathbf{r} = [r_1, \dots, r_M]^\top$. We define $r_m = 1/\rho_m$, the inverse of the tuning parameter ρ_m for each \mathbf{x}_m . Now, we can imagine that an exposure that is not closely associated with the response will be assigned a value of r_m close to 0, which corresponds to a larger value of ρ_m . This larger value of ρ_m means that this exposure would contribute less to the exposure-response relationship, as depicted in the second panel of Figure 3.4.

We now define the kernel matrix $\mathbf{K}_{\mathbf{X}, \mathbf{r}}$ as the $n \times n$ matrix with (i, j) th element $k(\mathbf{x}, \mathbf{x}' | \mathbf{r})$. To allow r_m to equal 0 with non-zero probability, we first define an indicator variable determining whether or not a predictor is included in the variable, which is denoted and distributed as

$$\delta_m \sim \text{Bernoulli}(\pi),$$

where π is the prior probability of inclusion. Now, we can assume a “slab-and-spike” prior on r_m , distributed as

$$r_m | \delta_m \sim \delta_m f(r_m) + (1 - \delta_m) P_0,$$

where $f(\cdot)$ is some pdf with support \mathbb{R}^+ , and P_0 denotes the density with point mass at 0.

While this process of component-wise variable selection works well in a typical multiple regression setting, it can lead to unreliable estimates in situations where the exposures are highly correlated with each other, which is common in exposure mixture

studies. In this case, the correlated components contribute similar information to the model, and component-wise variable selection is not able to distinguish which exposure is important. BKMR deals with this problem by introducing hierarchical variable selection (Bobb et al., 2015).

Hierarchical variable selection involves partitioning the predictors $\mathbf{x}_1, \dots, \mathbf{x}_M$ into G groups, denoted \mathcal{S}_g with $g = 1, \dots, G$. These groups should be selected by the user based on prior knowledge, with the aim of keeping within-group correlation high and between-group correlation low (Bobb et al., 2015). For instance, consider a situation with 4 chemicals, Hg, Pb, As, and Sn. If Hg, Pb, and As were strongly correlated with each other and each weakly correlated with Sn, we might define $\mathcal{S}_1 = \{\text{Hg}, \text{Pb}, \text{As}\}$ and $\mathcal{S}_2 = \{\text{Sn}\}$.

The indicators from $r_m | \delta_m$ are now distributed as

$$\begin{aligned} \boldsymbol{\delta}_{\mathcal{S}_g} | \omega_g &\sim \text{Multinomial}(\omega_g, \boldsymbol{\pi}_{\mathcal{S}_g}), g = 1, \dots, G, \text{ and} \\ \omega_g &\sim \text{Bernoulli}(\pi), \end{aligned}$$

where $\boldsymbol{\delta}_{\mathcal{S}_g} = \{\delta_m | \mathbf{x}_m \in \mathcal{S}_g\}$ and $\boldsymbol{\pi}_{\mathcal{S}_g}$ are vectors of indicator variables and prior probabilities, respectively, of a exposure \mathbf{x}_m in group \mathcal{S}_g entering the model. By this approach, at most one exposure in each group is allowed to enter the model (Bobb et al., 2015).

While hierarchical variable selection resolves the issue of multicollinearity, it requires specifying subgroups of predictors a priori and assumes that one exposure in each group can capture the information of the rest. Hence, care should be taken to justify the partitioning of exposures when taking this approach (Bobb et al., 2015).

Note also that the posterior means of δ_m generated from these variable selection procedures represent the posterior probability of inclusion of \mathbf{x}_m . We can interpret

these posterior inclusion probabilities (PIPs) as measures of the relative importance of each exposure. These measures can be used to understand the contribution of each exposure to the health outcome of interest in the model (Bobb et al., 2015).

3.2.5 Prior specification

In this section, we specify the default prior distributions and parameters used by the BKMR algorithm (Bobb et al., 2015).

BKMR, by default, assumes $\rho_m = 1/r_m \sim \text{Unif}(a_r, b_r)$, a flat prior between a_r and b_r for which the default values are 0 and 100, respectively (Bobb, 2017a). This defines the prior probability of ρ as equally distributed across any value from 0 to 100. This inverse of this prior corresponds to the slab component of the “slab-and-spike” prior, where $r_m|\delta_m \sim \delta_m \text{Unif}^{-1}(a_r, b_r) + (1 - \delta_m)P_0$. As a flat prior, this distribution should be chosen when we have no prior knowledge about the smoothness of the exposure-response function, with hyperparameters a_r and b_r selected to represent the range of values we expect ρ to potentially span.

We have seen that the smoothness of a kernel machine regression responds strongly to different values of $r_m = 1/\rho$, and, accordingly, the model fit of BKMR is sensitive to their prior distribution. In general, the PIPs generated from the variable selection procedure are particularly sensitive to this prior, though their relative importance tends to remain stable (Bobb, Claus Henn, Valeri, & Coull, 2018). As such, the BKMR algorithm also offers the options to define uniform and gamma priors for the $r_m = 1/\rho$.

Moreover, BKMR assumes that the prior probability of including a predictor (δ_m) or group of predictors (ω_g) in the model is distributed $\pi \sim \text{Beta}(a_\pi, b_\pi)$. The default hyperparameters are $a_\pi = b_\pi = 1$, which represent a flat, uninformative prior between 0 and 1. When the hierarchical selection approach is applied, equal values for $\pi_{\mathcal{S}_g}$,

the probabilities of inclusion for each component in group \mathcal{S}_g , are assumed.

Finally, BKMR assumes that the inverse of the variance of the residuals is distributed $\sigma^{-2} \sim \text{Gamma}(a_\sigma, b_\sigma)$, with default values of $a_\sigma = b_\sigma = 0.001$, and that the vertical scale of h is parameterized by $\lambda \equiv \tau\sigma^{-2} \sim \text{Gamma}(a_\lambda, b_\lambda)$, with default values of a_λ, b_λ such that the mean and variance of λ are both equal to 10.

3.2.6 The MCMC algorithm

Briefly, we discuss the algorithm used to find the solution in the BKMR package (Bobb et al., 2015, 2018), with commentary on its implications for the model fitting process.

BKMR uses a Markov chain Monte Carlo (MCMC) algorithm with a mix of Gibbs and Metropolis-Hastings samplers to estimate the posterior distributions of the parameters. In particular, a Gibbs step is used to update the distribution of σ^2 while a Metropolis-Hastings step is used to update the distribution of λ . For component-wise and hierarchical variable selection, $(\mathbf{r}, \boldsymbol{\delta}, \boldsymbol{\omega})$ are sampled jointly using a Metropolis-Hastings sampling scheme.

While each distribution generated by the Gibbs step is always accepted, the distributions for λ and r_m generated by the Metropolis-Hastings steps are accepted based on an acceptance rate (Wagaman & Dobrow, 2021). The standard deviation of the proposal distribution controls the acceptance rate and as such acts as a tuning parameter (Bobb, 2017b). In general, increasing the standard deviation leads to lower acceptance rates. Acceptance rates that are too low lead to slower convergence, but rates that are too high can cause convergence to a non-optimal distribution.

A major computational limitation of BKMR is that at each iteration of the MCMC algorithm, the $n \times n$ augmented kernel matrix $\mathbf{K}_{\mathbf{Z}, \mathbf{r}}$ must be inverted multiple times. To offset this, BKMR can employ a Gaussian predictive process which involves spec-

ifying a set of l points, or “knots,” that are a subset of the predictor space. The vector of predictors can be approximated by projection onto this lower dimensional space, which allows the algorithm to perform inversions on an $l \times l$ matrix. A general suggestion is to use this approach to speed up the algorithm when n is large and to specify $l \approx n/10$ (Bellavia, 2021).

3.3 Bayesian semiparametric regression (BSR)

In this section, we introduce the theory of BSR. First, we define the notation that we will be using for spline regression (much of it designed to be consistent with our BKMR presentation):

- X_m is a predictor variable in the predictor matrix \mathbf{X} with $m = 1, \dots, M$, measuring exposure variables or covariates
- \mathbf{x}_i is a vector of values for a single observation in \mathbf{X} with $i = 1, \dots, n$
- \mathbf{z}_i is a vector of covariates for a single observation in the matrix \mathbf{Z} , which contains a set of covariates, with $i = 1, \dots, n$
- Y_i is an observation of \mathbf{Y} , measuring the health outcome in this case
- $f(\cdot)$ relates \mathbf{x}_i to Y_i by a set of basis functions, $b_j(X)$
- β_j is a weight on the j th basis function
- P is the order of the basis expansion
- K is a set of ξ_k , $k = 1, \dots, K$, interior knots defining $K + 1$ disjoint intervals, and
- $\varepsilon_i \stackrel{\text{iid}}{\sim} N(0, \sigma^2)$ are the residuals of the response.

And, we define the notation that we will be using specific to BSR:

- \widetilde{X}_m is a d -dimensional basis function expansion of X_m

- $\widetilde{X}_{m_1 m_2}$ is a d^2 -dimensional basis expansion of the interaction between X_{m_1} and X_{m_2}
- $f^{(h)}(\cdot)$, where $h = 1, \dots, H$ are a set of functions that sum up to $f(\cdot)$
- $\zeta = \{\zeta_{mh}\}$ is an indicator for whether the m th predictor is included in the h th function
- $\beta_S^{(h)}$ is a vector of all the coefficients on the predictors in function h
- σ_β^2 is the prior variance on the coefficients, and
- Σ_β is a diagonal matrix with the variances of the multivariate slab prior, $\sigma^2 \sigma_\beta^2$, on the diagonals.

3.3.1 Spline regression

We begin by introducing spline regression, with attention to its specific implementation in BSR. Spline regression is a semiparametric regression technique that can be used to capture non-linear effects. In this introduction, we follow the presentation of spline regression provided by Antonelli et al. (2020), with additional details and explanation from Hastie, Tibshirani, & Friedman (2009).

BSR uses spline regression to define the regression relationship as

$$Y_i = f(\mathbf{x}_i) + \mathbf{z}_i^\top \boldsymbol{\beta}_\mathbf{z} + \varepsilon_i,$$

where f is defined by a set of basis functions on the exposures, \mathbf{x}_i , \mathbf{z}_i and $\boldsymbol{\beta}_\mathbf{z}$ are the covariates and their associated weights, and ε_i is a random variable from $\varepsilon \stackrel{\text{iid}}{\sim} N(0, \sigma^2)$. BSR uses natural spline bases (Antonelli et al., 2020). In order to understand how these are constructed, we start with a broad definition of basis expansions, before exploring linear, cubic, and then natural spline bases.

We determine the basis expansion by considering a piece-wise function of X_m with

some order P and some set of K knots defining $K + 1$ disjoint intervals. BSR places knots at uniformly sized quantiles within the boundaries of X_m . The most commonly used orders are $P = 1, 2$, and 4 , the constant, linear, and cubic splines, respectively. To begin, let us consider a continuous piece-wise linear spline basis (i.e., $P = 2$) of a one-dimensional X with two interior knots. In this case, we use the following four basis functions:

$$b_1(X) = 1, \quad b_2(X) = X, \quad b_3(X) = (X - \xi_1)_+, \quad b_4(X) = (X - \xi_2)_+,$$

where ξ_1 and ξ_2 are the two interior knots, and t_+ denotes the positive part. These bases are used to construct the regression model $f(X) = \sum_{j=1}^4 \beta_j b_j(X)$, which requires estimating $K + P = 4$ parameters. We can check the continuity restrictions at the knots by seeing that $f(\xi_1^-) = \beta_1 + \xi_1 \beta_2$ and $f(\xi_1^+) = \beta_1 + \xi_1 \beta_2 + (\xi_1 - \xi_1) \beta_3$ are equal, and likewise at the second knot (Hastie et al., 2009).

Now, in the case of exposure mixtures, we want smoother functions that can capture the non-linear relationship between the response and the predictors. We can achieve this by increasing the order to $P = 4$ and using a cubic spline, with continuous first and second derivatives at the knots. The cubic spline is the lowest-order spline for which knot-discontinuity cannot be detected by the human eye. For example, for one X with two interior knots, we use the following six basis functions:

$$\begin{aligned} b_1(X) &= 1, & b_2(X) &= X, & b_3(X) &= X^2, \\ b_4(X) &= X^3, & b_5(X) &= (X - \xi_1)_+^3, & b_6(X) &= (X - \xi_2)_+^3. \end{aligned}$$

Now, the regression model is defined as $f(X) = \sum_{j=1}^6 \beta_j b_j(X)$ and requires estimating $K + P = 6$ parameters. It can be shown that $f'(\xi_i^-) = f'(\xi_i^+)$ and $f''(\xi_i^-) = f''(\xi_i^+)$,

and so forth (Hastie et al., 2009).

However, the behavior of polynomials near the boundaries of X , where there is less information, can be erratic. Natural cubic splines, also referred to as just natural splines, address this by imposing an additional restriction of linearity at the boundaries of X . Paradoxically, this also leads to a simpler model with four fewer parameters to estimate. A general definition of the K basis functions for a natural spline with interior knots ξ_j , $j = 1, \dots, K$, is given by:

$$b_1(X) = 1, \quad b_2(X) = X, \quad b_{k+2}(X) = d_k(X) - d_{K-1}(X), \\ d_k(X) = \frac{(X - \xi_k)_+^3 - (X - \xi_K)_+^3}{\xi_K - \xi_k}.$$

Here, the regression model is defined as $f(X) = \sum_{j=1}^K \beta_j b_j(X)$, with K parameters (Hastie et al., 2009). BSR uses natural splines to specify the regression relationship.

3.3.2 Toy example

In the following section, we illustrate spline regression using the same toy example used to introduce kernel machine regression. See Chapter 3.2.3 and Figure 3.1 for details on the parameters used to generate simulated data.

As in Chapter 3.2.3, we consider a case where we want to model the relationship between a single exposure and a response variable, where the true relationship between x and Y is defined as $Y = e^{\frac{x}{10}} + 2 \sin(\frac{x}{2})$. We fit a series of linear, cubic, and then natural spline regressions to illustrate the general framework of a natural spline regression.

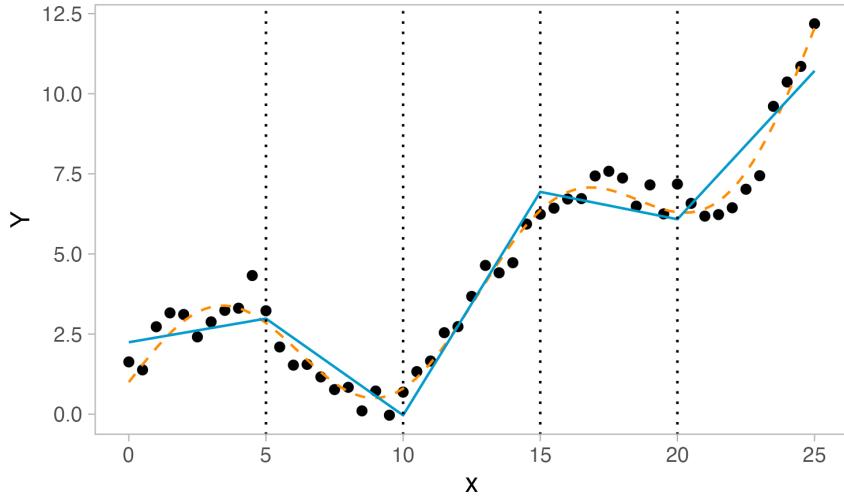


Figure 3.5: Linear spline regression (blue) with four knots (dotted lines) compared to the true relationship (orange).

Figure 3.5 illustrates the fit proposed by a linear spline regression with order $P = 2$. We can see that the implementation of knots allows for even a linear fit to capture more of the nuances in this nonlinear relationship, as compared to a standard linear regression.

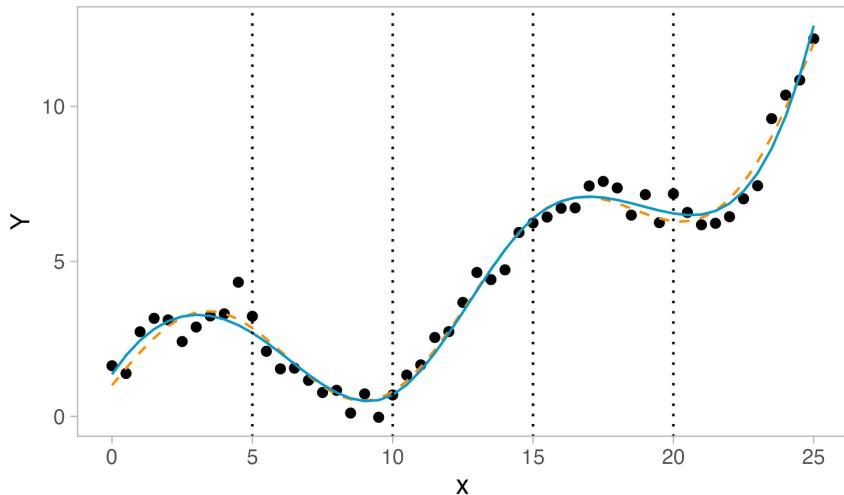


Figure 3.6: Cubic spline regression (blue) with four knots (dotted lines) compared to the true relationship (orange).

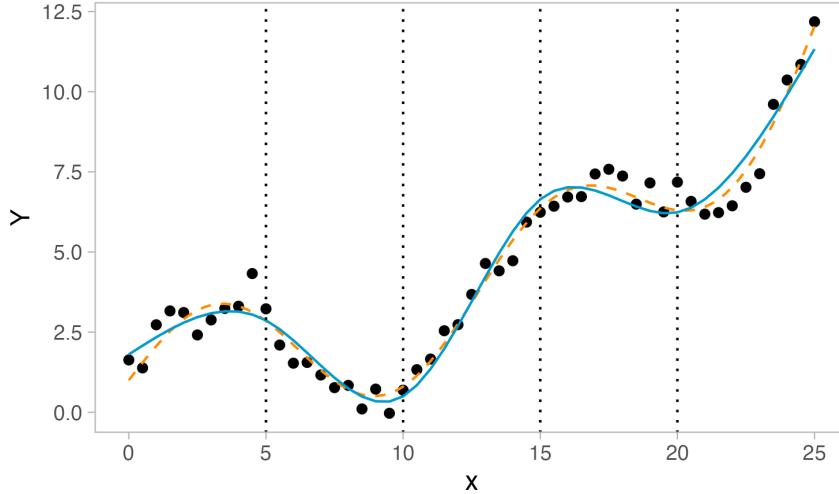


Figure 3.7: Natural spline regression (blue) with four knots (dotted lines) compared to the true relationship (orange).

However, this linear spline regression is still unable to fully estimate the nonlinearity in our example. Increasing the order to $P = 4$ with a cubic spline regression offers additional flexibility. Figure 3.6 illustrates the fit proposed by this model. Here, we can see the benefits of using a cubic polynomial relationship in a nonlinear setting: the estimated relationship is continuous at the knots, and the nonlinear relationship has been flexibly captured.

Our final modification involves imposing linearity constraints on the boundaries of x to implement a natural spline regression. Figure 3.7 shows the fit estimated using a natural spline regression. The fitted line is only slightly different than that proposed by a cubic spline regression in Figure 3.6. The most noticeable difference is that the slopes of the tails of the natural spline regression are less extreme than for the cubic spline regression.

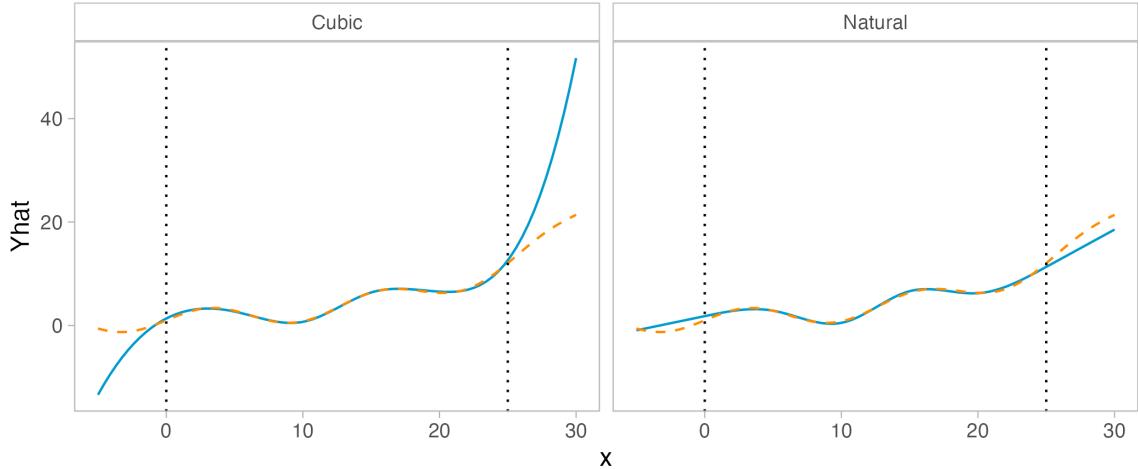


Figure 3.8: Natural and cubic spline regression (blue) compared to the true relationship (orange) extrapolated outside the bounds of x (dotted lines).

Extrapolation outside the scope of x allows us to see the effect of the linearity constraints imposed by natural regression. Figure 3.8 demonstrates how the cubic spline regression behaves erratically outside the bounds of x , as the cubic polynomial lines tend toward $\pm\infty$, while the natural spline regression follows a more appropriate linear trend. As the natural spline regression is more reliable near the boundaries of x and also simpler to estimate, BSR adopts the use of natural splines.

3.3.3 Model formulation in BSR

Now that we have defined natural splines, we introduce BSR, following the presentation in Antonelli et al. (2020). We demonstrate the construction of f in BSR by first assuming a two-dimensional case with exposures X_1 and X_2 . We define

$$f(X_1) = \widetilde{X}_1\boldsymbol{\beta}_1, \quad f(X_2) = \widetilde{X}_2\boldsymbol{\beta}_2,$$

$$f(X_1, X_2) = \widetilde{X}_1\boldsymbol{\beta}_1 + \widetilde{X}_2\boldsymbol{\beta}_2 + \widetilde{X}_{12}\boldsymbol{\beta}_{12},$$

where $\widetilde{X}_m = [b_{m1}(X_m), \dots, b_{md}(X_m)]$ represents a d -dimensional basis function expansion for $m = 1, 2$, and $\widetilde{X}_{12} = [b_{11}(X_1)b_{21}(X_2), b_{11}(X_1)b_{22}(X_2), \dots, b_{1d}(X_1)b_{2d}(X_2)]$ represents a d^2 -dimensional basis expansion of the interaction between X_1 and X_2 . d is an influential tuning parameter. BSR by default assumes that all exposures have the same number of degrees of freedom and uses the Watanabe-Akaike (WAIC) model selection criterion to select d , which approximates leave one out cross validation. Note that we must explicitly model the effect of the interaction term by assuming a multiplicative interaction between the basis functions of the predictors.

Extending to the multi-dimensional setting, BSR assumes the following general model formulation:

$$f(\mathbf{x}_i) = \sum_{h=1}^H f^{(h)}(\mathbf{x}_i),$$

$$f^{(h)}(\mathbf{x}_i) = \sum_{m_1=1}^M \tilde{x}_{im_1} \boldsymbol{\beta}_{m_1}^{(h)} + \sum_{m_1=2}^M \sum_{m_2 < m_1} \tilde{x}_{im_1m_2} \boldsymbol{\beta}_{m_1m_2}^{(h)} + \dots,$$

where $f^{(h)}(\mathbf{x}_i)$ includes a summation of all M -way interactions. The inclusion of all M -way interactions makes the model far too overparameterized. Moreover, $f(\mathbf{x}_i)$ is a sum of k different functions $f^{(h)}(\mathbf{x}_i)$ where a value for H is selected in order to capture all exposure effects in the model. Each of the H functions has the same functional form, and so the regression coefficients for a function $f^{(h)}(\mathbf{x}_i)$ are only identifiable up to a constant — this means that there are multiple sets of coefficients that could be estimated from the same data.

3.3.4 Sparsity inducing priors

In order to handle the overparameterization and non-identifiability of the model, BSR implements multivariate sparsity inducing priors. In this section, we follow the presentation provided in Antonelli et al. (2020).

First, we define indicators $\zeta = \{\zeta_{mh}\}$ representing whether the m th exposure is included in the h th function:

$$P(\zeta_{mh} = 1) = \tau_h^{\zeta_{mh}}(1 - \tau_h)^{1 - \zeta_{mh}} I(A_h \not\subset A_{h'} \forall h' \neq h \text{ or } A_h = \{\}),$$

where $A_h = \{m : \zeta_h = 1\}$.

Here, the indicators follow a Bernoulli distribution with prior probability of inclusion τ_h . The posterior means of ζ , i.e. the PIPs, can be interpreted as measures of relative variable importance. We include an indicator function $I()$ that represents whether the function h contains a unique set of predictors. This indicator ensures that no function contains exposures that are a subset of those in another function, h' , in which case this function would be redundant and thus removed from the model entirely.

Now, we assume a multivariate slab-and-spike prior on the regression coefficients:

$$P(\beta_S^{(h)} | \zeta) = \left(1 - \prod_{m \in S} \zeta_{mh}\right) P_0 + \left(\prod_{m \in S} \zeta_{mh}\right) \psi_1(\beta_S^{(h)}),$$

where S is some subset of $1, 2, \dots, m$.

Here, P_0 denotes the density with point mass at $\mathbf{0}$, and $\psi_1()$ is a multivariate normal distribution with mean $\mathbf{0}$ and covariance Σ_β , a diagonal matrix with $\sigma^2 \sigma_\beta^2$ on the diagonals.

3.3.5 Prior specification

In this section, we discuss the priors and their default specifications in BSR (Antonelli et al., 2020).

The priors on Σ_β , the diagonal matrix with $\sigma^2 \sigma_\beta^2$ on the diagonals, control the shrinkage of $\beta_S^{(h)}$. Variable selection is sensitive to the choice of prior on this parameter.

ter, so BSR implements an empirical Bayes strategy to obtain a prior distribution for σ_β^2 based on the data. While this is not a fully Bayesian approach, it has been shown that this strategy works better in practice (Antonelli et al., 2020). Additionally, the default prior for σ^2 is assumed to follow a Gamma(0.001, 0.001) distribution.

However, when there is a weak relationship between the exposures and relationship, the estimated prior variance for the slab σ_β^2 can be very small. In this case, the shape of the slab approximates the point mass of 0 at the spike, and the PIPs become difficult to accurately estimate. BSR avoids this by imposing a lower bound on the variance. This is determined by establishing a constant value for τ_h , the prior probability of inclusion, for all h and then permuting the rows of Y (i.e., breaking up the relationship). Then, a grid of values for σ_β^2 are tested until some predefined threshold of the posterior probability of inclusion is obtained (e.g., 0.25 for a main effect and 0.05 for a two-way interaction). If the empirical Bayes estimate for σ_β^2 is less than this lower bound, then the lower bound is used instead.

Finally, BSR assumes that $\tau_h \sim \text{Beta}(L, \gamma)$, which defines the prior probability of including a predictor for all functions h . If L is some predefined constant, and $\gamma = m$, the number of predictors, then the prior amount of sparsity should increase as the number of predictors increases (Antonelli et al., 2020).

3.3.6 The MCMC algorithm

We also briefly discuss the MCMC algorithm employed by BSR (Antonelli et al., 2020).

BSR uses an MCMC algorithm to obtain posterior distributions of σ^2 and τ_h . In particular, Gibbs samplers are employed to sample σ^2 and τ_h from their full distributions and to update ζ and $\beta_S^{(h)}$. Every T MCMC iterations, BSR uses a Monte Carlo expectation maximization algorithm with a Gibbs sampler to update σ_β^2 . The

empirical Bayes estimate is obtained once σ_β^2 converges, at which point the MCMC runs conditional on this estimated variance.

Notably, this algorithm must deal with the explicit specification of interaction terms in the model. Any additive univariate effect or lower-order interaction term is, by definition, a subset of some higher-order interaction term. As the MCMC algorithm searches the model space, it might accept a move to a higher-order interaction and get stuck in a local mode when, in reality, a simpler model should be preferred. BSR handles this challenge by imposing a constraint in the MCMC algorithm: if the inclusion of a p th order interaction term is being considered, then the algorithm must also evaluate all $(p - 1)$ th order models. If the truth is some lower-order model, then this strategy avoids the undesirable convergence to a local mode. When the model is complex, maintaining reversibility of updates under this strategy can be computationally challenging with a Gibbs sampler; in this case, using a Metropolis Hastings sampler is computationally faster (Antonelli et al., 2020).

3.4 Detecting interactions

In Section 3.1, we highlighted the challenges of analytically testing for the presence of interactions in exposure mixture studies. These challenges motivated a theoretical exploration of BKMR and BSR in Sections 3.2 and 3.3. Now, we discuss and compare the options that BKMR and BSR provide for inference on the presence of interactions. We also include discussion on theoretical advantages and disadvantages to each. Importantly, we note that it is not possible to detect interactions between a covariate and an exposure within the model specifications of BKMR or BSR.

3.4.1 BKMR

Since the flexible h function in kernel machine regression allows us to forgo any assumptions about the nature of the relationship between the health outcome and exposures, BKMR can potentially capture complex interactions between exposures. The challenge with using BKMR to do this, however, is that there is no formal framework for conducting inference on the presence of interactions.

Currently, the most common approach to detecting interactions is through a qualitative assessment of visual diagnostic plots (Bobb, 2017a). Two- or three-way interactions can be assessed by plotting the estimated exposure-response relation for one/two exposures at various quantiles of another exposure, while setting all other exposures at fixed quantile values. For instance, if we are interested in the interaction between X_1 and X_2 , we can plot the estimated regression line against X_1 at the 0.25, 0.5, and 0.75 quantiles of X_2 and vice versa. In the three-way case of X_1 , X_2 , and X_3 , we can plot the estimated regression surface against X_1 and X_2 at the 0.25, 0.5, and 0.75 quantiles of X_3 . If the shape of the estimation changes meaningfully, then there might be evidence of an interaction.

A slightly more formal inferential approach for two-way interactions involves using summary statistics (Bobb, 2017a, 2017b). In this case, we can calculate the difference in estimated response values for X_1 at two quantiles, say, 0.25 and 0.75, of X_2 and then generate a confidence interval. If we observe that the interval does not contain 0, then there is evidence of an interaction. The choice of quantiles here is important. If there is a parachute-like regression surface between the response and two exposures, the summary statistics might mask the true nature of the relationship.

Notably, if we specify hierarchical variable selection to handle multicollinearity, then only one exposure in each a priori defined group can enter the model. If there

exists some true interaction between exposures in one group, then BKMR will be unable to incorporate it into the final model. Moreover, interactions between exposures in separate groups can only be identified if both are selected into the final model based on their within-group PIPs. Hence, if detecting interactions is a goal when using BKMR with hierarchical variable selection, groups should be carefully selected, and the influence of group membership should be considered in model interpretation.

3.4.2 BSR

Providing formal inference on the presence of interactions was one of the primary motivations for the development of BSR. BSR explicitly incorporates interaction terms in its model formulation, and the model fitting process assigns PIPs for any m -dimensional interaction from the posterior means of the ζ matrix. Such probabilities can be used as a quantifiable measure of the strength of a potential interaction. We can also compare PIPs for interactions with the PIPs for their individual components, which can be used to compare exposures' interactive effects with their marginal effects.

The visualization and summary statistics approaches available in BKMR are also possible in BSR. In particular, it is helpful to follow up the identification of a potential interaction with a visual assessment using the estimated exposure-response relationship at fixed quantiles of other predictors. The major benefit of BSR is that the PIPs serve as a quantifiable uncertainty metric for the presence of interactions.

3.4.3 Differences between BKMR and BSR

We have explained how the inferential framework of BSR improves upon the BKMR approach for the detection of complex interactions. We also briefly compare general features of their model formulations.

While BKMR is a fully nonparametric approach, BSR is a semiparametric approach because it makes distributional assumptions about the data (i.e., that the relationship can be adequately captured by a d -dimensional natural spline basis expansion). As BKMR uses the kernel technique, its implementation can become computationally intensive for datasets with large n , as it scales with n^2 , while BSR is able to scale with n (Antonelli et al., 2020).

BSR is highly sensitive to the choice of d , the degrees of freedom. While it employs a WAIC approach to selecting the best d , this parameter introduces an additional tuning step in the analysis. Both approaches can be highly sensitive to the specification of certain priors. BSR offers an empirical Bayes strategy to estimate σ_β^2 , the variance of a exposure's prior probability of inclusion. On the other hand, the choice of prior on the influential smoothing parameter, ρ , in BKMR is up to the user.

We also note that BKMR offers a hierarchical variable selection approach to dealing with collinearity between exposures. While this is an additional decision that must be specified by the user, it offers a formal approach to dealing with collinear exposures. BSR does not explicitly account for collinearity in its model formulation, which can lead to erroneous interpretations of variable importance if unaccounted for.

Chapter 4 Simulations

4.1 Past simulation studies

Here, we preface our simulation study with an overview of examples in the literature which compare various methods for exposure mixture studies using simulations. Taylor et al. (2016) conclude that, in general for exposure mixture studies, no single method consistently outperforms others across all situations and, importantly, that a method should be chosen based on the question of interest. Thus, for each study, we highlight not only the findings, but also the data-generating scenarios and the identified question of interest.

Lazarevic et al. (2020) compare the performance of a broad range of methods for accurate variable selection of important exposures. They simulated exposure data using a multivariate copula based on real-world data and the response by specifying a regression model with only a subset of truly significant exposures and a normal error term. Two correlation structures were considered — one with the original Spearman correlation matrix and one with the values halved — as well as two signal-to-noise ratios — one with an R^2 for the true model at 10% and one at 30%. They found that BKMR, along with three other flexible regression methods that allow for nonlinearity, provided more accurate variable selection results compared to two machine learning methods. Moreover, they observed that, in general, low signal-to-noise ratios had a stronger impact on performance than did increasing multicollinearity.

Hoskovec et al. (2021) compare Bayesian methods, including BKMR, while considering 4 research questions: accurate estimation, selection of important exposures, exclusion of unimportant exposures, and identification of interactions. They use observed exposure and covariate data to simulate response data using regression relationships; they considered three exposure-response scenarios of varying complexity and included two-way multiplicative interaction terms. For each simulated dataset, they randomly assigned exposures to be active components of the mixture to incorporate variability in the data. Overall, they found that Bayesian methods outperformed traditional linear regressions, and that BKMR performed best when the exposure-response function takes on a complex form.

Most recently, Pesenti et al. (2023) compare BKMR, BSR, and the Bayesian Least Absolute Shrinkage and Selection Operator (LASSO) for variable selection. Data were generated using a multivariate normal with moderate and strong correlation structures specified manually by the researchers. They found that, in situations with additive and linear exposure-response relationships, Bayesian LASSO was appropriate. Across the other scenarios, BKMR generally performed best, while BSR selected exposures with high heterogeneity when the sample size was smaller due to the influence of the degrees of freedom, d , tuning parameter. Notably, multicollinearity did not generally lead to spurious variable selection.

Finally, we briefly comment on studies by Sun et al. (2013) and Barrera-Gómez et al. (2017), whose explicit goal is to compare methods for identifying interactions. Both studies generate exposure data using the correlation structure from an existing dataset; Sun et al. (2013) uses a multivariate lognormal, while Barrera-Gómez et al. (2017) uses a multivariate normal. Both only consider two-way, multiplicative interactions. While neither of these studies consider the methods used in this thesis, they find that, in general, models that formally allow for interaction effects perform

better than models that only allow for univariate additive effects.

4.2 Methods

The goal of our simulation study is to provide guidance on the choice between BSR and BKMR for characterizing a diverse range of complex interactions between predictors. In particular, we aim to extend findings from previous simulation studies by considering a more comprehensive range of interaction types, including different effect sizes, non-multiplicative interactions, and three-way interactions. We also explore interactions between exposures and categorical covariates, a previously understudied form of interaction in exposure mixture studies. Hereafter, we refer to exposures and chemicals interchangably.

4.2.1 MADRES data

In order to make our simulations comparable to real-world exposure mixture studies, we based our simulation data on the Maternal And Developmental Risks from Environmental and Social Stressors (MADRES) pregnancy cohort. The MADRES cohort is an ongoing, prospective pregnancy cohort of predominantly lower-income, Hispanic women in Los Angeles, California, which began in 2015 (Bastain et al., 2019). Urine samples were collected by participants at their first visit, and questionnaires were administered during their first visit, with follow-ups at the first, second, and third trimesters. See Bastain et al. (2019) for further details on study design.

Howe et al. (2020) previously examined the effect of prenatal metal mixtures of birth weight (BW) for gestational age (GA) in this cohort. They used BKMR to identify associations between metal mixtures and BW for GA, as well as BSR to conduct inference on interactions between metals. Using BKMR, they found that, of the

metals in the mixture, mercury and nickel were most strongly associated with BW for GA. Moreover, BKMR results suggested that a potential interaction between mercury and nickel exists; however, when run through BSR, the PIP for this interaction was extremely small, despite being the highest of all two-way interactions.

Data from the study by Howe et al. (2020) were obtained from publicly available data in the Human Health Exposure Resource (HHEAR) Data Repository, which has been approved under Icahn School of Medicine at Mount Sinai IRB Protocol #16-00947. The Digital Object Identifiers associated with the urinary trace element data and epidemiological data are 10.36043/1945_159 and 10.36043/1945_177, respectively. All analyses were conducted in R v4.3.2 (R Core Team, 2013).

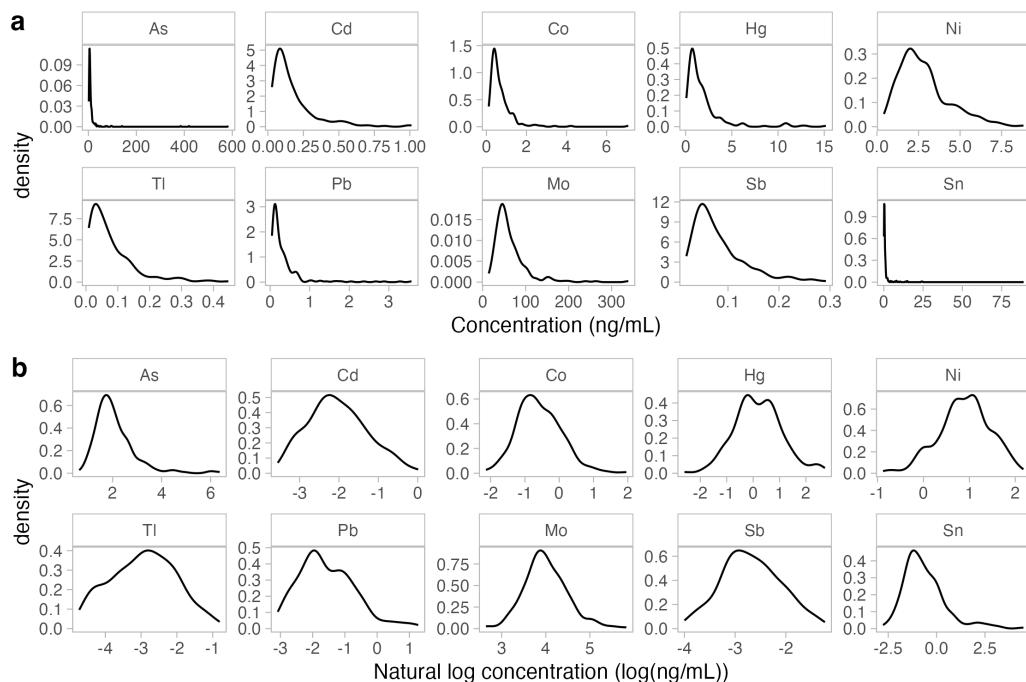


Figure 4.1: Distributions of original (a) and natural log transformed (b) concentrations of metals in MADRES cohort ($n=252$).

We followed the approach by Howe et al. (2020) for preparing the data for analysis. This resulted in retaining 10 metals in analysis: arsenic (As), cadmium (Cd),

cobalt (Co), mercury (Hg), nickel (Ni), molybdenum (Mo), lead (Pb), antimony (Sb), tin (Sn), and thallium (Tl). Howe et al. (2020) used speciated As, but this was not available in HHEAR, so we used total As. Metals were expressed in nanograms per milliliter (ng/mL) and natural log transformed to reduce right-skewness (Figure 4.1). Among the full range of covariates considered by Howe et al. (2020), we used the subset of 4 that were available in HHEAR: any smoke exposure during pregnancy, maternal prepregnancy body mass index (BMI), maternal age during first trimester, and maternal race by ethnicity and birth place. We chose not to include study site, as there was a study site with only 1 participant. Race by ethnicity and birth place was collapsed into the following categories: non-Hispanic white, non-Hispanic black, non-Hispanic other, Hispanic born in the US, and Hispanic born outside the US. We observed 8 missing values for BMI in the data from HHEAR, which were not reported by Howe et al. (2020). We mean imputed these missing values. Distributions of covariates are shown in Figure 4.2. Our final analytic dataset included 252 participants, which was 10 fewer than in Howe et al. (2020), likely due to small discrepancies in their dataset and the one made available in HHEAR.

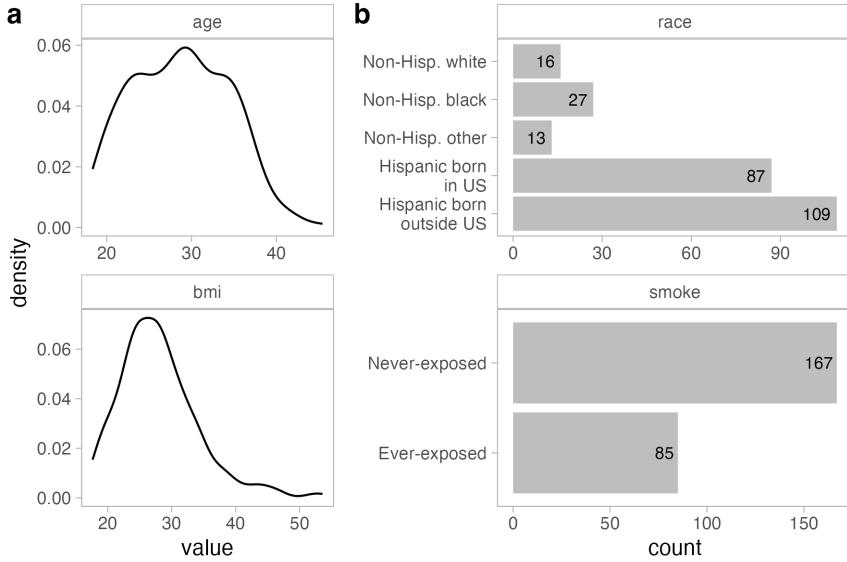


Figure 4.2: Distributions of continuous (a) and categorical (b) covariates in the MADRES cohort ($n=252$).

4.2.2 Using copulas to simulate predictor data

We simulated exposure and covariate data (hereafter referred to collectively as predictors) using a multivariate Gaussian copula fit on the 252 participants in the MADRES cohort. We used copulas as they can preserve both the correlation structure and marginal distributions from the observed data, allowing us to replicate conditions in a real-world scenario.

First, we briefly introduce copulas in the context of their use in this simulation, based on the presentation in Nelsen (2006). Copulas are joint cumulative distribution functions (CDFs) defined on the unit cube $[0, 1]^n$ that capture the dependence between n uniformly distributed marginals. Sklar's theorem allows us to apply copulas to our observed data. Sklar's theorem states that, if $H(x_1, \dots, x_n)$ is a joint CDF of the marginal CDFs $F_1(x_1), \dots, F_n(x_n)$, then there exists a copula C such that, for all (x_1, \dots, x_n) in (X_1, \dots, X_n) ,

$$H(x_1, \dots, x_n) = C(F_1(x_1), \dots, F_n(x_n)).$$

Note that, by the probability integral transform, or the universality of the uniform, the CDFs $F_1(x_1), \dots, F_n(x_n)$ are distributed uniformly.

We used the `copula` package in R to fit copulas and generate random data (Hofert, Kojadinovic, Maechler, & Yan, 2023). We transformed the observed continuous predictor values to uniform distributions based on their empirical marginal CDFs, a process called generating “pseudo-random” samples. We used the checkerboard copula approach for generating pseudo-random samples for smoke exposure, a binary variable (Genest & Nešlehovà, 2007). We coded smoke exposure as 0’s and 1’s, generated a pseudo-random sample, and then “jittered” the values with uniform random noise. There is currently no widely accepted approach for generating pseudo-random samples from unordered categorical variables with more than two levels. Thus, we excluded race by ethnicity and birthplace from the copula model. While this means that our simulated datasets did not preserve any potential association between race and exposures, Figure 4.3 suggests that there is little to no visible association between race and exposures in the observed dataset.

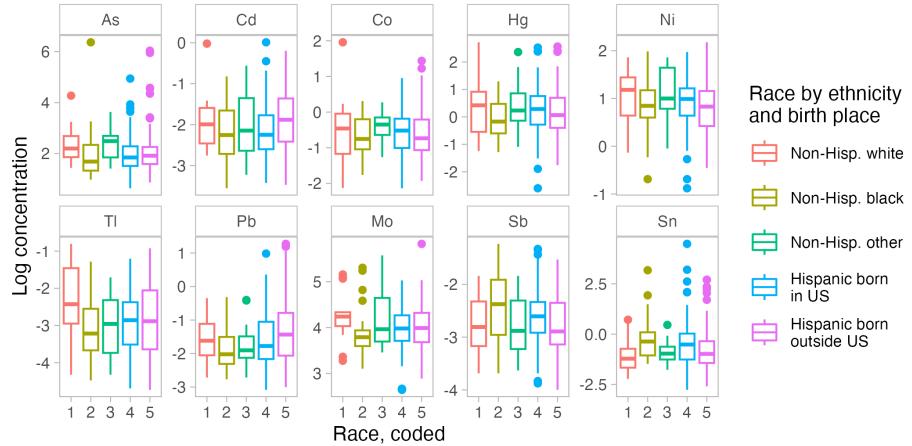


Figure 4.3: Association between race by ethnicity and birth place and metal exposures in the MADRES cohort ($n=252$).

Various families of copulas have been described, each of which specifies a different shape for the dependence structure. We performed model selection to identify the copula that best approximates the dependence structure of our data. We fit the set of multivariate copulas used by Lazarevic et al. (2020) in their simulation study, which included the Gaussian, t , Gumbel, Frank, Clayton, and Joe copulas. We fit two t copulas with 4 and 10 degrees of freedom, which controls dependence at the tails of the distributions, as well as a t copula where the degrees of freedom was determined during the fitting process. The Gumbel, Frank, Clayton, and Joe copulas require a θ parameter, which controls dependence between the distributions. We fit two versions of these copulas with $\theta = \{2, 4\}$. Among these, the Gaussian copula minimized the Akaike information criterion and maximized the likelihood, so we proceeded with this model. The Gaussian copula assumes a bivariate normal dependence structure between the marginal CDFs.

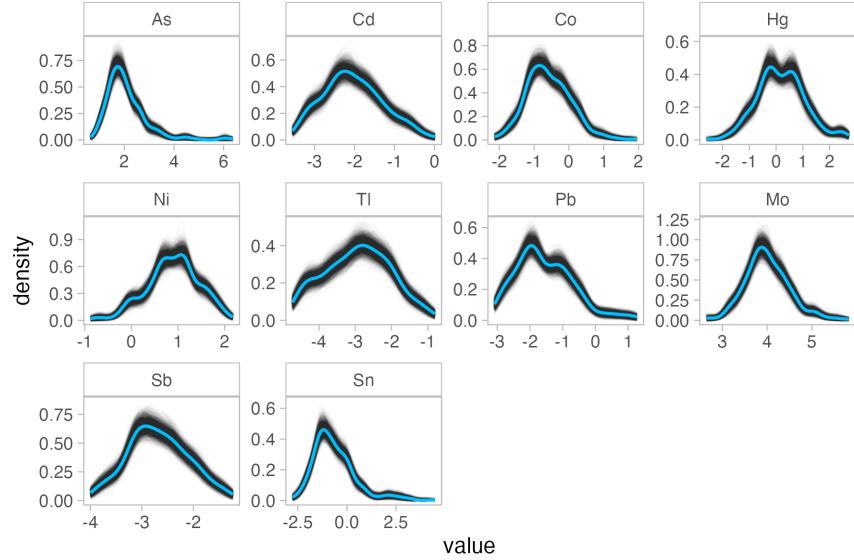


Figure 4.4: Distributions of log-transformed exposures from observed data (blue) and 2100 simulated smaller size ($n=252$) datasets (gray).

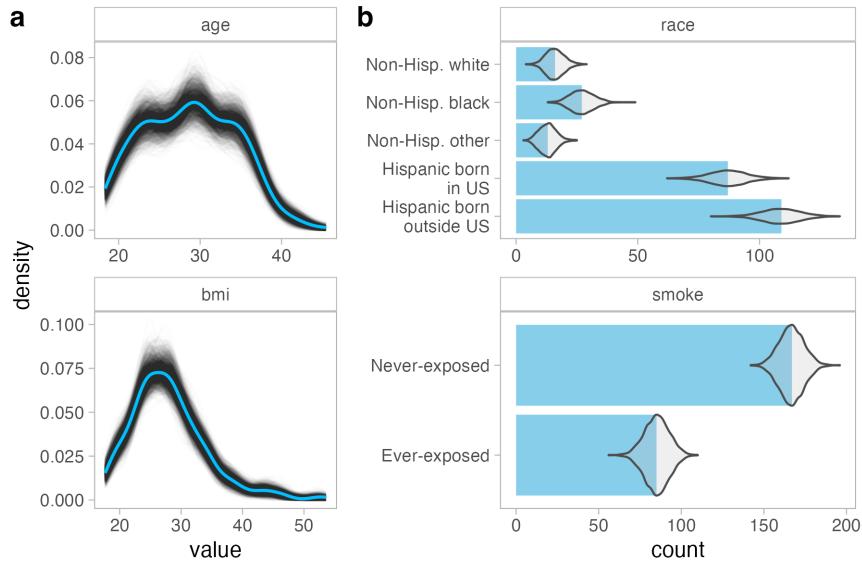


Figure 4.5: Distributions of continuous (a) and categorical (b) covariates from observed data (blue) and 2100 simulated smaller size ($n=252$) datasets (gray).

We simulated predictor data by randomly sampling from the fitted multivariate Gaussian copula distribution. All pseudo-random samples were then

back-transformed to their original distributions using empirical marginal CDFs. We simulated the race by ethnicity and birthplace variable by randomly assigning observations to each of the five categories based on proportions in the observed dataset.

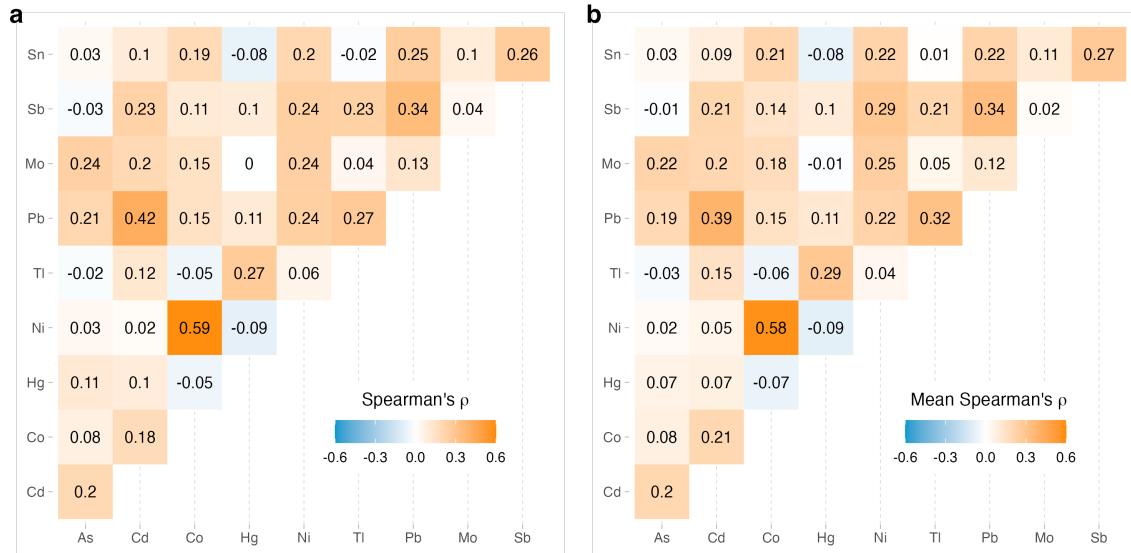


Figure 4.6: Spearman's correlation heat maps of exposures from observed data (a) and averaged across 2100 smaller size ($n=252$) simulated datasets (b).

We generated one set of simulated datasets with the same sample size as the observed dataset ($n=252$), which is typical in many cohort studies. We also generated another set of simulated datasets with a larger sample size ($n=1000$), which has become increasingly common with the rise of larger-scale studies. The goal of this choice was to inform sample size considerations in study design. We verified that the original structure of the observed dataset were preserved by visually comparing univariate distributions of exposures (Figure 4.4) and covariates (Figure 4.5), as well as the correlation structure using Spearman's ρ (Figure 4.6). Distributions of Spearman's correlation were approximately normal (Figure A.15). Plots for the larger size simulated datasets were similar (Figures A.16, A.17, and A.18).

4.2.3 Simulating predictor-response relationships

Health outcome responses were simulated under several different scenarios, each of which included different effect sizes and functional forms for the interactions. All scenarios were run for both the smaller ($n=252$) and larger ($n=1000$) sample sizes.

In the first scenario, we specified a “base case” model:

$$Y = \text{Hg} + \frac{3}{1 + \exp(-4\text{Ni})} + \frac{1.5}{1 + \exp(-4\text{Sn})} - \text{Sb}^2 + 0.5\text{Sb} \\ + \text{age} + 0.5\text{bmi} + 0.5\text{race}_{\text{black}} + 0.5\text{race}_{\text{hispanic}} + 1.5\text{smoke} + \varepsilon,$$

where $\varepsilon \stackrel{\text{iid}}{\sim} N(0, 5)$. This model includes a linear term for Hg, two S-shaped logistic terms for Ni and Sn with varying effect sizes, and a symmetric inverse U-shaped quadratic term for Sb (Figure A.1). Moreover, we included covariate terms as linear effects in the model. We chose the standard deviation on the normal random error term in order to achieve an R^2 of around 0.1-0.3 in a multiple linear regression that included only the true functional form of the significant chemicals (Figure A.19). This R^2 range approximates realistic signal-to-noise ratios in exposure mixture studies (Lazarevic et al., 2020).

In subsequent scenarios, we added an additional interaction term to the base case model. First, we considered interactions between two exposures. We defined four cases of interest: a two-way interaction between exposures that are univariately significant, a two-way interaction between exposures that are univariately insignificant, a two-way interaction between exposures that are moderately collinear, and a three-way interaction. For each case, we considered two functional forms — multiplicative and polynomial — and a lower and higher effect size, which we set by defining the weight on the interaction term in the model. The higher effect sizes were selected in

Table 4.1: Specification of interaction terms in simulations.

Effect size		
	Lower	Higher
Univariately significant		
Multiplicative	0.35Hg*Ni	0.7Hg*Ni
Polynomial	0.13Hg*(Ni-1) ²	0.26Hg*(Ni-1) ²
Univariately insignificant		
Multiplicative	0.35Cd*As	0.7Cd*As
Polynomial	0.125Cd*(As-1) ²	0.25Cd*(As-1) ²
Highly correlated		
Multiplicative	0.3Ni*Co	0.6Ni*Co
Polynomial	0.1Ni*(Co-1) ²	0.2Ni*(Co-1) ²
Three-way interaction		
Multiplicative	0.3Hg*Ni*Tl	0.6Hg*Ni*Tl
Polynomial	0.09Hg*(Ni-1) ² *Tl	0.18Hg*(Ni-1) ² *Tl

order to achieve a power of approximately 0.5 at $\alpha = 0.05$ in the smaller sample size ($n=252$) case, using a multiple linear regression with the true functional form of the chemicals specified and the covariate terms included. The lower effect sizes were set equal to half of the higher effect size. Table 4.1 shows the specification of interaction terms. See Appendix A.1, Figures A.2-A.14, for 3D surfaces of the two-way interaction terms. Next, we considered interactions between the race by ethnicity and birthplace covariate (hereafter referred to as race for concision) and an exposure. We are interested in cases where the health effects of an exposure are higher in one group compared to the rest. In a real-world scenario, such interactions can arise from excess amounts of social stress experienced by a group due to racism. To model this, we increased the coefficient Hg in Non-Hispanic Black individuals ($n=27$ in the original MADRES cohort) for the first scenario, and in Hispanic individuals born outside the US ($n=109$ in the original MADRES cohort) for the second scenario. The goal of this choice was to assess the impact of group size on detectability of an interaction,

and to quantify the potential value of oversampling the minority group. For each scenario, we specified a lower effect size by increasing the coefficient on Hg by $1.5 \times$ (i.e. from $1 \times \text{Hg}$ to $1.5 \times \text{Hg}$) in the target group, and a higher effect size by increasing the coefficient on Hg by $2 \times$ (i.e. from $1 \times \text{Hg}$ to $2 \times \text{Hg}$).

This resulted in a total of 42 scenarios ([1 base case + 5 interaction cases \times 2 effect sizes \times 2 functional forms] \times 2 sample sizes = 42). For each scenario, we generated 100 simulated datasets to fit our models on, resulting in a total of 4200 datasets. Hereafter, we refer to the two different effect sizes of interactions using “lower” and “higher,” and we refer to the two different sample sizes as “small” and “large,” or “smaller” and “larger.”

4.2.4 Models

We ran four methods on our simulated datasets. All metal concentrations and continuous covariates were standardized in analysis to keep values scale-free.

To get a baseline, we ran a multiple linear regression, including all exposures and covariates as linear, additive terms in the model. We refer to this model as the naive MLR. Then, we ran a multiple linear regression with the true model explicitly specified by excluding non-significant exposures and specifying the known form of non-linear terms and non-additive interactions. We refer to this model as the oracle MLR. In scenarios with an interaction between race and Hg, we collapsed race into a binary variable indicating whether or not the original race category was interacting with Hg before running oracle MLR’s, in order to simplify the detection of the interaction.

Next, we ran BKMR using the `bkmr` package in R (Bobb, 2022; Bobb et al., 2018). We chose to implement component-wise variable selection rather than hierarchical selection to make simulation results more interpretable, and because there was only moderate multicollinearity in the observed and simulated data. We specified the

default priors (Bobb et al., 2015, and as listed in Chapter 3.2.5), which is common in the literature for BKMR Pesenti et al. (2023). We ran the MCMC sampler for 50,000 iterations, as recommended by Bobb et al. (2018), and discarded the first 25,000 iterations for burn-in. BKMR does not provide the option to run multiple chains or to thin chains. For larger size datasets, we sped up computations by employing a Gaussian predictive process on 100 knots specified evenly across the predictor space.

We ran BSR using the `NLInteraction` package in R (Antonelli, 2018). We specified the default priors (Antonelli et al., 2020, and as listed in Chapter 3.3.5), which is common in the literature for BSR (e.g., Howe et al., 2020; Pesenti et al., 2023). Antonelli et al. (2020) suggests separately fitting models for degrees of freedom $d = \{1, 2, 3, 4\}$ and selecting the value for d which minimizes WAIC. We used the default Gibbs sampler, as opposed to the Metropolis Hasting sampler. Due to time constraints in this thesis, we first fit BSR on the grid of values for d using 5,000 MCMC iterations to obtain the empirical Bayes estimate for σ_β^2 and then another 5,000 MCMC iterations to obtain the posterior distributions, discarding the first 2,500 iterations for burn-in each time. We selected d based on the WAIC criterion on these preliminary models. Then, we fit the full BSR model using 50,000 MCMC iterations to obtain the empirical Bayes estimate and then another 50,000 MCMC iterations to obtain the posterior distributions, discarding the first 25,000 iterations for burn-in each time. We ran two chains to verify convergence, thinning each chain by selecting every 8th iteration to reduce autocorrelation based on default settings. In a small test run on five smaller size datasets for each scenario containing interactions between exposures, as well as the base case, we found that using 5,000 iterations selected the same degrees of freedom as using 50,000 iterations 86% of the time (see Appendix A.1, Figure A.20).

Finally, we ran stratified BKMR and BSR models in scenarios where we simulated

an interaction between race and Hg. This involved running five separate models for each race category, each with the same settings specified above. For the smaller size datasets, we often observed convergence issues in BKMR within the smaller race categories. As such, for smaller size datasets, we also assess the impact of collapsing the three smaller race categories (Non-Hispanic white, black, and other) into one category before stratifying. This is a common practice in real-world studies where sample sizes for certain categories are low.

For all models, we saved run-times for the fitting process on the high-performance computing cluster. Due to an error in our code and time constraints in this thesis, we were not able to obtain run times for stratified BSR models. We checked convergence for a selection of BKMR and BSR models using trace plots (Appendix A.2, Figure A.21).

4.2.5 Model assessment

We assessed model performance based on detection of significant univariate chemicals as well as detection of interactions. For the naive and oracle MLRs, we considered a *p*-value less than 0.05 to indicate detection of a significant term. For BKMR and BSR, we used the median probability model, which considers a PIP greater than or equal to 0.5 to indicate detection of a significant term (Barbieri & Berger, 2004).

While BSR provides PIP's to quantify detection of interactions, BKMR does not. As such, for BKMR, we considered formal detection of an interaction based on confidence intervals constructed around the estimated response. Specifically, we first calculated the difference in estimated response at a chemical's 0.25 and 0.75 quantiles. Then, we assessed whether this quantity differed at the 0.25 and 0.75 quantiles of one (or two, for three-way interactions) other chemicals in the interaction, while holding all other chemicals at their 0.5 quantiles, by constructing a 95% confidence interval

of the difference in differences. We followed the code in the `SingVarIntSummaries()` function in the `bkmr` package for constructing confidence intervals (Bobb, 2022). Notably, for two-way interactions, the ordering of the chemicals in this comparison does not matter. To see why, see (A.1) in Appendix A.1. However, for three-way interactions, the order does matter. Thus, we considered a three-way interaction to be detected if at least one of the three confidence intervals was significantly greater than zero. We used the Bonferroni correction to adjust for multiple comparisons, creating 98.3% confidence intervals to achieve an overall 95% confidence level (Dunn, 1961; Tyler J. VanderWeele & Mathur, 2019).

For both BKMR and BSR, we also visually assessed detection of interactions by plotting the estimated exposure-response surface for one chemical while fixing one (or two, for three-way interactions) other chemicals at their 0.1, 0.5, and 0.9 quantiles. In all scenarios, we calculated the sensitivity as the proportion of times a significant term was correctly detected. Due to time constraints in this thesis, we only calculated the false discovery rates, or, the proportion of times a significant term is incorrectly detected, for two-way interactions between chemicals. Future work should include the calculation of false discovery rates for all interactions.

For stratified models, we compared the estimated response across each separate model. Specifically, for BKMR, we computed a confidence interval for the difference in estimated response at the 0.25 and 0.75 quantiles of Hg on each subcategory of race, following the code in the `SingVarRiskSummaries()` function in the `bkmr` package (Bobb, 2022). We adjusted for multiple comparisons based on the Bonferroni procedure by constructing 5 simultaneous 99% confidence intervals, in order to achieve an overall 95% confidence level (Dunn, 1961; Tyler J. VanderWeele & Mathur, 2019). We considered an interaction as correctly detected if (1) there was at least one overlap between the target group's confidence interval and all other confidence intervals, and

- (2) all other confidence intervals overlapped.

However, for BSR, we were not able to find a method in the literature for combining variances from estimated responses at two different sets of predictor values. Therefore, we visualized and compared the estimated exposure-response relationship in each of the stratified models as a qualitative way to assess for interactions. We also generated these diagnostic plots for BKMR. Moreover, due to time constraints in this thesis, we only considered sensitivity, as opposed to also considering false discovery rates. Future work should involve exploring methods for estimating contrasts along continuous predictors for a more formal method of inference on BSR output, as well as consideration of false discovery rates.

4.3 Results

4.3.1 Base case

We start by presenting results from models run on the base case scenario, in which the true relationship contained no interactions. Figure 4.7 displays the distribution of p-values and PIPs from this scenario, while Table 4.2 summarizes model sensitivity and false discovery rates based on these values. Note that insignificant chemicals were not included in the oracle MLR, which is why their distributions are omitted from this output.

Table 4.2: Sensitivity and false discovery rate (FDR) of chemicals in base case scenario.

	Sensitivity				FDR					
	Hg	Ni	Sb	Sn	As	Cd	Co	Mo	Pb	Tl
Naive MLR										
Small	0.80	0.70	0.12	0.24	0.05	0.07	0.02	0.07	0.03	0.08
Large	1.00	1.00	0.51	0.71	0.02	0.04	0.08	0.13	0.03	0.03
Oracle MLR										
Small	0.84	0.94	0.95	0.35	-	-	-	-	-	-
Large	1.00	1.00	1.00	0.89	-	-	-	-	-	-
BKMR										
Small	0.86	0.92	0.95	0.52	0.30	0.33	0.36	0.38	0.41	0.40
Large	1.00	1.00	1.00	0.77	0.12	0.12	0.14	0.13	0.08	0.13
BSR										
Small	0.51	0.67	0.88	0.17	0.06	0.04	0.04	0.04	0.04	0.05
Large	1.00	1.00	1.00	0.62	0.01	0.00	0.03	0.02	0.03	0.00

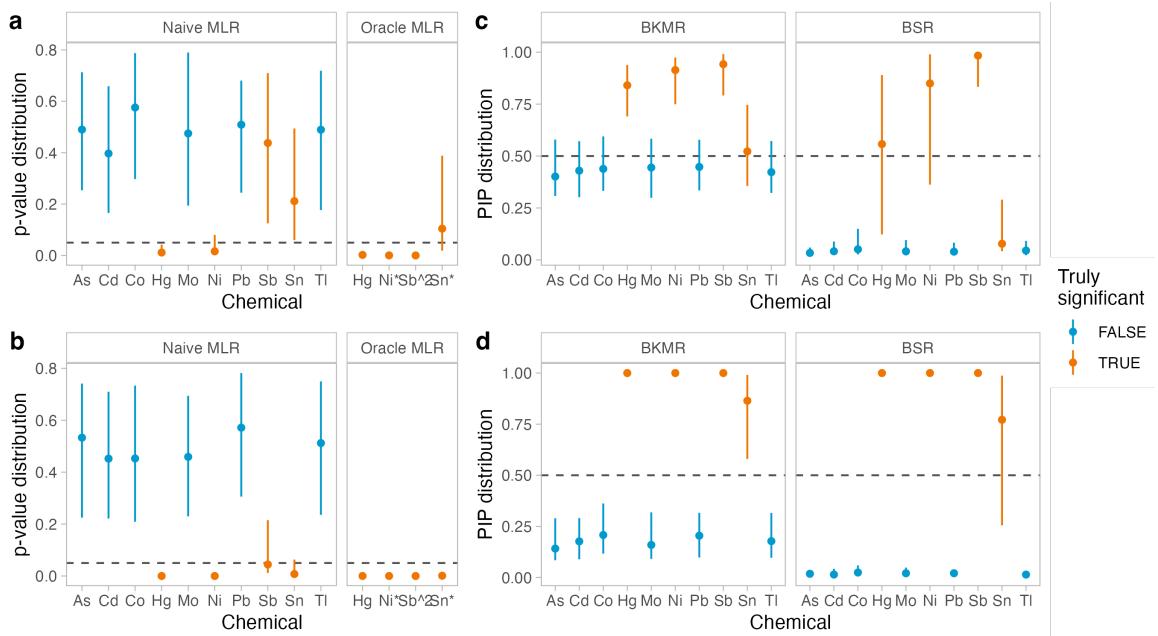


Figure 4.7: P-value distributions from smaller (a) and larger (b) size datasets and PIP distributions from smaller (c) and larger (d) size datasets.

The strongest detected effects in the naive MLR come from Hg, with a sensitivity

of 0.8 and 1 in the smaller and larger size datasets, respectively. This is likely because Hg is the only linear term in the model. Ni and Sn have an S-shaped curve with higher and lower effect sizes, respectively, so the naive MLR detects a slight linear signal from them. Sb, which has a U-shaped curve, is the hardest to pick up. On the other hand, the oracle MLR consistently detects Hg, Ni, and Sb. The smaller size oracle MLRs only occasionally pick up Sn, likely due to the lower effect size.

BKMR has similar sensitivity rates as the oracle MLR, ranging from 0.52-0.95 in the smaller size datasets and 0.77-1.00 in the larger size datasets. However, BKMR also has, by far, the highest false discovery rates, ranging from 0.30-0.41 in the smaller size datasets and 0.08-0.14 in the larger size datasets. This is likely due to the default choice of an inverse uniform distribution from 0 to 100 for the “slab” component on the “slab-and-spike” prior on r_m . Choosing a prior that assigns higher probability to smaller values of r_m should reduce the false discovery rate. In contrast, BSR tends to have slightly lower sensitivity rates than BKMR, raning from 0.17 to 0.88 in the smaller size datasets and 0.62-1.00 in the larger size datasets, but the false discovery rates are much lower, ranging from 0.04-0.05 in the smaller size datasets and 0-0.03 in the larger size datasets.

Overall, this base case scenario confirms that the multiple regression and Bayesian models behave as expected. We also recognize that, for univariate significance metrics, BKMR tends to produce higher sensitivity and false discovery rates, while the opposite is true for BSR.

4.3.2 Univariate sensitivity

Now, we provide a brief overview of univariate sensitivity metrics from all scenarios with an interaction between chemicals. We are particularly interested in cases where it appears that the inclusion of an interaction term influences the detection rate of

Table 4.3: Overall sensitivity for univariate chemicals in all scenarios with interactions between chemicals.

Type	Effect size	Small (n=252)				Large (n=1000)			
		Naive	Oracle	BKMR	BSR	Naive	Oracle	BKMR	BSR
Hg-Ni									
Mult.	Lower	0.48	0.62	0.86	0.58	0.80	0.84	0.94	0.91
Mult.	Higher	0.50	0.70	0.82	0.68	0.80	0.95	0.91	0.92
Poly.	Lower	0.50	0.70	0.87	0.64	0.80	0.92	0.93	0.92
Poly.	Higher	0.46	0.62	0.80	0.57	0.80	0.88	0.92	0.93
Cd-As									
Mult.	Lower	0.46	0.78	0.81	0.56	0.78	0.94	0.94	0.92
Mult.	Higher	0.43	0.80	0.84	0.55	0.80	0.95	0.97	0.93
Poly.	Lower	0.46	0.78	0.78	0.56	0.82	0.94	0.96	0.92
Poly.	Higher	0.46	0.76	0.82	0.52	0.78	0.93	0.94	0.90
Ni-Co									
Mult.	Lower	0.49	0.65	0.85	0.60	0.80	0.84	0.95	0.92
Mult.	Higher	0.52	0.73	0.81	0.60	0.79	0.94	0.93	0.91
Poly.	Lower	0.52	0.67	0.85	0.64	0.80	0.89	0.93	0.89
Poly.	Higher	0.45	0.60	0.78	0.56	0.85	0.88	0.93	0.92
Hg-Ni-Tl									
Mult.	Lower	0.48	0.69	0.84	0.58	0.81	0.90	0.93	0.91
Mult.	Higher	0.44	0.73	0.80	0.56	0.82	0.94	0.95	0.92
Poly.	Lower	0.44	0.68	0.84	0.55	0.79	0.89	0.95	0.92
Poly.	Higher	0.48	0.73	0.80	0.62	0.77	0.94	0.92	0.92

univariate chemicals.

Table 4.3 summarizes the sensitivity of univariate chemicals in all scenarios with interactions between chemicals, comparing the form of interactions, effect sizes, size of datasets, and models. See Table A.1 in Appendix A.2 for false discovery rates, as well as Figures A.22-A.29 in Appendix A.2 for the full p-value and PIP distributions for all scenarios with interactions between chemicals. In general, the detection rates of univariate chemicals that participate in an interaction differ in comparison to the base case. First, we briefly note that the sensitivity for univariate chemicals that participate in interactions is reduced for oracle MLRs, compared to the base case

(Table 4.3 and Figures A.24 and A.25). However, as the oracle MLRs contain explicit interaction terms, the p-values for univariate terms that participate in an interaction are not interpretable.

Now, for the naive MLR, BKMR, and BSR, chemicals that are marginally insignificant but participate in an interaction can occasionally be detected, depending on their form, effect size, and the sample size of the data. For instance, in scenarios with a higher effect polynomial interaction between As and Cd, both of which are univariately insignificant, the larger size naive MLR has a sensitivity of 0.67 for Cd (Figure A.23), BKMR 0.78, and BSR 0.55. In comparison, the sensitivities are all lower in scenarios with the higher effect multiplicative interaction between As and Cd. This is likely because, in the theoretical model for this scenario, Cd exhibits a strong positive relationship with the health response at lower levels of As, which is then attenuated at higher levels of As (Figure A.10). On the other hand, in the case of a multiplicative interaction, the positive relationship between Cd and the health response at lower levels of As becomes inverted at higher levels of As (Figure A.8), which would be more difficult to detect when only considering additive effects. This demonstrates that non-additive interactions may occasionally be detected through univariate terms depending on their form, and when the effect size and sample size are large enough.

Finally, univariate sensitivity for chemicals that are marginally significant — in our case, Hg and Ni — are not noticeably affected by participation in an interaction. For instance, the naive MLR, BKMR, and BSR had sensitivities of 0.80, 0.86, and 0.51, respectively, for Hg in the base case with the smaller size dataset. In scenarios with a higher effect size multiplicative interaction between Hg and Ni, the sensitivities were 0.77, 0.88, and 0.58 for the naive MLR, BKMR, and BSR, respectively. As such, we confirm that participation in an interaction does not affect univariate sensitivity,

in our simulation scenarios.

The findings from this section suggest the impact of interpreting univariate effects from models without considering potential interactions. If a chemical participates in an interaction but is, itself, not significant, then it can occasionally be detected as significant, depending on the form of the interaction, its effect size, and the sample size. On the other hand, if the chemical is itself significant, the detection of its effect should not be affected by the presence of an interaction.

4.3.3 Two-way interactions between chemicals

This section describes the ability of BKMR and BSR to detect two-way interactions between chemicals, using results from the oracle MLR as a baseline. We recall that sensitivities for BKMR were generated by the confidence interval approach, which required an arbitrary choice of the 0.75 and 0.25 quantiles for comparing the estimated response. On the other hand, sensitivities for BSR were based on the PIPs that it provides for interaction terms.

Table 4.4 summarizes the sensitivity of the oracle MLR, BKMR, and BSR for two-way interactions. The oracle MLR consistently has much greater sensitivity for interactions than both BKMR and BSR. First, we discuss smaller size datasets. At the lower effect size of interactions, the oracle MLR has sensitivities of 0.15-0.24, while BKMR and BSR have much lower sensitivities of 0-0.03, excluding BSR’s sensitivity of 0.07 for the multiplicative interaction between Hg and Ni. Now, for the higher effect size interactions in the smaller size datasets, the oracle MLR has a sensitivity of around 0.5, which is as we designed. In comparison, for Hg and Ni, BKMR has sensitivities of only 0.11 and 0.03 for the multiplicative and polynomial interactions, respectively, while BSR has sensitivities of only 0.10 and 0.14. For interactions between Cd and As, and between Ni and Co, BKMR and BSR have sensitivities ranging

Table 4.4: Sensitivity to interactions in all scenarios with two-way interactions between exposures.

Interaction type	Effect size	Small (n=252)			Large (n=1000)		
		Oracle	BKMR	BSR	Oracle	BKMR	BSR
Hg-Ni							
Multiplicative	Lower	0.24	0.01	0.07	0.48	0.21	0.28
	Higher	0.50	0.11	0.10	1.00	0.88	0.77
Polynomial	Lower	0.14	0.01	0.03	0.54	0.18	0.27
	Higher	0.48	0.03	0.14	1.00	0.76	0.76
Cd-As							
Multiplicative	Lower	0.15	0.00	0.00	0.59	0.04	0.01
	Higher	0.52	0.01	0.02	0.99	0.57	0.39
Polynomial	Lower	0.18	0.00	0.00	0.57	0.00	0.00
	Higher	0.52	0.00	0.00	0.99	0.03	0.21
Ni-Co							
Multiplicative	Lower	0.18	0.01	0.01	0.52	0.03	0.00
	Higher	0.50	0.02	0.01	0.98	0.52	0.09
Polynomial	Lower	0.16	0.00	0.00	0.53	0.00	0.00
	Higher	0.54	0.00	0.02	0.97	0.05	0.05

from only 0-0.02. Therefore, in smaller size datasets, it is very difficult for BKMR and BSR to detect interactions, particularly when the effect size is low, or both chemicals are not marginally significant (which is the case for Cd and As and Ni and Co). Now, in larger size datasets, interactions are detected much more frequently by BKMR and BSR. In general, for interactions between Hg and Ni, the sensitivities of BKMR and BSR have values around 0.2-0.3 less than those for the oracle MLR. As a result, for the higher effect size interactions, BKMR and BSR have relatively high sensitivities ranging from 0.76-0.88. While both do not achieve the sensitivity of 1 that the oracle MLR does, they can still detect these interactions relatively reliably. We also note that neither BKMR nor BSR consistently outperforms the other in this case — BSR would thus be more preferable as it has a more formal framework for conducting

inference.

In comparison, for interactions between Cd and As, which are both marginally insignificant, BKMR and BSR still struggle to detect a significant effect even in the larger size datasets. At the lower effect size, sensitivities range from 0-0.04, though at the higher effect size, sensitivities range from 0.03-0.57. We note that cases with higher sensitivities for interactions (e.g., the higher effect size multiplicative interaction) are associated with higher univariate detection rates for Cd and As in both BKMR (Figure A.27) and BSR (Figure A.29). Thus, we suggest that detection of interactions is associated with detection of univariate effects. Interactions between Hg and Ni are easier to detect because they are, themselves, marginally significant. However, interactions between marginally insignificant chemicals are likely to only be detected if the form and effect size of the interaction are such that the chemicals can also be detected marginally.

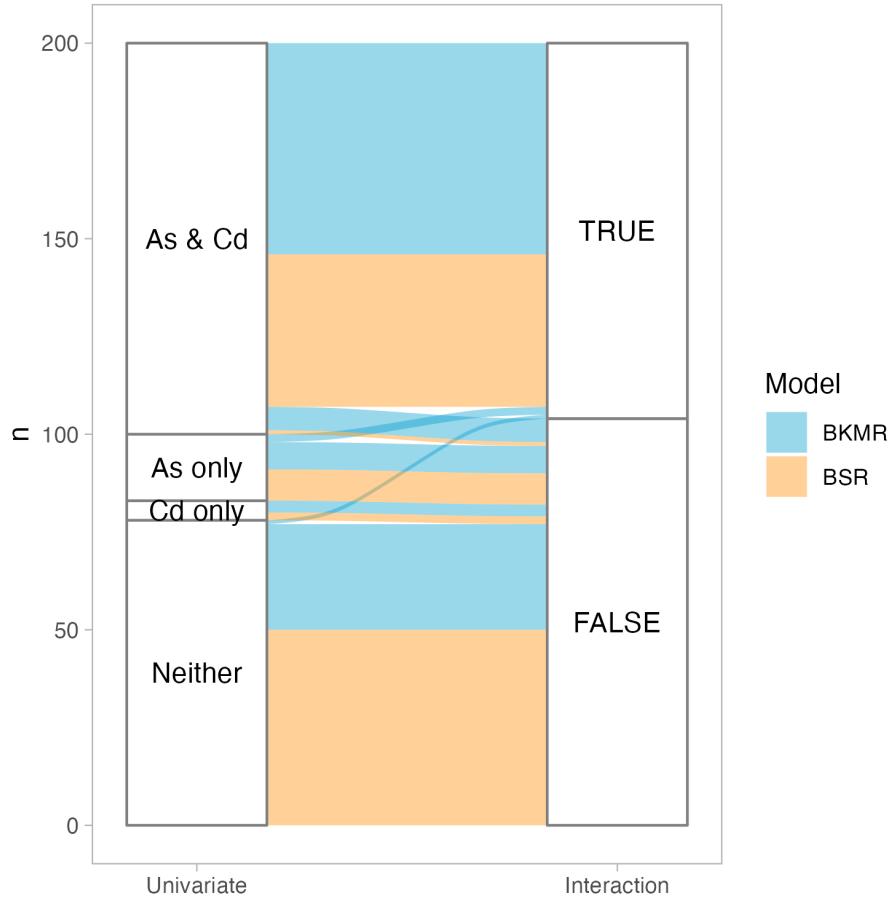


Figure 4.8: cd as flow chart.

BKMR and BSR's sensitivities for Ni and Co, which have moderate to strong multicollinearity, are similar to their sensitivities for Cd and As in the larger size dataset. Since Co is not marginally significant, it is difficult to determine whether low detection rates for this case are due to Co's univariate insignificance or its multicollinearity. We do note, though, that while BKMR has similar sensitivities of around 0.5 for the higher effect multiplicative interaction between Cd and As (both of which are marginally insignificant) and between Ni and Co, BSR has a 0.39 sensitivity for Cd and As and a much lower 0.09 sensitivity for Ni and Co. Thus, BSR may have lower sensitivity for interactions between collinear chemicals compared to BKMR,

Table 4.5: False discovery rate of interactions in all scenarios with two-way interactions between exposures.

Interaction type	Effect size	Small (n=252)		Large (n=1000)	
		BKMR	BSR	BKMR	BSR
Hg-Ni					
Multiplicative	Lower	0.0011	0.0030	0.0034	0.0125
	Higher	0.0020	0.0020	0.0048	0.0159
Polynomial	Lower	0.0014	0.0014	0.0034	0.0148
	Higher	0.0009	0.0032	0.0064	0.0180
Cd-As					
Multiplicative	Lower	0.0011	0.0032	0.0039	0.0123
	Higher	0.0018	0.0020	0.0059	0.0150
Polynomial	Lower	0.0025	0.0016	0.0036	0.0136
	Higher	0.0002	0.0018	0.0034	0.0168
Ni-Co					
Multiplicative	Lower	0.0009	0.0023	0.0025	0.0120
	Higher	0.0011	0.0009	0.0025	0.0150
Polynomial	Lower	0.0020	0.0034	0.0036	0.0141
	Higher	0.0011	0.0030	0.0016	0.0173

but more simulations are necessary in order to verify this.

Next, Table 4.5 summarizes the false discovery rate of BKMR and BSR for two-way interactions. Both methods perform well in all scenarios, with false discovery rates below 0.02. This confirms that the above results for sensitivity did not occur by chance. For smaller size datasets, both BKMR and BSR have almost negligible false discovery rates, ranging from 0.0002-0.0025 for BKMR and 0.0009-0.0034 for BSR. In larger size datasets, false discovery rates increase slightly for BKMR, ranging from 0.0016-0.0064. On the other hand, false discovery rates increase notably for BSR in the larger size datasets, ranging from 0.012-0.018. Therefore, false discovery rates for interactions, while still low, should be taken into consideration for BSR with larger sample sizes. In exposure mixture studies, a visual assessment of the

estimated exposure-response relationship is often used to characterize the form of a potential interaction, and a common choice for diagnostic plots involves estimating the exposure-response relationship for one chemical at various quantiles of the second (e.g., Howe et al., 2020; Valeri et al., 2017). Figure 4.9 depicts such plots for all scenarios with interactions between Hg and Ni.

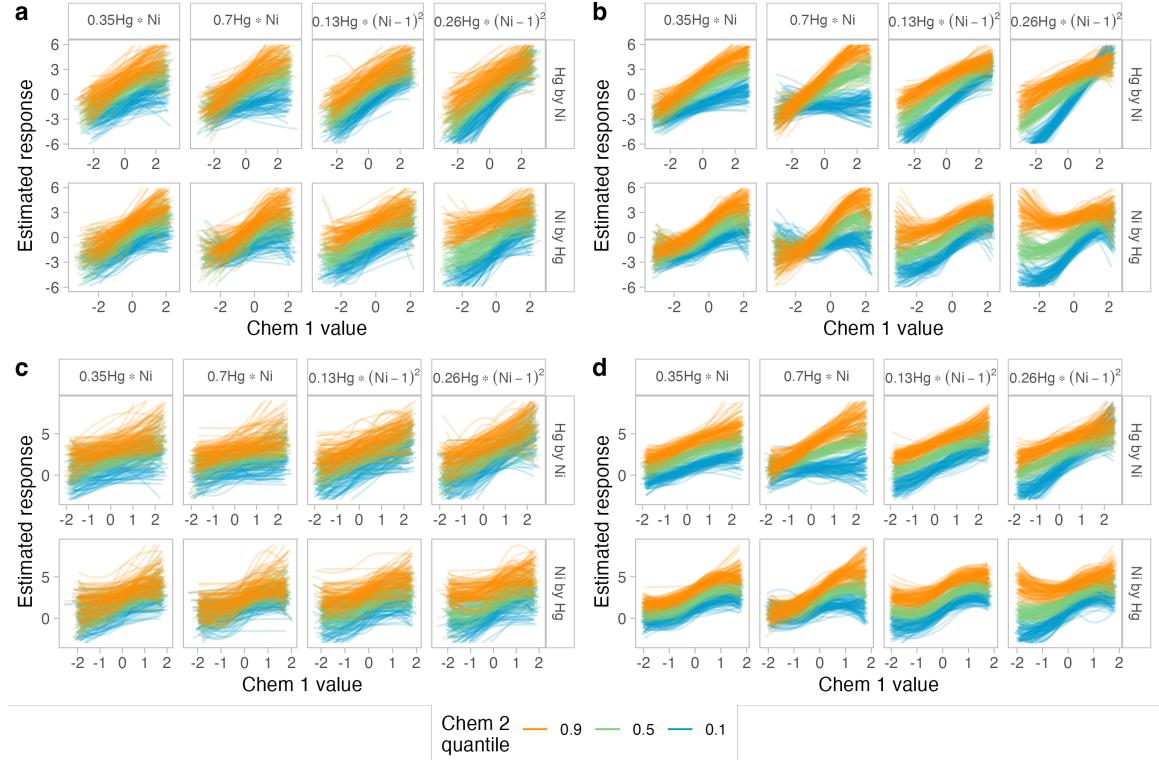


Figure 4.9: Exposure-response relationships estimated by BKMR in small (a) and large (b) datasets and BSR in small (c) and large (d) datasets, using the first chemical fixed at quantiles of another to assess interactions between Hg and Ni. All other chemicals are fixed at 0.5 quantiles.

The sensitivities in Table 4.4 are reflected by the patterns in the diagnostic plots. For instance, the second column of Figures 4.9b and 4.9d visualizes the higher effect size, multiplicative interaction between Hg and Ni estimated by BKMR and BSR, respectively. Both models have a sensitivity of 0.76 for this interaction, which is

confirmed by the clear difference in the exposure-response relationship between various quantiles of the second chemical. Moreover, the exposure-response relationships are shaped similarly to their associated cross-sections in the 3D theoretical model displayed in Figure A.6.

Assessing both directions of the pairwise comparison in these plots (e.g., Hg at quantiles of Ni, as well as Ni at quantiles of Hg) is important as, depending on the true form of the interaction, one direction may have more separation between the estimated relationship at various quantiles. For instance, in the aforementioned example with Hg and Ni, it appears that assessing the relationship between Hg and the health outcome at quantiles of Ni leads to clearer separation than the other way around.

Similar diagnostic plots for all other scenarios, which have similar patterns as those discussed here for Hg and Ni, are shown in Figures A.32-A.39 in Appendix A.2. In particular, we confirm that the low sensitivities observed in scenarios with interactions between Cd and As, as well as Ni and Co are reflected by estimated exposure-response relationships that do not appear to be associated with interactions. Moreover, it appears that, in Figures A.34 and A.38, the higher effect size, polynomial interactions between Cd and As and Ni and Co are somewhat captured by BKMR, which reflects their associated sensitivities of 0.57 and 0.52, respectively. Overall, we confirm that patterns in visual diagnostic plots reflect metrics of importance for interactions in both BKMR and BSR.

4.3.4 Three-way interactions between chemicals

Next, we discuss the ability of BKMR and BSR to detect three-way interactions between chemicals. Table 4.6 summarizes the sensitivity of the oracle MLR, BKMR, and BSR for three-way interactions between Hg, Ni, and Tl. Visual plots of the

Table 4.6: Sensitivity to trivariate interactions between Hg, Ni, and Tl.

Interaction type	Effect size	Small (n=252)			Large (n=1000)		
		Oracle	BKMR	BSR	Oracle	BKMR	BSR
Multiplicative	Lower	0.19	0.00	0	0.45	0.01	0.00
	Higher	0.50	0.01	0	0.97	0.00	0.01
Polynomial	Lower	0.10	0.00	0	0.48	0.00	0.00
	Higher	0.49	0.00	0	0.96	0.05	0.00

estimated exposure response relationship for one chemical, while holding the two others in the interaction at their 0.1, 0.5, and 0.9 quantiles, are shown in Figures A.40-A.43. Due to time constraints, we did not obtain false discovery rates for these interactions. The oracle MLR sensitivities are similar to the two-way scenarios. As in the case of two-way interactions with marginally insignificant chemicals, BKMR and BSR are generally unable to detect these interactions, with sensitivities ranging from 0-0.05. While Hg and Ni are both marginally significant, Tl is not. Similar to the Ni-Co case, it is difficult to determine whether these patterns are due to inherent difficulties in detecting three-way interactions, or the marginal insignificance of Tl.

4.3.5 Interactions between race and an exposure

This section includes results for scenarios with an interaction between race, a categorical covariate, and Hg.

Table 4.7 summarizes the sensitivity of the oracle MLR and BKMR. Note that we were unable to provide formal metrics of importance for interactions from BSR. In total, BKMR failed to converge in either the non-Hispanic white or non-Hispanic other category in 311 out of 400 of the smaller size datasets, which are captured in the “Uncollapsed” column of this table. All BKMR models run on datasets with the three smallest race categories, collapsed into one group, converged. In general,

Table 4.7: Sensitivity to interactions between the categorical race variable and Hg.

Interaction in	Effect size	Small (n=252)		Large (n=1000)	
		Uncollapsed		Collapsed*	
		Oracle	BKMR	BKMR	Oracle
non-Hisp. black [†]	Lower	0.07	0.00	0.00	0.21
	Higher	0.19	0.00	0.00	0.51
Hisp. born outside US [‡]	Lower	0.12	0.00	0.00	0.39
	Higher	0.24	0.02	0.03	0.83

* "Collapsed" refers to scenarios where the smallest three race categories are collapsed into one stratified model.

[†] Original n=27

[‡] Original n=109

interactions between a categorical variable and a continuous variable are harder to detect. Even in larger datasets where the effect of Hg was doubled in the largest race category (i.e., Hispanic born outside US), the oracle MLR had a sensitivity of 0.83, while BKMR had a much lower sensitivity of 0.21. This is the only scenario in which BKMR's sensitivity exceeded 0.03. Thus, BKMR is generally not able to detect interactions with high sensitivity.

Similar to interactions between chemicals, we can create visual plots of the estimated relationship between Hg and the response within each stratified BKMR and BSR model. Figure 4.10 displays such plots; in each panel, the estimated relationship in the race category with the interaction is plotted on top, to distinguish it from the other categories.

In some cases, it appears that some degree of interaction is being detected by BKMR and BSR. For instance, in the large dataset, when the effect of Hg is increased by 150% (the lower effect size) in the category Hispanic born outside US, there appears to be some separation in the estimated relationship in that category (shown in red), compared to the other four. However, BKMR's sensitivity in this scenario was only

0.03, indicating that it was under-powered to formally detect this interaction. Based on these plots, it also appears that BSR detects a significant effect from Hg less often than BKMR does, as most of the estimated exposure-response relationships are flatter. This is confirmed in Table A.2, which displays the sensitivity for Hg in each of the stratified BKMR and BSR model. Thus, BSR is likely more affected by the smaller sample sizes from stratification than BKMR, at least with respect to its univariate metrics of variable importance.

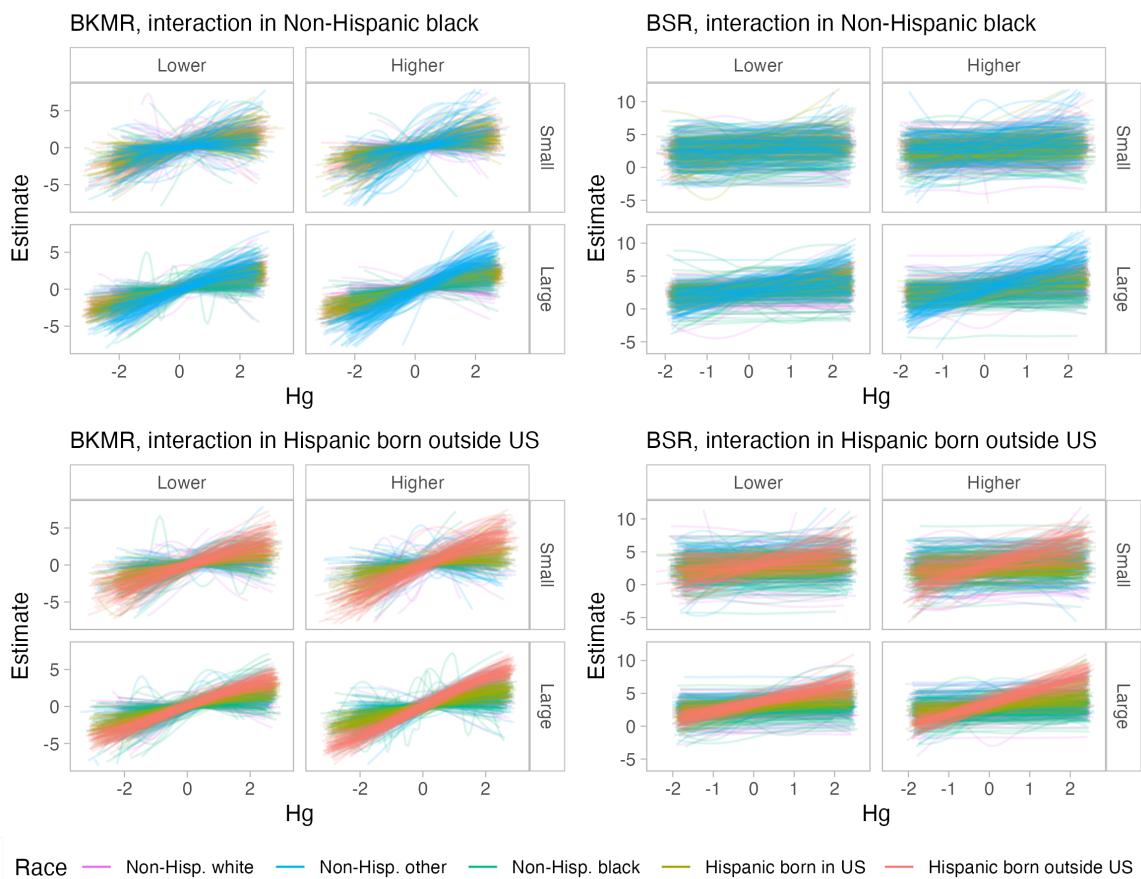


Figure 4.10: Relationship between Hg and response estimated by stratified BKMR and BSR models in smaller and larger datasets. All other chemicals are fixed at 0.5 quantiles. Lower and higher refer to effect sizes, while small and large refer to dataset sizes.

Therefore, while stratified BKMR and BSR models are, in theory, capable of

detecting interactions between a categorical covariate and an exposure, it is difficult to use them for this purpose in practice. The flexibility of BKMR and BSR means that it is not possible to directly conduct inference on the effect sizes of specific chemicals. For BKMR, we are able to construct confidence intervals around the difference of the estimated response at two quantiles of a chemical, and to then compare these confidence intervals between race categories. However, this is a more informal method of inference, as the choice of quantiles is relatively arbitrary. Moreover, for both BKMR and BSR, it is likely that the reduced sample sizes in each stratified model significantly under-power the model for accurately estimating the exposure-response relationship.

Thus, this section highlights the difficulty of using current flexible Bayesian regression methods for detecting interactions between a categorical covariate and a chemical in exposure mixture studies.

4.3.6 Run-time analysis

Finally, we comment on run-times for fitting models on the high-performance computing cluster.

Table 4.8 summarizes the average run-time for each model and sample size, under different interaction scenarios (i.e., various effect sizes and forms of interactions). For model fitting, we used 50,000 MCMC iterations. “BSR df” refers to the process for determining the optimal degrees of freedom for the spline regression, while “BSR mod” refers to model fitting process. We determined the degrees of freedom in BSR by fitting a grid of four values, each with 1/10 of the MCMC iterations we used for the full model. However, in a full analysis, one should determine the degrees of freedom using the full set of MCMC iterations, so the full run-time for BSR would be approximately four times that reported in the “BSR mod” row. We also recall that

BKMR was fit using a Gaussian predictive process with 100 knots in the larger size datasets to reduce computational time.

The naive and oracle MLRs take a fraction of a second to run, in both the smaller and larger size datasets, while run-times range from around 15 minutes for BKMR in the smaller size datasets to around 4 hours for BSR (which includes the degrees of freedom selection process) in the larger size datasets. While both Bayesian models are slow, BKMR is still faster than BSR, even when BSR's lengthy degrees of freedom selection process is not factored in. In the smaller size datasets, BKMR takes about 1/6 of the time BSR does, and in the larger size datasets, BKMR takes about 1/2 of the time BSR does. BKMR's speed in comparison to BSR is more pronounced in the smaller size datasets, as BKMR scales with n^2 , while BSR scales with n . The Gaussian predictive process likely improves BKMR's speed in the larger size datasets by a wide margin. Moreover, BSR's time may also be attributed to the empirical Baye's strategy for estimating the influential σ_β^2 parameter, which requires a second set of 50,000 MCMC iterations to run. We also note that BSR appears to take slightly longer in cases with an interaction of higher effect size, compared to the lower effect size, while BKMR's run-time does not appear to be influenced by effect size. Overall, BKMR may be a slightly better choice in settings with smaller datasets, if computational burden is a limiting factor. Table 4.9 summarizes the average run-times of the naive MLR, oracle MLR, and stratified BKMR in scenarios with an interaction between race and Hg. Again, we note that we were unable to get run-times for BSR within the timeframe of this thesis. However, based on observations of stratified BSR in the high-performance computing cluster, we estimate that it took around 20 hours for all stratified models on one smaller size dataset to run, and 15 hours for one larger size dataset. We suspect that the longer run-time required for smaller size datasets is a result of the MCMC algorithm. We used a Gibbs sampler to

Table 4.8: Average run-times in all scenarios with interactions between two or more chemicals, as well as the base case.

Model	Sample size	Base	Multiplicative		Polynomial	
			Lower	Higher	Lower	Higher
Naive	Small	0.0032 s	0.0016 s	0.002 s	0.0016 s	0.0017 s
	Large	0.002 s	0.002 s	0.0035 s	0.0031 s	0.0025 s
Oracle	Small	0.0015 s	0.0015 s	0.0015 s	0.0019 s	0.0016 s
	Large	0.0044 s	0.0018 s	0.0018 s	0.0019 s	0.0024 s
BKMR	Small	13.56 m	15.21 m	15.51 m	15.20 m	15.17 m
	Large	1.64 h	1.68 h	1.62 h	1.64 h	1.59 h
BSR df	Small	30.11 m	33.15 m	32.92 m	33.81 m	35.11 m
	Large	57.22 m	58.02 m	1.06 h	57.75 m	1.05 h
BSR mod	Small	1.37 h	1.36 h	1.42 h	1.44 h	1.49 h
	Large	2.92 h	2.81 h	3.06 h	2.87 h	3.04 h

fit BSR — in cases where the model is complex, maintaining reversibility of updates can be computationally challenging (Antonelli et al., 2020). As in the previous case, the MLRs took a fraction of a second to run. The average run-time for BKMR on the smaller size dataset, when added up across all stratified models, is just slightly higher than for the unstratified models. The average run-time for BKMR on the larger size dataset, again added up across all stratified models, is slightly lower than the for the unstratified models. This demonstrates the dependency of BKMR’s run-time on n^2 , as we did not use a Gaussian predictive process to speed up the stratified models. Finally, based on rough observations of BSR, it was clear that the stratified BSR models took much longer to run than the unstratified BSR models, likely due to challenges with the MCMC algorithm in the reduced sample size. This is a major limitation for using stratified BSR models to detect interactions between a categorical covariate and an exposure.

Table 4.9: Average run-times in scenarios with an interaction between the categorical race covariate and Hg.

Model	Race	Small (n=250)	Large (n=1000)
Naive	-	0.0021 s	0.0035 s
Oracle	-	0.0019 s	0.0022 s
BKMR	Non-Hispanic white	2.50 m	3.20 m
	Non-Hispanic black	4.01 m	4.24 m
	Non-Hispanic other	1.42 m	3.34 m
	Hispanic born in US	5.37 m	29.24 m
	Hispanic born outside US	5.65 m	52.20 m
	Collapsed non-Hispanic	4.17 m	-

Note:

Original sample sizes of race category: Non-Hispanic white (n=16), Non-Hispanic black (n=27), Non-Hispanic other (n=13), Hispanic born in US (n=87), Hispanic born outside US (n=109), and Collapsed non-Hispanic (n=56=16+27+13).

4.4 Discussion

Our simulation study provides guidance on the detection and characterization of a wide range of interactions using flexible Bayesian regression techniques.

First, the base case scenario, with no interactions, confirms that BKMR and BSR behave as expected. We affirm the results of previous studies, which find that BKMR is able to flexibly capture complex additive exposure-response relationships (i.e., no interactions), though false discovery rates can be higher than other methods (Hoskovec et al., 2021; Lazarevic et al., 2020). Similar to Pesenti et al. (2023), we also find that BKMR generally has higher sensitivity than BSR, especially in smaller size datasets.

Next, in cases with interactions between chemicals, we also assessed the univariate signals of chemicals that participated in an interaction. We found that marginally significant chemicals that participated in interactions could occasionally be detected

through their univariate effects, depending on the true form of the interaction and if its effect size was large enough. Moreover, the univariate effects of marginally significant chemicals were not detected less often when they participated in an interaction. Together, these results suggest that, at least in the scenarios explored in this simulation, failing to assess for an interaction that would otherwise have been detected should not affect univariate signals, and interactions may sometimes be detected as univariate effects.

Overall, we found that BKMR and BSR did not detect two-way interactions as well as the oracle MLR. This suggests that the flexibility afforded by BKMR and BSR led to drawbacks in sensitivity compared to an ideal (and unrealistic) case, where we knew the true form of the interaction. Still, in smaller size datasets with an interaction between Hg and Ni, which are themselves marginally significant, BKMR and BSR occasionally detected the signal. And, in larger size datasets, BKMR and BSR produced sensitivities within 0.2-0.3 of the sensitivities produced by the oracle MLR. Sensitivities for the larger effect sizes of interactions ranged from 0.76 to 0.88, which is relatively reliable.

However, in cases where at least one of the chemicals participating in the interaction was not marginally significant, BKMR and BSR were generally not able to detect the interaction. [*update with new analysis? then compare to past w/ interactions*]

We note that false discovery rates for BKMR and BSR were not Based on all these scenarios, BKMR and BSR are generally comparable for detecting interactions. These results extend the findings from (**presenti_comparative_2023?**) by providing a more comprehensive range of interactions and guidance for the use of BKMR and BSR for the detection of interactions. Moreover, to our knowledge, this is the first simulation study of interactions in exposure mixtures since those performed by sun and barrera. note improvements/changes. we also note that *interactiosn dependent*

on univariate effects???

- can guide the analytic process of searching for interactions
- BKMR and BSR generally comparable for interactions
- difficult to detect interactions, especially in smaller size datasets and when they are not marginally significant
- it may be the case that Ni and Co were difficult to detect because Co was not significant, and not because of multicollinearity
- similar story for three-way interactions and Tl
- currently very hard to detect interactions between covariate and exposure.

Now, for interactions between a categorical covariate and

Finally, we briefly comment on run-times. As both BKMR and BSR are Bayesian models that use MCMC algorithms, it is computationally expensive to arrive at a solution. Moreover, BKMR and BSR require prior specifications that can affect the model fit. It would be time-intensive to fit a grid of prior settings in order to assess the impact of, say, the prior on the influential r parameter in BKMR in order to check the robustness of PIP values. Thus, time cost can be a major limitation for model implementation, and it should be taken into consideration particularly when datasets are large, or access to high-performance computing equipment is limited.

[remember to label figures in appendix + add code]

Conclusion

We will continue to encounter novel chemical entities in our day-to-day lives.

Statistical studies of the health risks associated with exposure to chemical pollutants are critical for making modern toxic landscapes more habitable.

As discussed in Chapter 2,

Our simulation study in Chapter 4 illustrates the challenges of detecting interactions. Still, we were able to achieve high sensitivities using BKMR and BSR to detect interactions between marginally significant chemicals. For

There can be differences in the performance of BKMR and BSR, but neither consistently outperforms the other. Thus, as BKMR is generally more reliable for univariate effects, and also computationally less intensive, we recommend BKMR for

This thesis summarizes the current capabilities of modern Bayesian statistical methods for characterizing complex interactions in exposure mixture studies. In particular, we highlight that such methods are under-powered for detecting potential interactions between

Future work . . .

- analyses would be improved if three-way fdr's were included and BSR run-times recorded
- going forward, change design of simulations study should try three-way interactions and multicollinearity on cases where the chemicals themselves are sig-

nificant

- figure out method of formal inference for BSR
- identify difficulty of detecting interactions between race and exposure
- continue to explore how studies of exposure can best protect the health and well-being of communities who live and experience the effects of toxicity
- see what happens with even more chemicals

Progressing toward a study of exposure that considers how bodies are related to the environment and to each other. As blah blah said, something something entanglement. But this is better!

Appendix A Supplemental output

This first appendix includes supplemental output for Chapter 4.

A.1 Methods

Figure A.1 depicts the exposure-response relationship for univariate exposures included in all models in simulation.

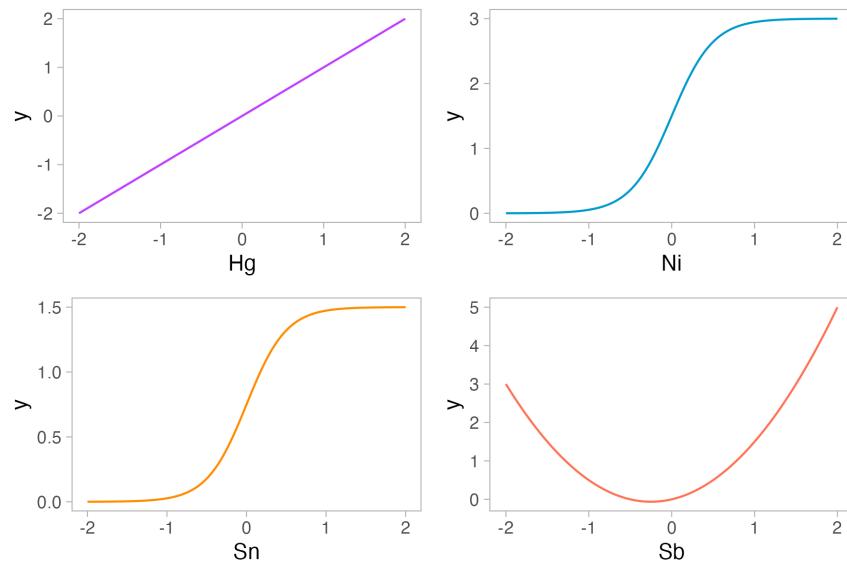


Figure A.1: Exposure-response relationship for univariate exposures in all models. Exposure values are log-scaled and then standardized.

Figures A.2-A.14 depict the exposure-response relationship for all two-way interactions specified in the simulation study.

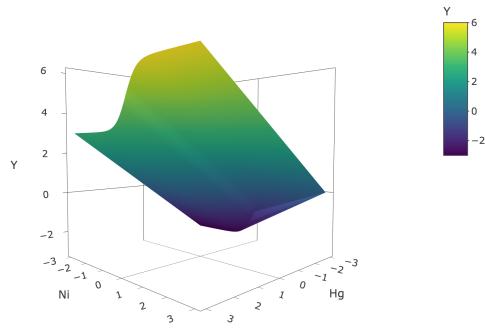


Figure A.2: Exposure-response surface for base case: $Y = Hg + \frac{3}{1+\exp(-4Ni)}$.

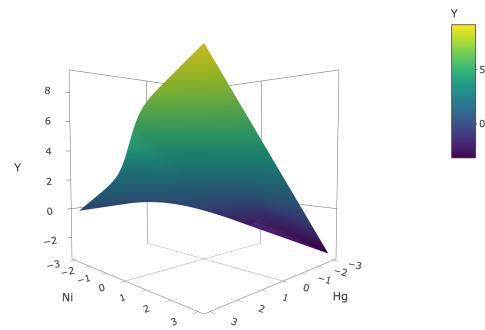


Figure A.3: Exposure-response surface for a multiplicative interaction between Hg and Ni at the lower effect size: $Y = Hg + \frac{3}{1+\exp(-4Ni)} + 0.35Hg*Ni$.

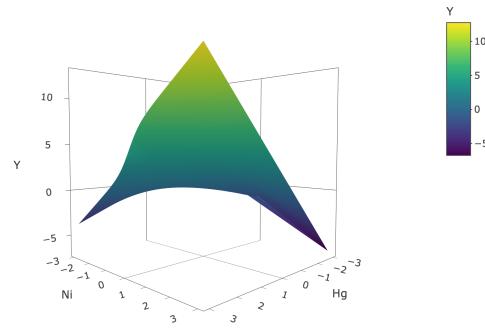


Figure A.4: Exposure-response surface for a multiplicative interaction between Hg and Ni at the higher effect size: $Y = \text{Hg} + \frac{3}{1+\exp(-4\text{Ni})} + 0.7\text{Hg}*\text{Ni}$.

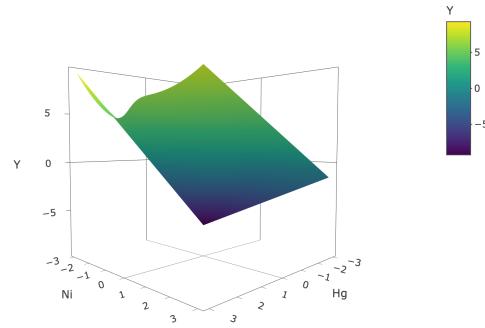


Figure A.5: Exposure-response surface for a polynomial interaction between Hg and Ni at the lower effect size: $Y = \text{Hg} + \frac{3}{1+\exp(-4\text{Ni})} + 0.3\text{Hg}*(\text{Ni}-1)^2$.

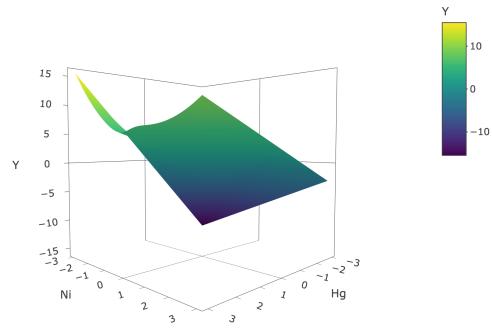


Figure A.6: Exposure-response surface for a polynomial interaction between Hg and Ni at the higher effect size: $Y = \text{Hg} + \frac{3}{1+\exp(-4\text{Ni})} + 0.6\text{Hg}*(\text{Ni}-1)^2$.

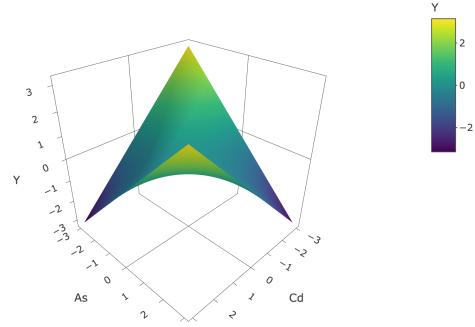


Figure A.7: Exposure-response surface for a multiplicative interaction between Cd and As at the lower effect size: $Y = 0.35\text{Cd}*\text{As}$.

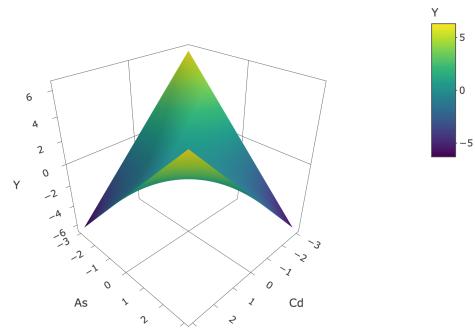


Figure A.8: Exposure-response surface for a multiplicative interaction between Cd and As at the higher effect size: $Y = 0.7\text{Cd}*\text{As}$.

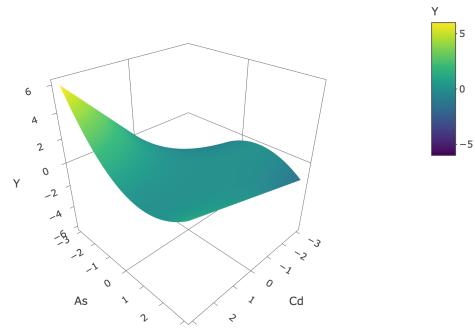


Figure A.9: Exposure-response surface for a polynomial interaction between Cd and As at the lower effect size: $0.125Cd*(As-1)^2$.

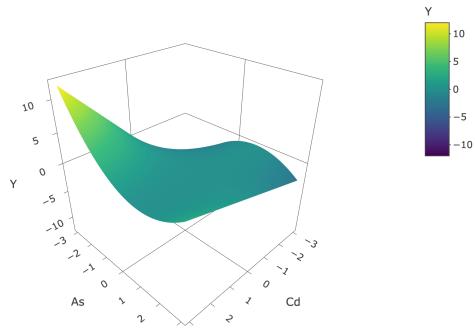


Figure A.10: Exposure-response surface for a polynomial interaction between Cd and As at the higher effect size: $0.25Cd*(As-1)^2$.

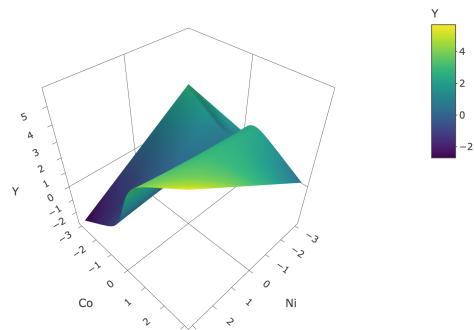


Figure A.11: Exposure-response surface for a multiplicative interaction between Ni and Co at the lower effect size: $Y = \frac{3}{1+\exp(-4Ni)} + 0.3Ni*Co$.

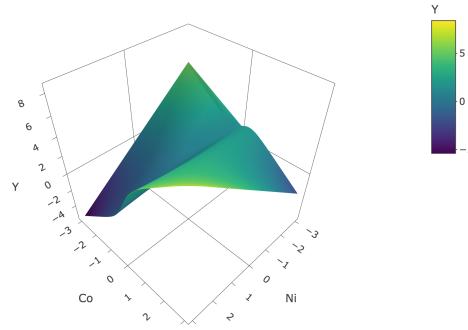


Figure A.12: Exposure-response surface for a multiplicative interaction between Ni and Co at the higher effect size: $Y = \frac{3}{1+\exp(-4Ni)} + 0.6Ni*Co$.

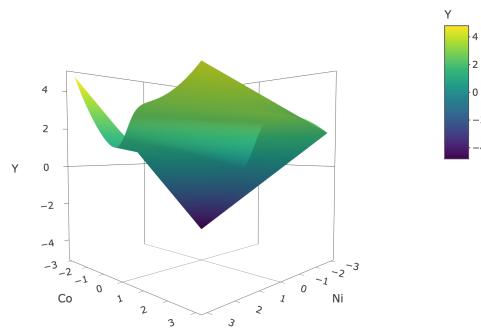


Figure A.13: Exposure-response surface for a polynomial interaction between Ni and Co at the lower effect size: $Y = \frac{3}{1+\exp(-4Ni)} + 0.09Ni*(Co-1)^2$.

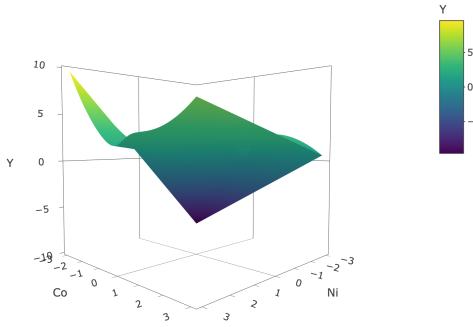


Figure A.14: Exposure-response surface for a polynomial interaction between Ni and Co at the lower effect size: $Y = \frac{3}{1+\exp(-4Ni)} + 0.18Ni*(Co-1)^2$.

Figure A.15 shows the detailed distribution of correlations in smaller size simulated datasets.

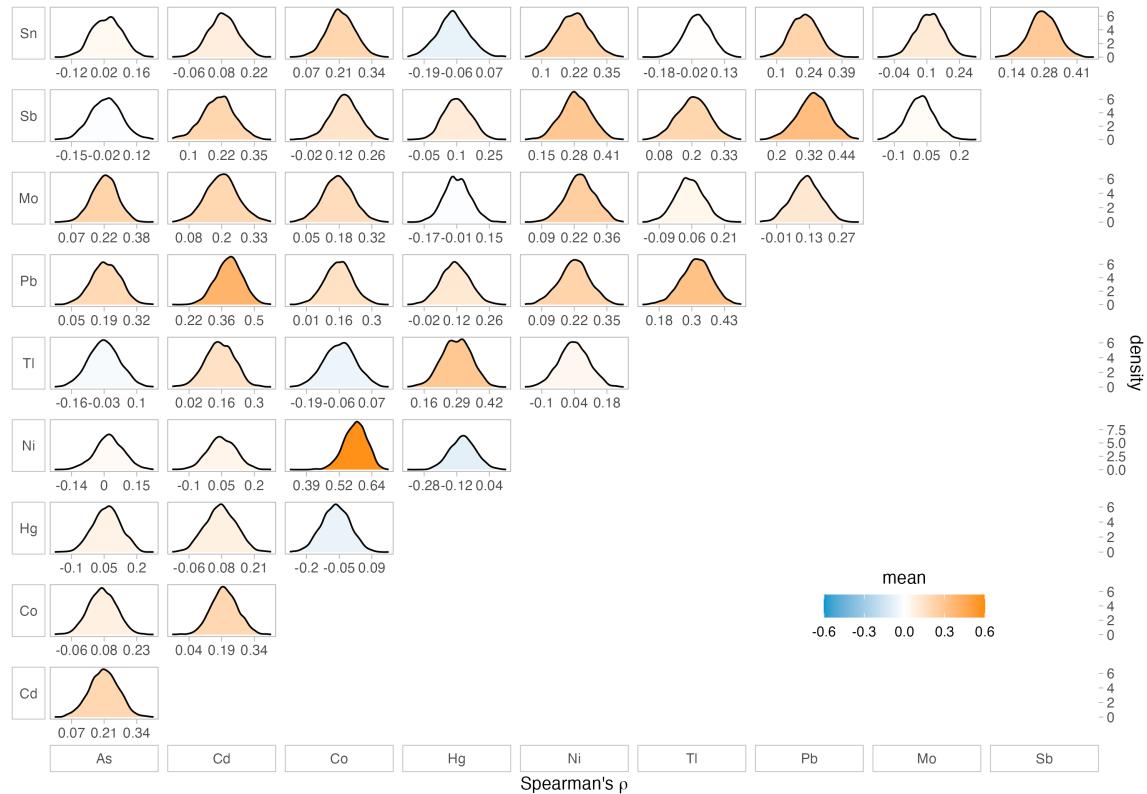


Figure A.15: Distributions of Spearman's correlation from 2100 smaller size ($n=252$) simulated datasets.

Figures A.16, A.17, and A.18 compare the marginal distributions of predictors and dependence structure between exposures of the observed dataset and simulated datasets of larger size ($n=1000$).

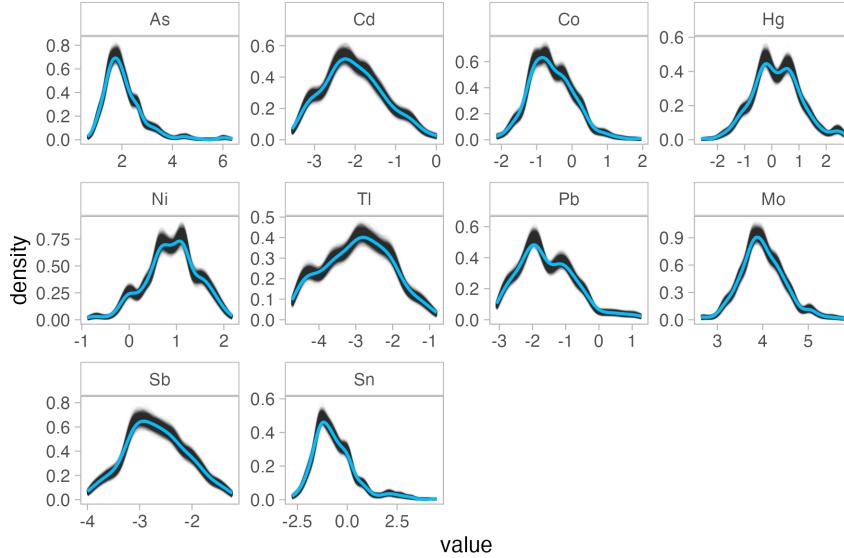


Figure A.16: Distributions of exposures from observed data (blue) and simulated larger size ($n=1000$) datasets (gray).

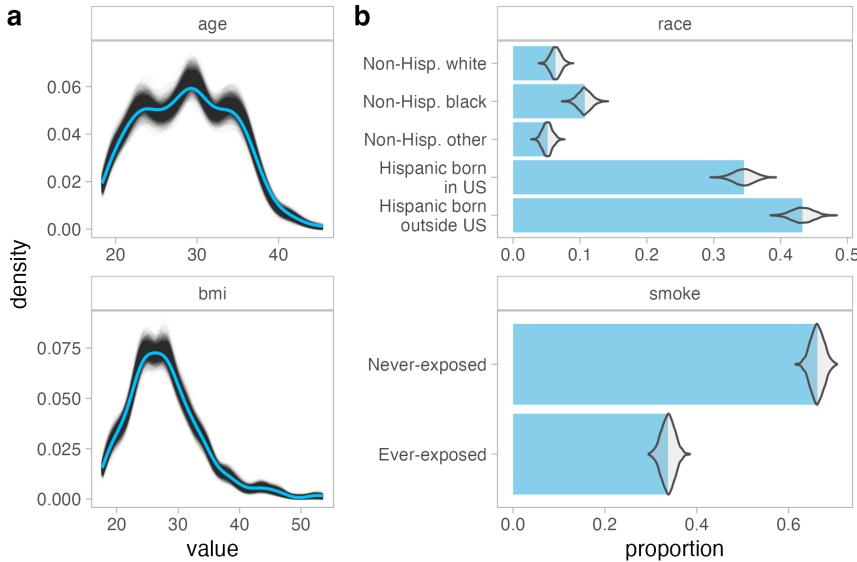


Figure A.17: Distributions of covariates from observed data (blue) and simulated larger size ($n=1000$) datasets (gray).

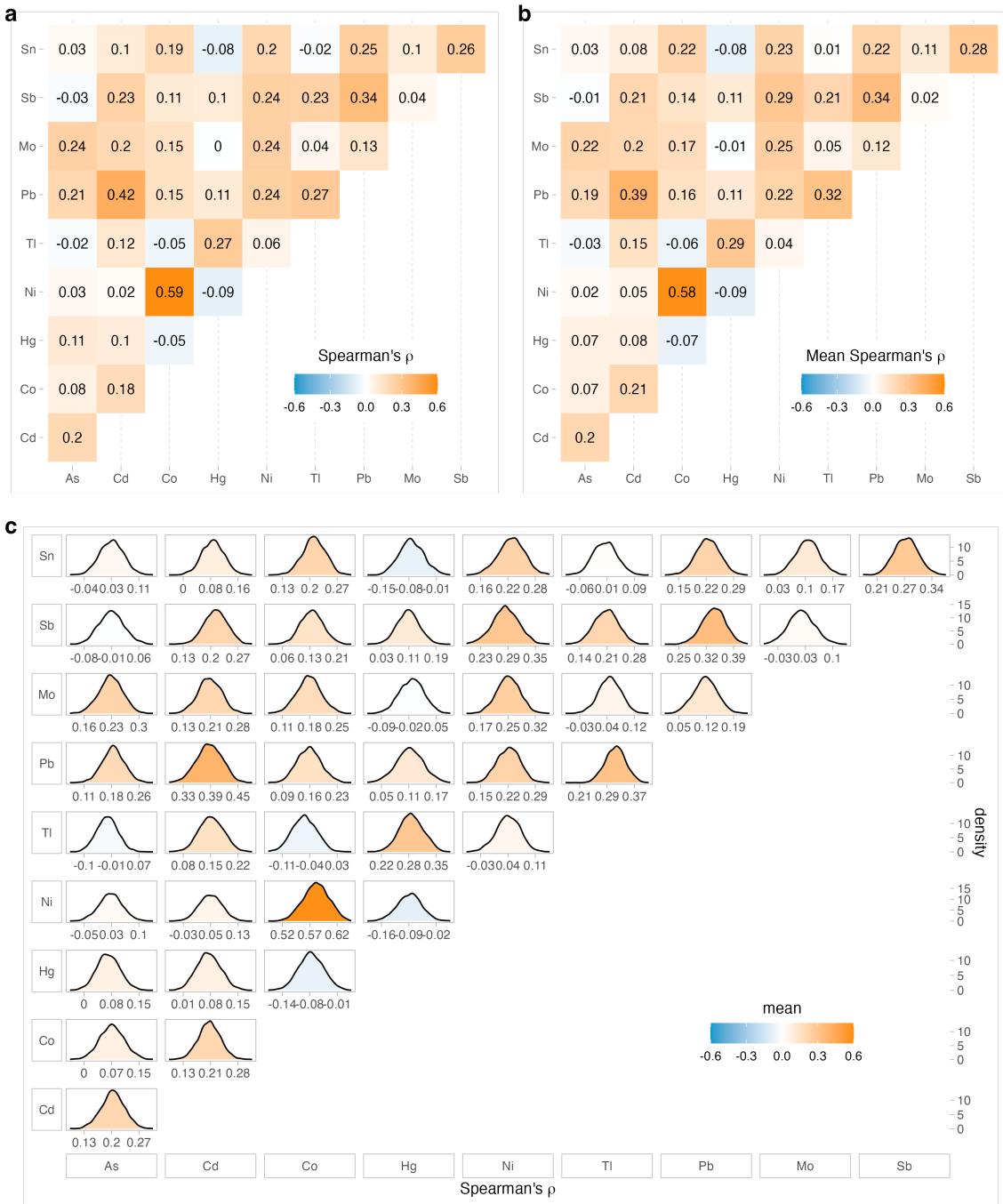


Figure A.18: Spearman's correlation heat maps of exposures from observed data (a) and averaged from 2100 larger size ($n=1000$) simulated datasets (b), as well as distributions of correlations from larger size simulated datasets (c).

Figure A.19 visualizes the distribution of R^2 values in smaller and larger size simulated datasets.

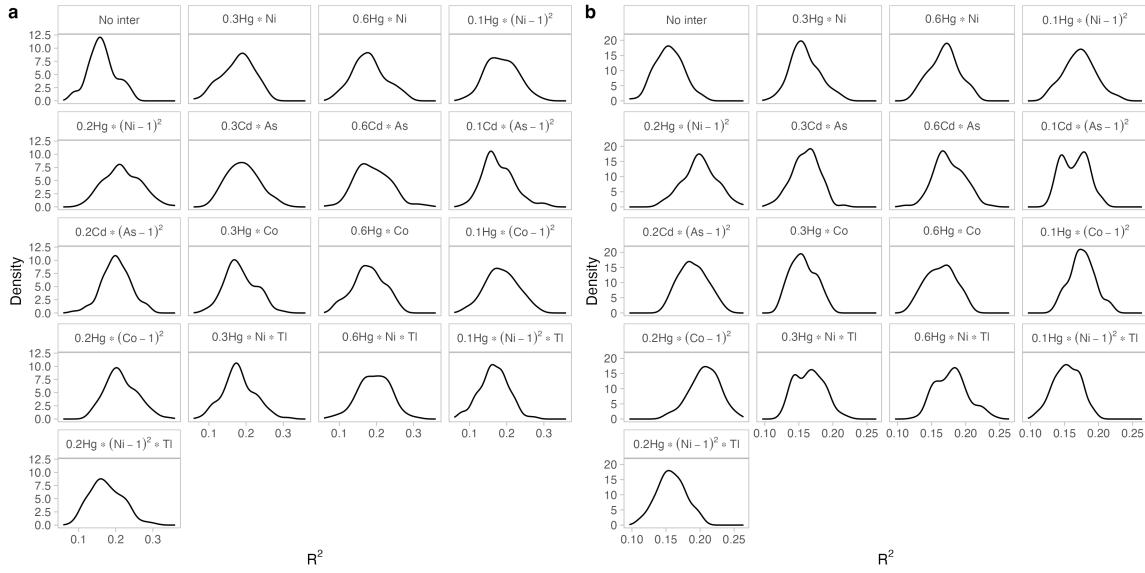
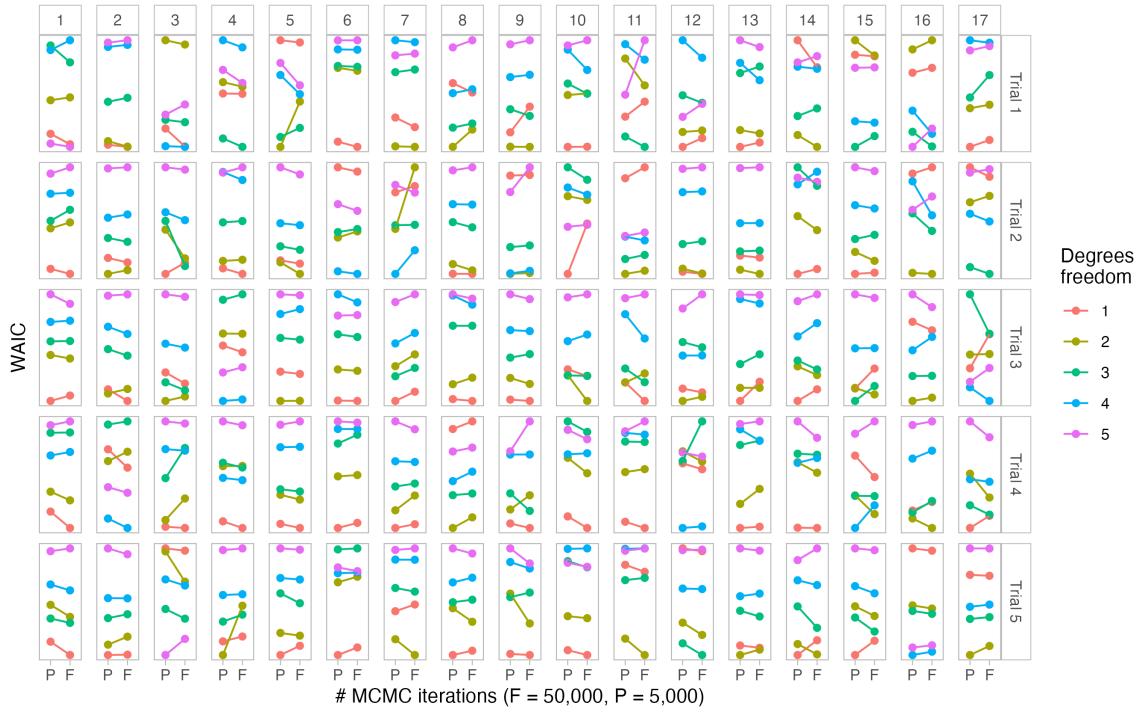


Figure A.19: R^2 values from multiple linear regressions with only the true functional form of significant exposures in smaller size (a) and larger size (b) simulated datasets.

Figure A.20 compares the degrees of freedom selected using the WAIC criterion when fitting BSR using 5,000 MCMC iterations to 50,000 MCMC iterations. We ran this test on five smaller size datasets from the 16 scenarios containing interactions between exposures, as well as from the base case.



Scenarios are labelled in the top strip as follows:

1 = base case; 2 = HgNi mult. small; 3 = HgNi mult. large; 4 = HgNi poly. small; 5 = HgNi poly. large; 6 = CdAs mult. small; 7 = CdAs mult. large; 8 = CdAs poly. small; 9 = CdAs poly. large; 10 = NiCo mult. small; 11 = NiCo mult. large; 12 = NiCo poly. small; 13 = NiCo poly. large; 14 = HgNiTi mult. small; 15 = HgNiTi mult. large; 16 = HgNiTi poly. small; 17 = HgNiTi poly. large

Figure A.20: Test comparing WAIC selection of degrees of freedom from BSR models fit with either 5,000 or 50,000 MCMC iterations.

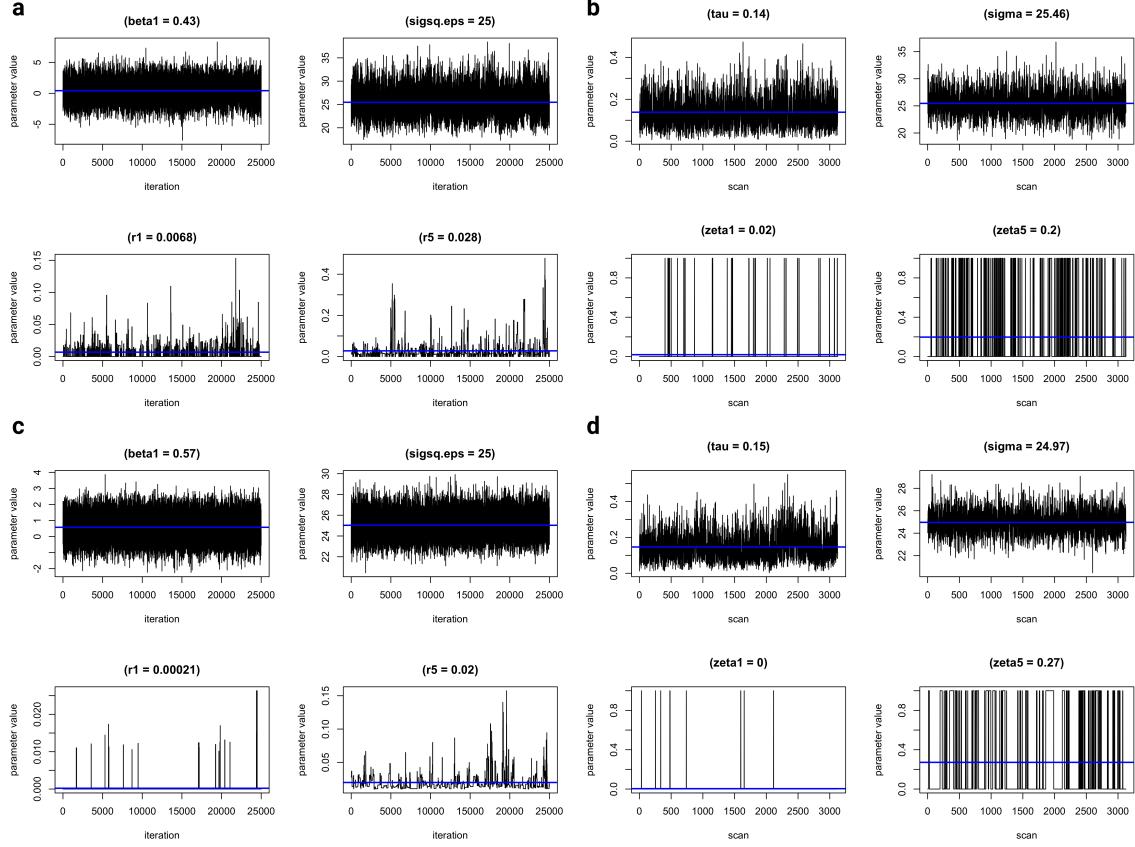


Figure A.21: Examples of trace plots from smaller size BKMR (a) and BSR (b) as well as larger size BKMR (c) and BSR (d) in scenarios with larger effect size interactions between Hg and Ni.

Finally, we show why the order of chemicals in the confidence intervalas we use to assess two-way interactions in BKMR do not matter. Let $\hat{Y}(X_{1a}, X_{2b})$ be the estimated response at the a th quantile of X_1 , the first chemical, the b th quantile of X_2 , the second chemical, while holding all other chemicals at their 0.5 quantiles. Then, the estimated confidence interval of the difference in the response X_1 's 0.75 and 0.25 quantiles, at both the 0.75 and 0.25 quantiles of X_2 , can be shown to be

equivalent to swapping the order of $X1$ and $X2$:

$$\begin{aligned}
& [\hat{Y}(X1_{0.75}, X2_{0.75}) - \hat{Y}(X1_{0.25}, X2_{0.75})] - [\hat{Y}(X1_{0.75}, X2_{0.25}) - \hat{Y}(X1_{0.25}, X2_{0.25})] \\
&= \hat{Y}(X1_{0.75}, X2_{0.75}) - \hat{Y}(X1_{0.25}, X2_{0.75}) - \hat{Y}(X1_{0.75}, X2_{0.25}) + \hat{Y}(X1_{0.25}, X2_{0.25}) \\
&= [\hat{Y}(X1_{0.75}, X2_{0.75}) - \hat{Y}(X1_{0.75}, X2_{0.25})] - [\hat{Y}(X1_{0.25}, X2_{0.75}) - \hat{Y}(X1_{0.25}, X2_{0.25})] \\
&= \hat{Y}(X1_{0.75}, X2_{0.75}) - \hat{Y}(X1_{0.75}, X2_{0.25}) - \hat{Y}(X1_{0.25}, X2_{0.75}) + \hat{Y}(X1_{0.25}, X2_{0.25})
\end{aligned} \tag{A.1}$$

A.2 Results

Figures A.22-A.29 display the full distributions of univariate p-values and PIPs for all models in scenarios with interactions between chemicals that were not included in Chapter 4.3.2.

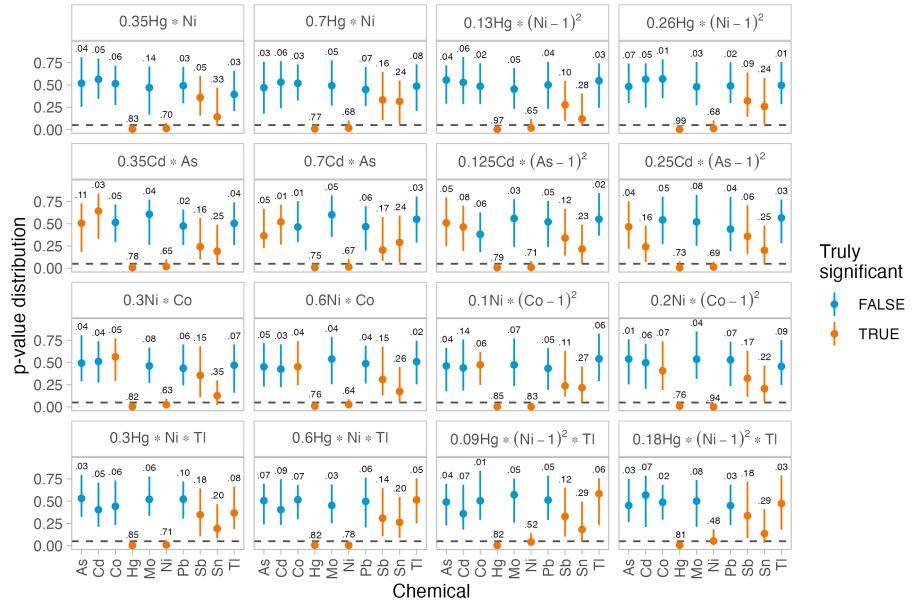


Figure A.22: P-value distributions of univariate chemicals from naive MLRs run on smaller size ($n=252$) datasets, in all scenarios with interactions between chemicals. Detection rates are displayed above a point-range with the median and first and third quartiles.

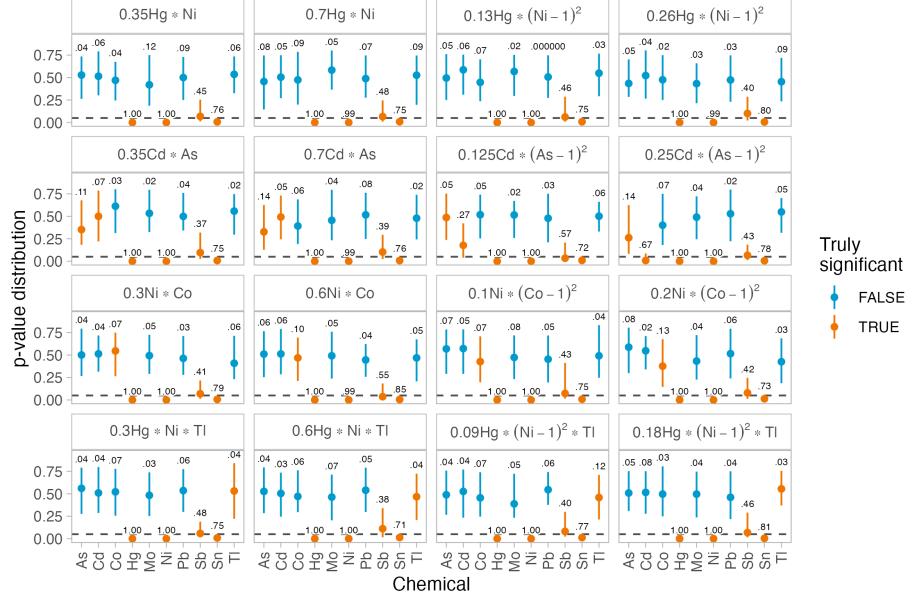


Figure A.23: P-value distributions of univariate chemicals from naive MLRs run on larger size ($n=1000$) datasets, in all scenarios with interactions between chemicals. Detection rates are displayed above a point-range with the median and first and third quartiles.

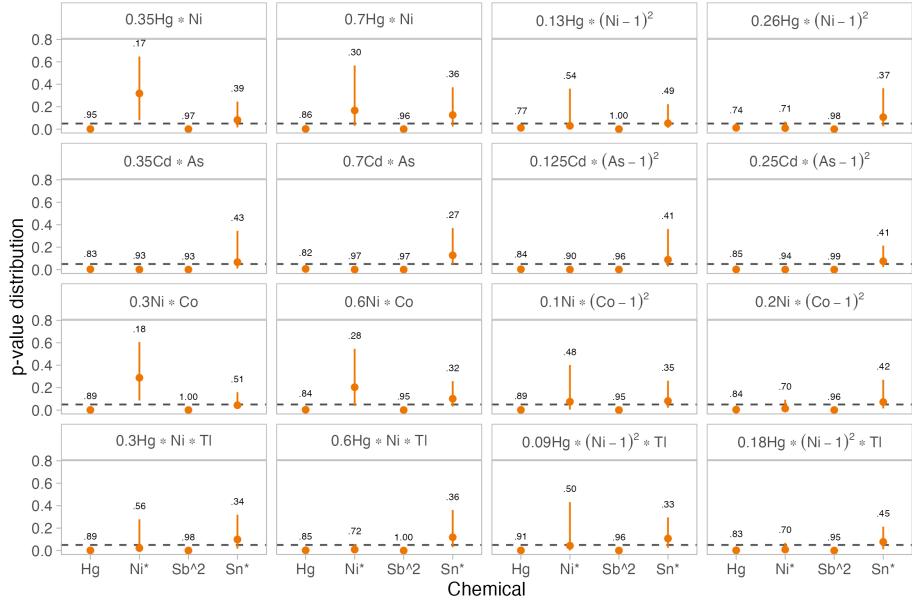


Figure A.24: P-value distributions of univariate chemicals from oracle MLRs run on smaller size ($n=252$) datasets, in all scenarios with interactions between chemicals. Sensitivities are displayed above a point-range with the median and first and third quartiles.

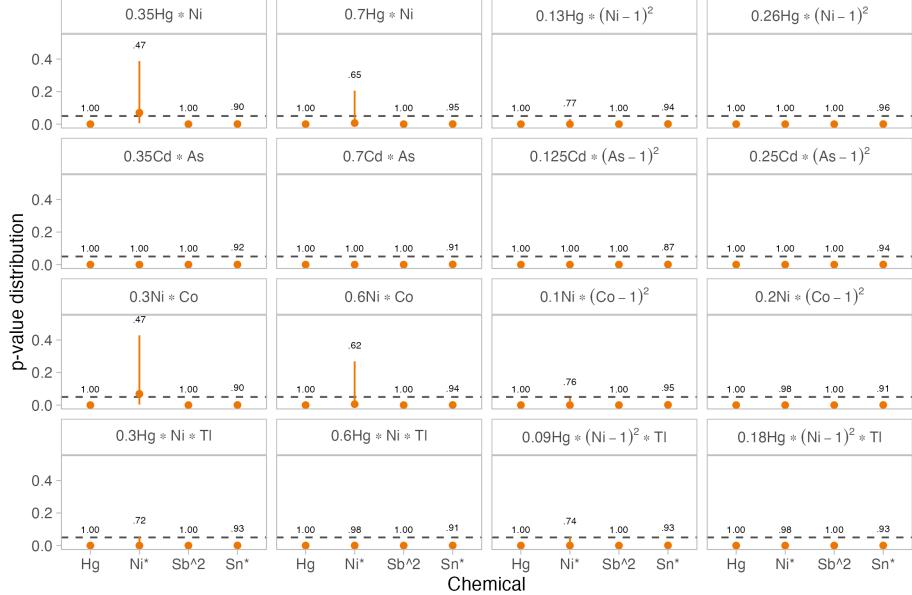


Figure A.25: P-value distributions of univariate chemicals from oracle MLRs run on larger size ($n=1000$) datasets, in all scenarios with interactions between chemicals. Sensitivities are displayed above a point-range with the median and first and third quartiles.

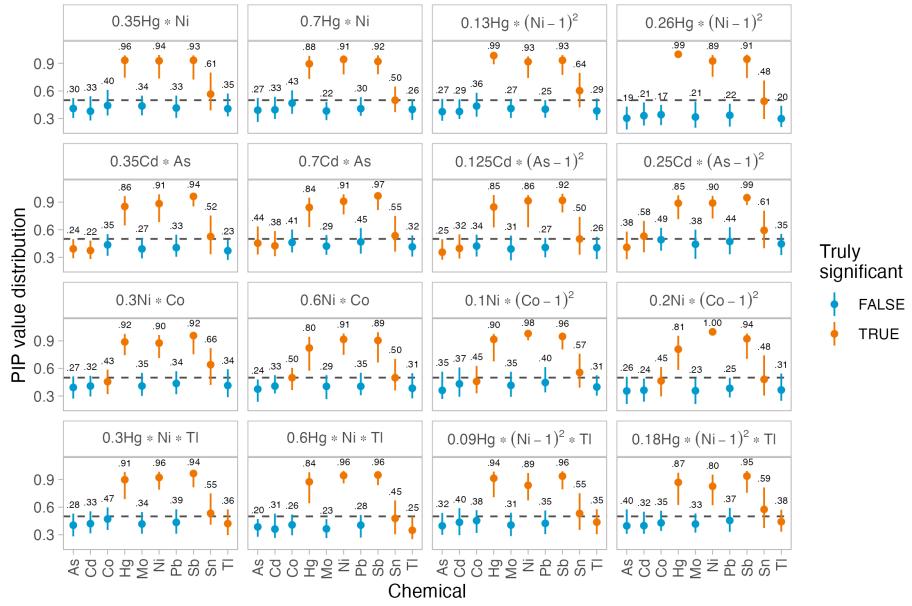


Figure A.26: PIP distributions of univariate chemicals from BKMR models run on smaller size ($n=252$) datasets, in all scenarios with interactions between chemicals. Detection rates are displayed above a point-range with the median and first and third quartiles.

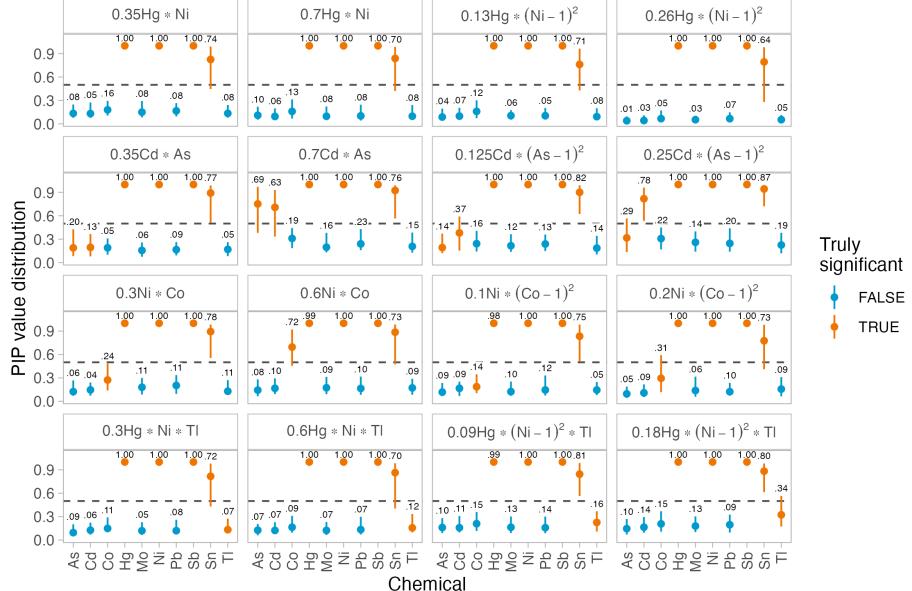


Figure A.27: PIP distributions of univariate chemicals from BKMR models run on larger size ($n=1000$) datasets, in all scenarios with interactions between chemicals. Detection rates are displayed above a point-range with the median and first and third quartiles.

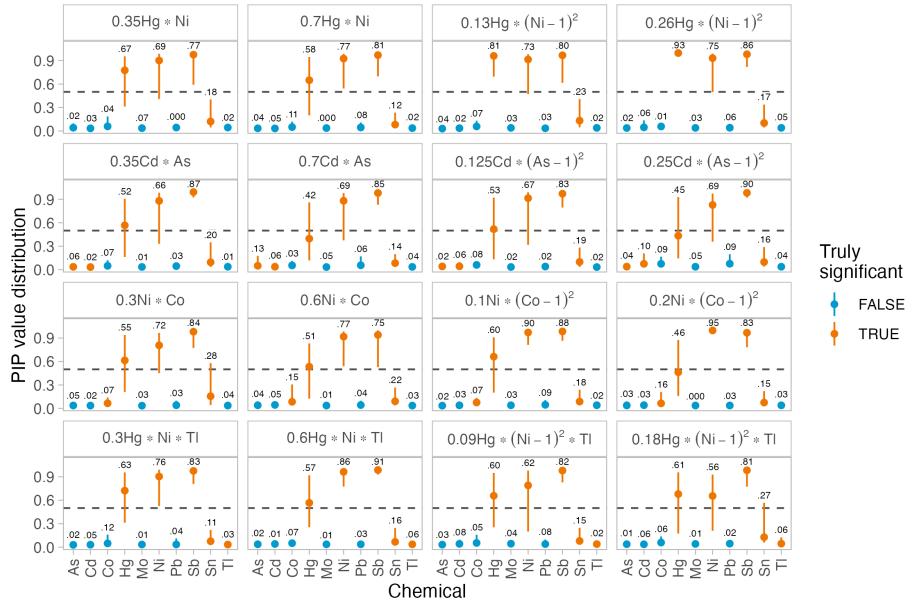


Figure A.28: PIP distributions of univariate chemicals from BSR models run on smaller size ($n=252$) datasets, in all scenarios with interactions between chemicals. Detection rates are displayed above a point-range with the median and first and third quartiles.

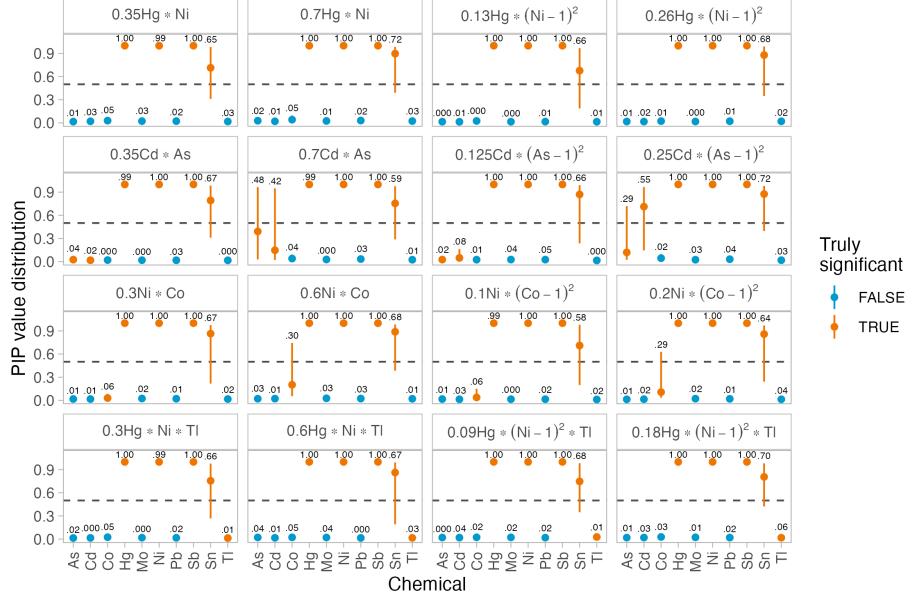


Figure A.29: PIP distributions of univariate chemicals from BSR models run on larger size ($n=252$) datasets, in all scenarios with interactions between chemicals. Detection rates are displayed above a point-range with the median and first and third quartiles.

Figures A.30 and A.31 display the full p-value distributions on interaction terms between chemicals in the oracle MLR models.

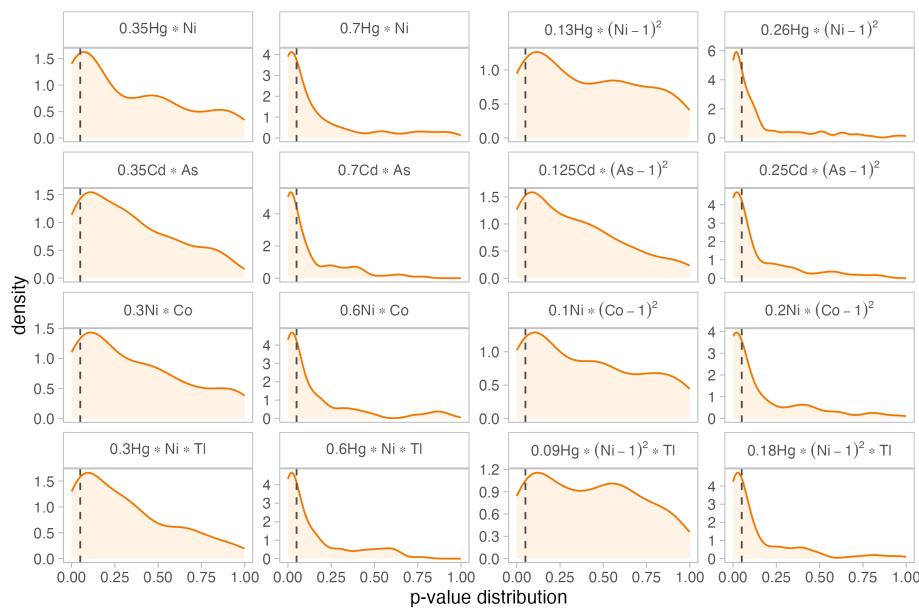


Figure A.30: P-value distributions of interaction terms from oracle MLRs run on smaller size ($n=252$) datasets, from all scenarios with interactions between chemicals.

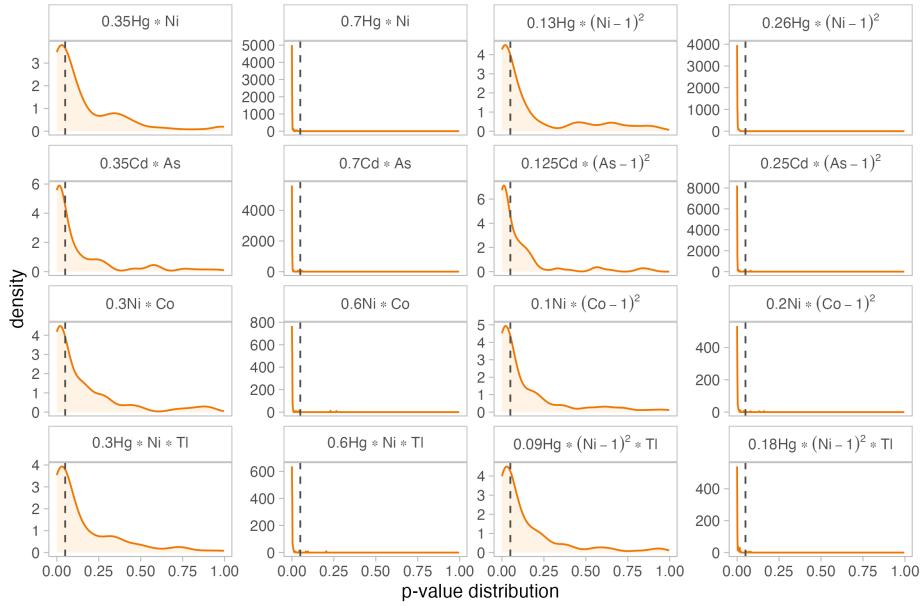


Figure A.31: P-value distributions of interaction terms from oracle MLRs run on larger size ($n=1000$) datasets, from all scenarios with interactions between chemicals.

Table A.1 summarizes the sensitivities and false discovery rates for univariate terms in scenarios with interactions between chemicals. Figures A.32-A.43 display the estimated exposure-response surface for one chemical while fixing one (or two, for three-way interactions) other chemicals at their 0.1, 0.5, and 0.9 quantiles, for all scenarios not included in Chapter 4.3.2.

Table A.1: Overall false discovery rate for univariate chemicals in all scenarios with interactions between chemicals.

Type	Effect size	Small			Large		
		Naive	BKMR	BSR	Naive	BKMR	BSR
Hg-Ni							
Mult.	Lower	0.06	0.34	0.03	0.07	0.09	0.03
Mult.	Higher	0.03	0.20	0.04	0.04	0.04	0.01
Poly.	Lower	0.04	0.29	0.04	0.04	0.07	0.00
Poly.	Higher	0.05	0.30	0.05	0.07	0.09	0.02
Cd-As							
Mult.	Lower	0.05	0.27	0.03	0.05	0.10	0.01
Mult.	Higher	0.07	0.44	0.07	0.16	0.30	0.16
Poly.	Lower	0.05	0.29	0.04	0.08	0.18	0.03
Poly.	Higher	0.04	0.38	0.06	0.06	0.34	0.16
Ni-Co							
Mult.	Lower	0.06	0.34	0.04	0.05	0.11	0.02
Mult.	Higher	0.06	0.29	0.05	0.06	0.12	0.06
Poly.	Lower	0.07	0.37	0.04	0.06	0.10	0.02
Poly.	Higher	0.04	0.34	0.05	0.06	0.20	0.07
Hg-Ni-Tl							
Mult.	Lower	0.06	0.36	0.04	0.05	0.08	0.02
Mult.	Higher	0.04	0.36	0.04	0.04	0.16	0.03
Poly.	Lower	0.05	0.35	0.05	0.06	0.13	0.02
Poly.	Higher	0.06	0.26	0.03	0.05	0.08	0.03

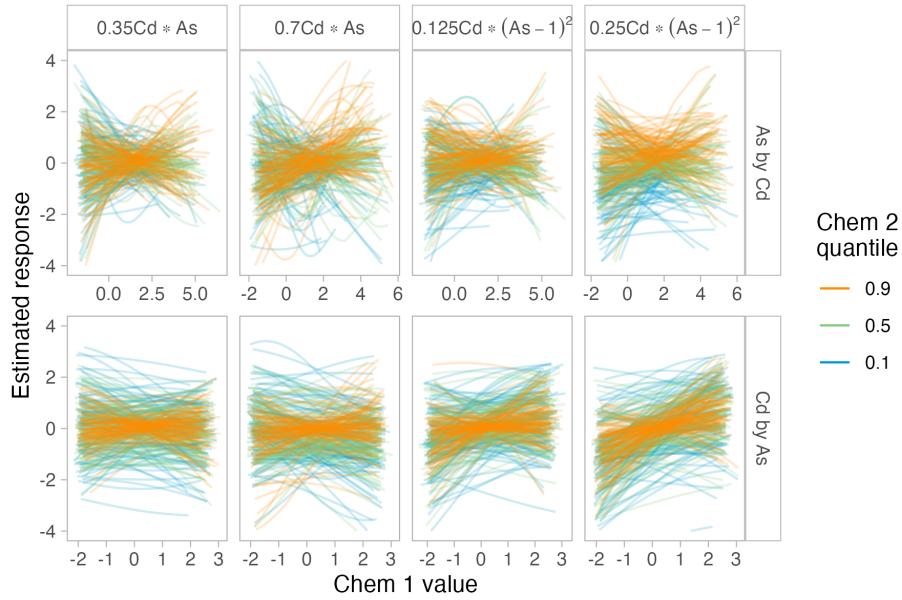


Figure A.32: Exposure-response relationships estimated by BKMR in smaller size ($n=252$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Cd and As. All other chemicals are fixed at 0.5 quantiles.

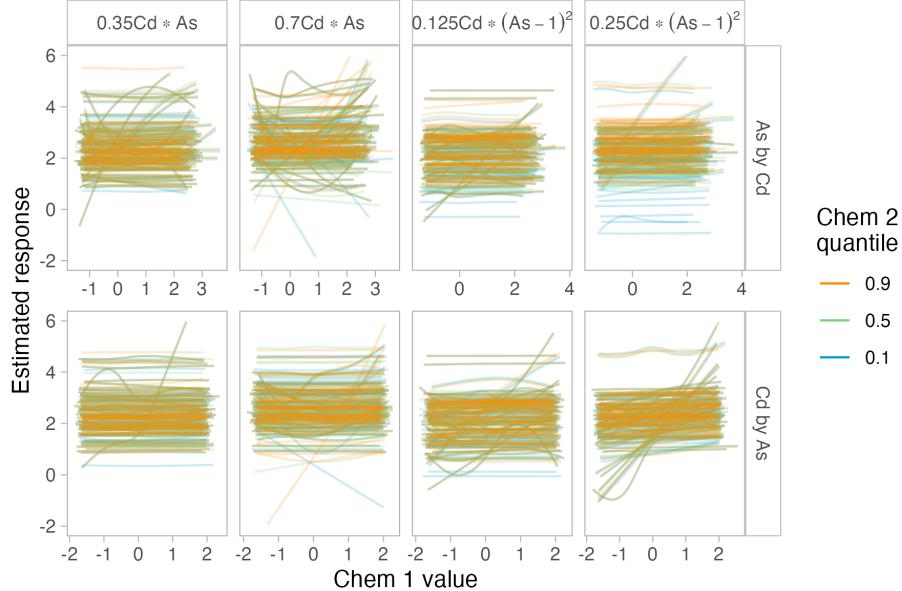


Figure A.33: Exposure-response relationships estimated by BSR in smaller size ($n=252$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Cd and As. All other chemicals are fixed at 0.5 quantiles.

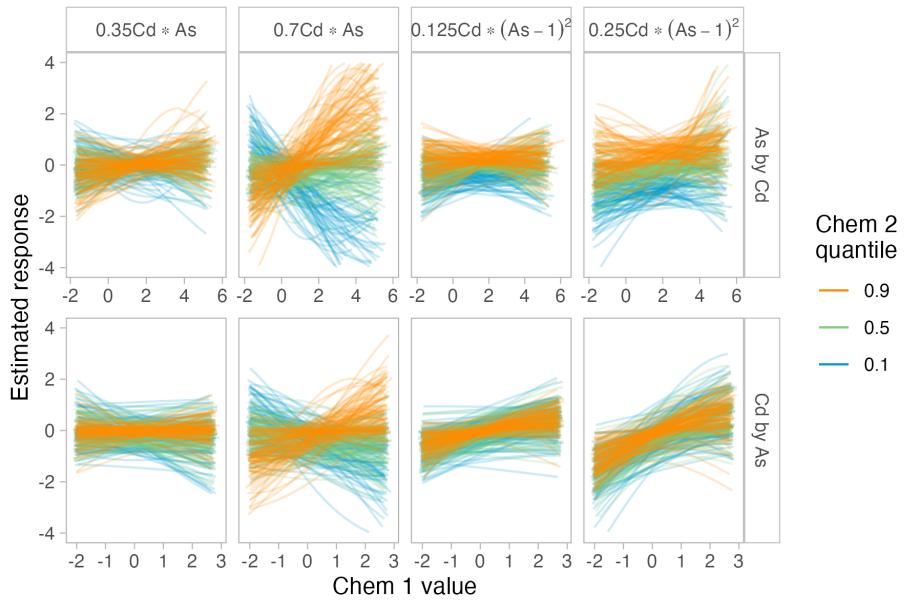


Figure A.34: Exposure-response relationships estimated by BKMR in larger size ($n=1000$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Cd and As. All other chemicals are fixed at 0.5 quantiles.

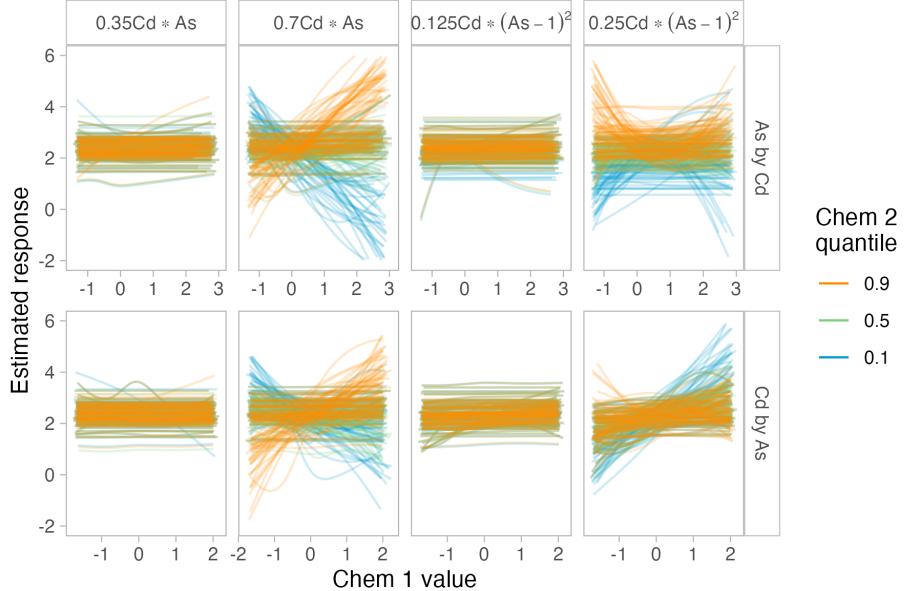


Figure A.35: Exposure-response relationships estimated by BSR in larger size ($n=1000$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Cd and As. All other chemicals are fixed at 0.5 quantiles.

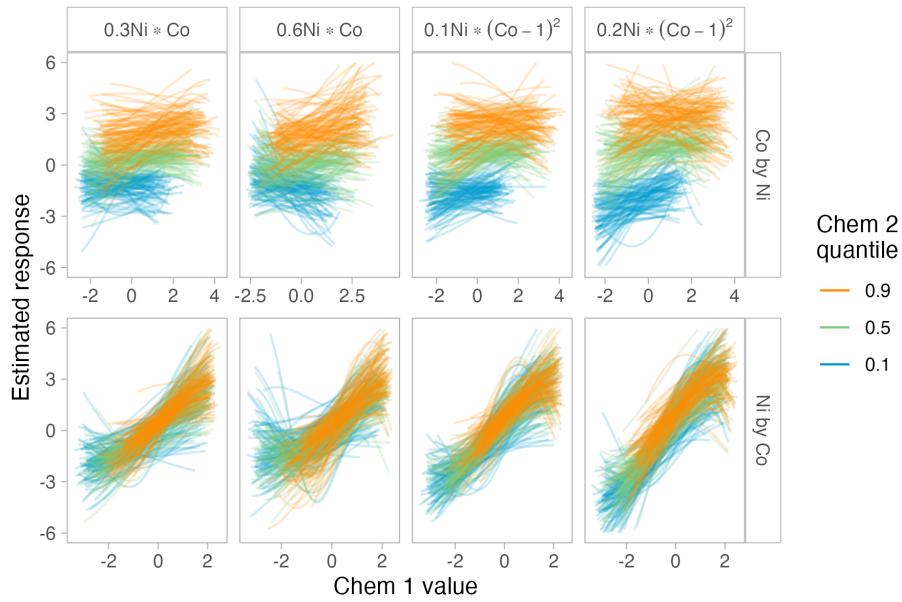


Figure A.36: Exposure-response relationships estimated by BKMR in smaller size ($n=252$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Ni and Co. All other chemicals are fixed at 0.5 quantiles.

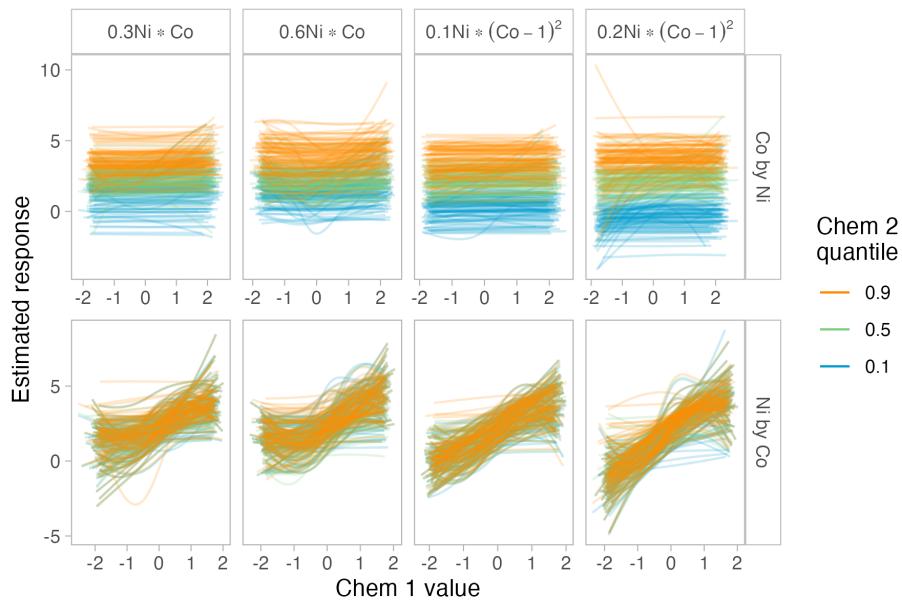


Figure A.37: Exposure-response relationships estimated by BSR in smaller size ($n=252$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Ni and Co. All other chemicals are fixed at 0.5 quantiles.

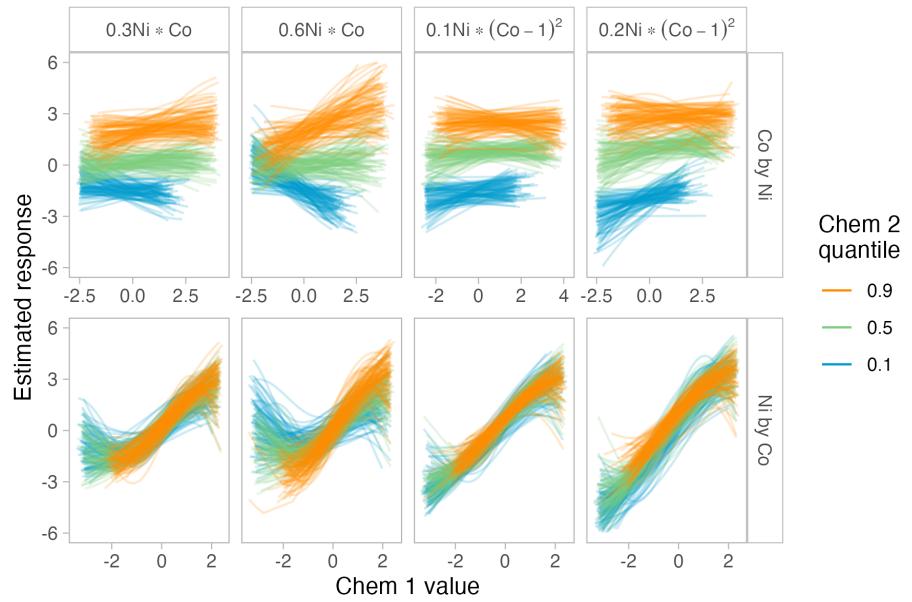


Figure A.38: Exposure-response relationships estimated by BKMR in larger size ($n=1000$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Ni and Co. All other chemicals are fixed at 0.5 quantiles.

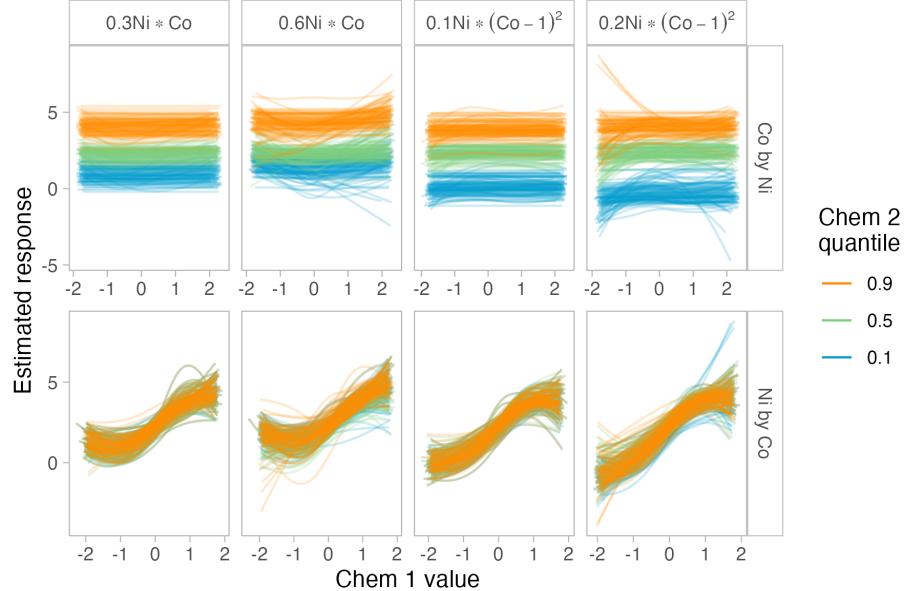


Figure A.39: Exposure-response relationships estimated by BSR in larger size ($n=1000$) datasets, using the first chemical fixed at quantiles of another to assess interactions between Ni and Co. All other chemicals are fixed at 0.5 quantiles.

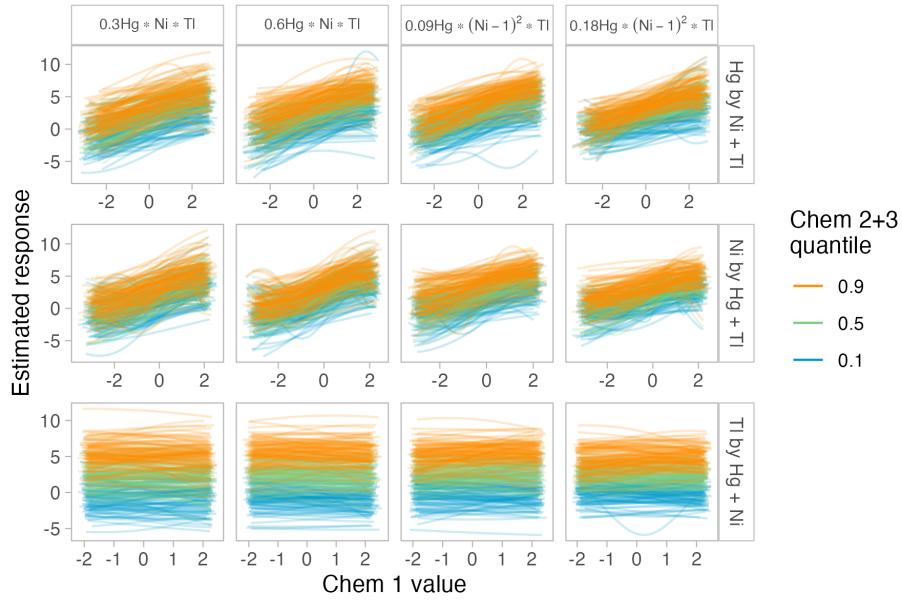


Figure A.40: Exposure-response relationships estimated by BKMR in smaller size ($n=252$) datasets, using the first chemical fixed at quantiles of two others to assess interactions between Ni, Hg, and Tl. All other chemicals are fixed at 0.5 quantiles.

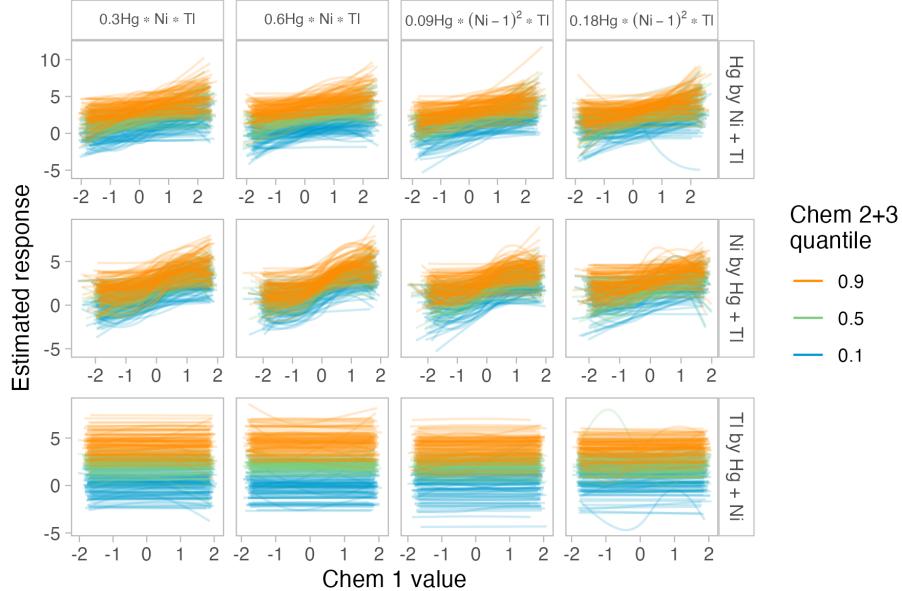


Figure A.41: Exposure-response relationships estimated by BSR in smaller size ($n=252$) datasets, using the first chemical fixed at quantiles of two others to assess interactions between Ni, Hg, and Tl. All other chemicals are fixed at 0.5 quantiles.

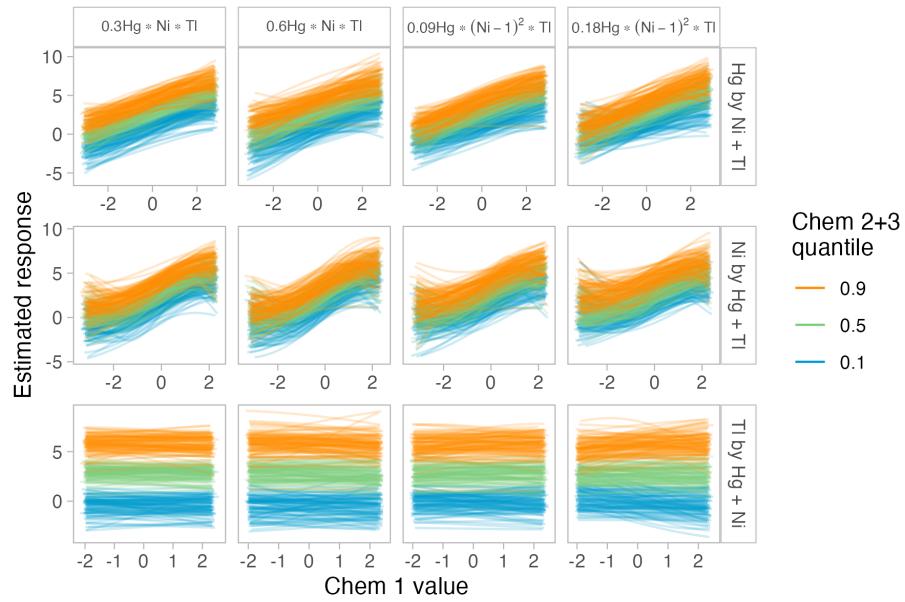


Figure A.42: Exposure-response relationships estimated by BKMR in larger size ($n=1000$) datasets, using the first chemical fixed at quantiles of two others to assess interactions between Ni, Hg, and Tl. All other chemicals are fixed at 0.5 quantiles.

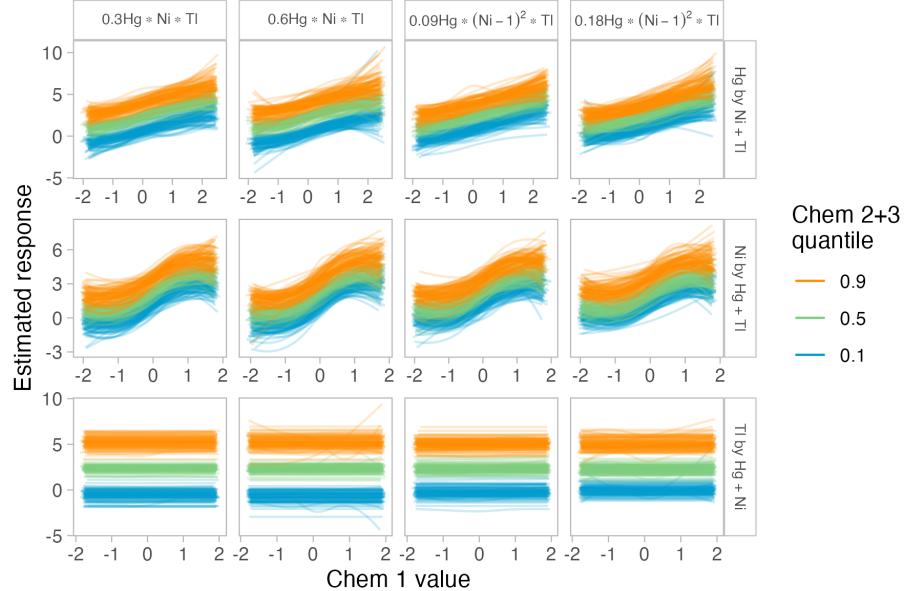


Figure A.43: Exposure-response relationships estimated by BSR in larger size ($n=1000$) datasets, using the first chemical fixed at quantiles of two others to assess interactions between Ni, Hg, and Tl. All other chemicals are fixed at 0.5 quantiles.

Table A.2 summarizes the sensitivities for Hg in scenarios with interactions between the categorical race covariate and Hg. Note that the naive and oracle MLRs do not have an associated race category, because we did not stratify them in our analysis.

Table A.2: Sensitivity for the univariate Hg term in all scenarios with an interaction between the categorical race covariate and Hg. Sensitivities for BKMR and BSR models are stratified by race.

Model	Race	Small race cat.		Large race cat.	
		Lower	Higher	Lower	Higher
Small					
Naive MLR	-	0.84	0.79	0.93	0.99
Oracle MLR	-	0.82	0.78	0.70	0.56
BKMR	Non-Hisp. white (n=16)	0.52	0.47	0.42	0.51
	Non-Hisp. black (n=27)	0.60	0.69	0.50	0.56
	Non-Hisp. other (n=13)	0.30	0.27	0.27	0.20
	Hisp. born in US (n=87)	0.56	0.50	0.57	0.60
	Hisp. born outside US (n=109)	0.68	0.63	0.89	0.97
	Collapsed non-Hisp. (n=56)	0.54	0.65	0.55	0.46
BSR	Non-Hisp. white (n=16)	0.32	0.30	0.42	0.40
	Non-Hisp. black (n=27)	0.26	0.41	0.22	0.23
	Non-Hisp. other (n=13)	0.36	0.35	0.32	0.40
	Hisp. born in US (n=87)	0.23	0.15	0.13	0.18
	Hisp. born outside US (n=109)	0.23	0.25	0.53	0.80
	Collapsed non-Hisp. (n=56)	0.17	0.33	0.23	0.16
Large					
Naive MLR	-	1.00	1.00	1.00	1.00
Oracle MLR	-	1.00	1.00	0.99	1.00
BKMR	Non-Hisp. white (n=16)	0.45	0.56	0.50	0.43
	Non-Hisp. black (n=27)	0.88	0.93	0.59	0.59
	Non-Hisp. other (n=13)	0.55	0.41	0.52	0.53
	Hisp. born in US (n=87)	0.90	0.93	0.88	0.95
	Hisp. born outside US (n=109)	0.92	0.94	1.00	1.00
BSR	Non-Hisp. white (n=16)	0.16	0.18	0.18	0.13
	Non-Hisp. black (n=27)	0.56	0.82	0.24	0.30
	Non-Hisp. other (n=13)	0.17	0.11	0.18	0.17
	Hisp. born in US (n=87)	0.76	0.70	0.71	0.70
	Hisp. born outside US (n=109)	0.79	0.85	1.00	1.00

Appendix B Code

This second appendix includes all of the R chunks of code that were hidden throughout the document.

B.1 Code for Chapter 3:

The code for this section generates a toy example, used to demonstrate the kernel machine regression and spline regression techniques.

```
#load packages
library(tidyverse)
library(stats)
library(splines)

# set theme for plots
theme_set(theme_light())
theme_update(panel.grid.major = element_blank(),
            panel.grid.minor = element_blank())
theme_update(
  strip.background = element_rect(color="gray", fill="white"),
  strip.text = element_text(color = "gray30")
)

#####
# generate simulated points
#####

# generate data from distribution
set.seed(0) # reproducibility
x <- seq(0, 25, length.out = 51)
Y <- exp(x/10) + 2*sin(x/2) + rnorm(51, mean = 0, sd = 0.5)
df <- data.frame(x, Y)

# plot data and linear regression line
q1 <- ggplot(df, aes(x, Y)) +
  geom_point() +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
```

```

geom_smooth(method = "lm", formula = "y~x",
            color = "deepskyblue3", fill = "gray70",
            linewidth = 0.5, se = F)

# save plot
ggsave("index/figures/ch3_toy1.png", plot = q1, device = "png",
       width = 5, height = 3)

#####
# kernel regression
#####

# get normal distribution of weights around query points
df$Weight <- dnorm(df$x, mean = 12.5, sd = 1)

# plot points colored by their weights
p1 <- ggplot(df, aes(x, Y)) +
  geom_point(aes(color = Weight)) +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
  geom_vline(xintercept = 12.5, linetype = "dotted") +
  theme(legend.position = "none")

# plot a curve of weights
normcurv <- data.frame(x = seq(0, 25, length.out = 250))
normcurv$Weight <- dnorm(normcurv$x, mean = 12.5, sd = 1)
p2 <- ggplot(normcurv, aes(x, Weight, color = Weight)) +
  geom_line() +
  scale_y_continuous(breaks = c(0, 0.2, 0.4)) +
  theme(legend.position = "none")

# stitch plots together
q2 <- cowplot::plot_grid(p1, p2, ncol = 1, rel_heights = c(0.7, 0.3))
q2

# save plot
ggsave("index/figures/ch3_toy2.png", plot = q2, device = "png",
       width = 5, height = 4)

# fit kernel regression with sigma = 1, bandwidth = 8/3
kmr_toy <- ksmooth(df$x, df$Y, kernel = "normal",
                     bandwidth = 8/3, x.points = df$x)
df <- df |>
  left_join(as.data.frame(kmr_toy), by = "x") |>
  rename(Yhat = y)

# plot kernel regression estimation
q3 <- ggplot(df) +
  geom_point(aes(x, Y)) +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
  geom_line(aes(x, Yhat), color = "deepskyblue3")
q3

# save plot
ggsave("index/figures/ch3_toy3.png", plot = q3, device = "png",
       width = 5, height = 3)

# fit kernel regression with sigma = 5, bandwidth = 40/3
kmr_toy_5 <- ksmooth(df$x, df$Y, kernel = "normal",
                      bandwidth = 40/3, x.points = df$x)

# fit kernel regression with sigma = 0.1, bandwidth = 8/30

```

```

kmr_toy_1 <- ksmooth(df$x, df$Y, kernel = "normal",
                      bandwidth = 8/30, x.points = df$x)

# re-join data
dfrho <- df |>
  left_join(as.data.frame(kmr_toy_5), by = "x") |>
  rename("rho = 50" = y) |>
  left_join(as.data.frame(kmr_toy_1), by = "x") |>
  rename("rho = 0.02" = y) |>
  select(-Yhat) |>
  pivot_longer(cols = c("rho = 50", "rho = 0.02"), values_to = "Yhat")

# plot kernel regression with two values of rho
qrho <- ggplot(dfrho) +
  geom_point(aes(x, Y)) +
  geom_line(aes(x, Yhat), color = "deepskyblue3") +
  facet_wrap(~name)
qrho

# save plot
ggsave("index/figures/ch3_toyrho.png", plot = qrho, device = "png",
       width = 7, height = 3)

```

```

#####
# spline regression
#####

kn <- c(5, 10, 15, 20) # 4 knots of equal width

# fit linear spline regression
spline_toy_line <- lm(Y ~ bs(x, knots = kn, degree = 1), data = df)
p_line <- predict(spline_toy_line, se = T)
df$Yhats_line <- p_line$fit

q4 <- ggplot(df) +
  geom_point(aes(x, Y)) +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
  geom_line(aes(x, Yhats_line), color = "deepskyblue3") +
  geom_vline(xintercept = kn, linetype = "dotted")
q4

# save plot
ggsave("index/figures/ch3_toy4.png", plot = q4, device = "png",
       width = 5, height = 3)

# fit cubic spline regression
spline_toy_cub <- lm(Y ~ bs(x, knots = kn, degree = 3), data = df)
p_cub <- predict(spline_toy_cub, se = T)
df$Yhats_cub <- p_cub$fit

# plot spline regression estimation
q5 <- ggplot(df) +
  geom_point(aes(x, Y)) +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
  geom_line(aes(x, Yhats_cub), color = "deepskyblue3") +
  geom_vline(xintercept = kn, linetype = "dotted")
q5

# save plot
ggsave("index/figures/ch3_toy5.png", plot = q5, device = "png",
       width = 5, height = 3)

```

```

# fit natural spline regression
spline_toy_nat <- lm(Y ~ ns(x, knots = kn), data = df)
p_nat <- predict(spline_toy_nat, se = T)
df$Yhats_nat <- p_nat$fit

# plot spline regression estimation
q6 <- ggplot(df) +
  geom_point(aes(x, Y)) +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
  geom_line(aes(x, Yhats_nat), color = "deepskyblue3") +
  geom_vline(xintercept = c(5, 10, 15, 20), linetype = "dotted")
q6

# save plot
ggsave("index/figures/ch3_toy6.png", plot = q6, device = "png",
       width = 5, height = 3)

# see what happens outside of the bounds
x_longer <- seq(-5, 30, length.out = 81)
y_longer_cub <- predict(spline_toy_cub,
                        newdata = data.frame(x = x_longer))
y_longer_nat <- predict(spline_toy_nat,
                        newdata = data.frame(x = x_longer))

df_longer <- data.frame(
  x = c(x_longer, x_longer),
  spline = c(rep("Cubic", 81), rep("Natural", 81)),
  Yhat = c(y_longer_cub, y_longer_nat)
)

# plot outside of bounds
qbounds <- ggplot(df_longer) +
  geom_line(aes(x, Yhat), color = "deepskyblue3") +
  geom_function(fun = function(x) exp(x/10) + 2*sin(x/2),
                linetype = "dashed", color = "darkorange") +
  geom_vline(xintercept = c(0, 25), linetype = "dotted") +
  facet_wrap(~spline)
qbounds

# save plot
ggsave("index/figures/ch3_toybounds.png", plot = qbounds,
       device = "png", width = 7, height = 3)

```

B.2 Code for Chapter 4:

The code for this section prepares the data from the MADRES study, generates simulated data, fits multiple linear regressions, BKMR, and BSR on the simulated data, and produces model output.

B.2.1 Code for Chapter 4.2.1:

First, we clean the data from the MADRES study. Note that this code requires two publicly available datasets, available from the HHEAR Data Repository, as outlined in Chapter 4.2.1.

```
# load packages
library(tidyverse)

# read in data
target <- read_csv("madres_data/1945_TARGETED_DATA.csv")
epi <- read_csv("madres_data/1945_EPI_DATA.csv")

#####
# clean target data
#####

target_small <- target |>
  # if below LOD, use LOD / sqrt(2)
  mutate(conc_mod = ifelse(Comment_code == 37,
                          LOD / sqrt(2),
                          Concentration)) |>
  # adjust for urine specific gravity: Ac = A × [(SGmean -1)/(SG-1)]
  mutate(conc_mod = conc_mod * ((mean(target$SG)-1)/(SG-1))) |>
  select(Project_ID, SID, PID, child_PID, Analyte_Code, conc_mod) |>
  group_by(SID) |>
  mutate(Project_ID = min(Project_ID)) |>
  ungroup() |>
  pivot_wider(names_from = Analyte_Code, values_from = conc_mod) |>
  # howe kept As, Cd, Co, Hg, Ni, Tl, and Pb in main, Mo, Sb, and Sn in supp
  # don't have modified version of As used in their paper
  select(Project_ID, SID, PID, child_PID,
         As, Cd, Co, Hg, Ni, Tl, Pb, Mo, Sb, Sn)

# save
write_csv(target_small, "madres_data/target_small.csv")

# only keep data from first trimester
target_first <- target_small |>
  group_by(child_PID) |>
  filter(Project_ID == min(Project_ID)) |>
  ungroup()

# save
write_csv(target_first, "madres_data/target_first.csv")
```

```
#####
# clean epi data
#####

# select relevant variables
epi_small <- epi |>
  # make new categorical variables
  mutate(mom_site = as.factor(mom_site),
         race = as.factor(case_when(
```

```

t1_demo_hispanic == 0 & t1_demo_race == 2 ~ 1, #non-hisp white
t1_demo_hispanic == 0 & t1_demo_race == 4 ~ 2, #non-hisp black
t1_demo_hispanic == 0 ~ 3, #other, non-hispanic
t1_demo_hispanic == 1 & t1_demo_usa == 1 ~ 4, #hispanic in US
t1_demo_hispanic == 1 & t1_demo_usa == 0 ~ 5, #hispanic NOT in US
.default = NA
)),
smoke = as.factor(ifelse(
  t1_smoke_preg == 1 | t2_smoke_preg == 1 | t3_smoke_preg == 1 |
  t1_smoke == 1 | t2_smoke == 1 | t3_smoke == 1, 1, 0
))) |>
# replace -99 with NA
mutate(across(where(is.numeric), ~ifelse(. == -99, NA, .))) |>
dplyr::select(child_pid, mom_site,
  age = t1_mat_age, # age, trimester 1
  bmi = t1_pre_BMI, # bmi
  race, # maternal r/e
  smoke, # ever-exposure to smoke
  gender, birthweight, GA # birthweight + gestational age
  # can't find anemia measure or AsB
)

# handle NA values
epi_imp <- epi_small |>
  # exclude birthweight (observed response)
  # exclude study site because of small categories
  select(-c(gender, birthweight, GA, mom_site)) |>
  # na's for smoke during preg, set to 0
  mutate(smoke = as.factor(ifelse(is.na(smoke), 0, smoke))) |>
  # impute mean for BMI
  mutate(across(where(is.numeric),
    ~ifelse(is.na(.), mean(.,na.rm = TRUE), .)))

```

```

#####
# combine epi and target data
#####
comb <- epi_imp |>
  left_join(target_first, by = c("child_pid" = "child_PID")) |>
  relocate(child_pid, Project_ID, SID, PID, mom_site, race, smoke)

# remove outliers
comb_small <- comb |>
  filter(Mo >= 1, Sb <= 1.4)

# save
write_csv(comb_small, "madres_data/base_data.csv")

```

B.2.2 Code for Chapter 4.2.2:

Next, we use copulas to simulate predictor data. We use the `copula` and `rslurm` packages in this section. This code was run on the Amherst HPC RStudio server.

```

# load packages
library(tidyverse)
library(copula)
library(rslurm)

```

```

# read data back in
comb_small <- read_csv("madres_data/base_data.csv")

# log-transform target data
comb_log <- comb_small |>
  mutate(across(10:19, log)) |>
  # factors back to numeric
  mutate(across(where(is.factor), as.numeric))

# check spearman's rho
cor(comb_log[, 7:19], method = "spearman")

#####
# fit copulas
#####

# create pseudo observations for continuous variables
u <- pobs(comb_log[, 7:19])

# fit checkerboard copula on smoke
prop_smoke0 <- 1 - mean(comb_log$smoke)
# jitter 0's and 1's uniformly within quantile
set.seed(0)
u_smoke <- comb_log$smoke |>
  map_dbl(\(x) {
    ifelse(x == 0, runif(1, 0, prop_smoke0), runif(1, prop_smoke0, 1))
  })
u[, 1] <- u_smoke

# fit copulas
cfit_gaus <- fitCopula(normalCopula(dim = 13, dispstr = "un"), u)
cfit_t1 <- fitCopula(tCopula(dim = 13, dispstr = "un",
                             df.fixed = FALSE), u)
cfit_t2 <- fitCopula(tCopula(dim = 13, dispstr = "un",
                             df = 4, df.fixed = TRUE), u)
cfit_t3 <- fitCopula(tCopula(dim = 13, dispstr = "un",
                             df = 10, df.fixed = TRUE), u)
cfit_gum1 <- fitCopula(gumbelCopula(4, dim = 13), u)
cfit_gum2 <- fitCopula(gumbelCopula(2, dim = 13), u)
cfit_frank1 <- fitCopula(frankCopula(4, dim = 13), u)
cfit_frank2 <- fitCopula(frankCopula(2, dim = 13), u)
cfit_clay1 <- fitCopula(claytonCopula(4, dim = 13), u)
cfit_clay2 <- fitCopula(claytonCopula(2, dim = 13), u)
cfit_joe1 <- fitCopula(joeCopula(4, dim = 13), u)
cfit_joe2 <- fitCopula(joeCopula(2, dim = 13), u)

# evaluate fit using AIC
aic_values <- sapply(list(cfit_gaus, cfit_t1, cfit_t2, cfit_t3,
                           cfit_gum1, cfit_gum2, cfit_frank1, cfit_frank2,
                           cfit_clay1, cfit_clay2, cfit_joe1, cfit_joe2
                         ), AIC)
names(aic_values) <- c("cfit_gaus", "cfit_t1", "cfit_t2", "cfit_t3",
                       "cfit_gum", "cfit_gum2", "cfit_frank1", "cfit_frank2",
                       "cfit_clay1", "cfit_clay2", "cfit_joe1", "cfit_joe2")
sort(aic_values)

# evaluate fit using likelihood
aic_values <- sapply(list(cfit_gaus, cfit_t1, cfit_t2, cfit_t3,
                           cfit_gum1, cfit_gum2, cfit_frank1, cfit_frank2,
                           cfit_clay1, cfit_clay2, cfit_joe1, cfit_joe2
                         ), logLik)
names(lik_values) <- c("cfit_gaus", "cfit_t1", "cfit_t2", "cfit_t3",
                       "cfit_gum", "cfit_gum2", "cfit_frank1", "cfit_frank2",

```

```

        "cfit_clay1", "cfit_clay2", "cfit_joe1", "cfit_joe2")
sort(lik_values)

# gaussian copula performs best, proceed with this
write_rds(cfit_gaus, "sim/gauscop.RDS")

#####
# simulate predictor data
#####

# read copula back in
cfit_gaus <- read_rds("sim/gauscop.RDS")

# extract rho
rho <- coef(cfit_gaus)

# create function for simulation
simulate_data <- function(data, n, rho, prop_smoke, prop_race) {
  #' data = original observed data
  #' n = sample size
  #' rho = rho values from normal copula
  #' prop_smoke = proportion smoke from observed dataset
  #' prop_race = table with race/eth values

  # simulate pseudo-observations from copula
  samp <- rCopula(n, normalCopula(rho, dim = ncol(data), dispstr = "un"))

  # transform pseudo-observations to observed marginal distributions
  sampt <- 1:ncol(data) |>
    purrr::map_dfc(
      \ (x) {
        if(names(data)[x] == "smoke") {
          # use observed probability threshold for smoke
          df <- data.frame(ifelse(samp[,x] < prop_smoke, 0, 1),
                           row.names = NULL)
        } else {
          # use empirical marginal CDF's for continuous
          df <- data.frame(quantile(data[[x]]), probs = samp[,x]),
                           row.names = NULL)
        }
        names(df) <- names(data)[x]
        return(df)
      }
    ) |>
    # randomly sample race
    mutate(race = sample(x = names(prop_race), prob = prop_race,
                         size = n, replace = T)) |>
    relocate(race)
  return(sampt)
}

# create function to run size 252 samples on hpc
run_sim1 <- function() {
  set.seed(0)
  out <- 1:2100 |>
    purrr::map(\(x) {
      mutate(simulate_data(comb_log_clip, n = nrow(comb_log_clip), rho = rho,
                           prop_smoke = 1-mean(comb_log_clip$smoke),
                           prop_race = table(comb_log$race)),
             race = as.numeric(race),
             sim = x)
    })
  return(out)
}

```

```

}

# send job to hpc for size 252 samples
sjob1 <- slurm_call(run_sim1,
                      global_objects = c('comb_log', 'comb_log_clip',
                                         'rho', 'simulate_data'),
                      jobname = 'sim_data1')

# get output
out1 <- get_slurm_out(sjob1)
write_rds(out1, "sim/sim_preds_sm.RDS")

# create function to run size 1000 samples on hpc
run_sim2 <- function() {
  set.seed(1)
  out <- 1:2100 |>
    purrr::map(\(x) {
      mutate(simulate_data(comb_log_clip, n = 1000, rho = rho,
                           prop_smoke = 1-mean(comb_log_clip$smoke),
                           prop_race = table(comb_log$race)),
             race = as.numeric(race),
             sim = x)
    })
  return(out)
}

# send job to hpc for size 1000 samples
sjob2 <- slurm_call(run_sim2,
                      global_objects = c('comb_log', 'comb_log_clip',
                                         'rho', 'simulate_data'),
                      jobname = 'sim_data2')

# get output
out2 <- get_slurm_out(sjob2)
write_rds(out2, "sim/sim_preds_lg.RDS")

```

Here, we visualize the observed and simulated predictor data.

```

# load packages
library(tidyverse)
library(latex2exp) # for printing latex on ggplot

# set theme for plots
theme_set(theme_light())
theme_update(panel.grid.major = element_blank(), panel.grid.minor = element_blank())
theme_update(
  strip.background = element_rect(color="gray", fill="white"),
  strip.text = element_text(color = "gray30")
)

#####
# observed data
#####

# read target data back in
target_first <- read_csv("madres_data/target_first.csv")

# create spearman's correlation matrix
cor_mat <- cor(target_first[, 5:14], method = "spearman")
cor_mat[lower.tri(cor_mat)] <- NA

```

```

# reshape correlation matrix to longer format
melt_cor <- reshape2::melt(cor_mat) |>
  mutate(label = ifelse(value == 1, NA, round(value, 2))) |>
  na.omit()

# create correlation heatmap
cor_orig <- melt_cor |>
  ggplot(aes(x = Var1, y = Var2, fill = value)) +
  geom_tile() +
  geom_text(aes(label = label), size = 3.5) +
  scale_fill_gradient2(
    limit = c(-0.6, 0.6), breaks = c(-0.6, -0.3, 0, 0.3, 0.6),
    low = "deepskyblue3", mid = "white", high = "darkorange",
    na.value = NA) +
  coord_fixed() +
  labs(x = NULL, y = NULL, fill = TeX(r"( Spearman's \$\rho\$ )")) +
  theme(
    panel.grid.major.x = element_line(color = "grey85",
                                       linewidth = 0.25,
                                       linetype = 2),
    panel.border = element_blank(),
    legend.justification = c(1, 0),
    legend.position = c(0.9, 0.1),
    legend.direction = "horizontal") +
  guides(fill = guide_colorbar(barwidth = 7, barheight = 1,
                               title.position = "top", title.hjust = 0.5)))
cor_orig

ggsave("index/figures/ch4_corr.png", width = 5, height = 5)

```

```

# read target and epi data back in
comb_small <- read_csv("madres_data/base_data.csv")

# log-transform target data
comb_log <- comb_small |>
  mutate(across(10:19, log)) |>
  # factors back to numeric
  mutate(across(where(is.factor), as.numeric))

# look at densities of exposures before log-transform
univ1 <- comb_small |>
  select(10:19) |>
  pivot_longer(cols = 1:10) |>
  mutate(name = factor(name, levels = names(comb_small)[10:19])) |>
  ggplot(aes(x = value)) +
  geom_density() +
  facet_wrap(~name, scales = "free", nrow = 2) +
  labs(x = "Concentration (ng/mL)")

# look at densities of exposures after log-transform
univ2 <- comb_log |>
  select(10:19) |>
  pivot_longer(cols = 1:10) |>
  mutate(name = factor(name, levels = names(comb_small)[10:19])) |>
  ggplot(aes(x = value)) +
  geom_density() +
  facet_wrap(~name, scales = "free", nrow = 2) +
  labs(x = "Natural log concentration (log(ng/mL))")

# plot in grid and save
cowplot::plot_grid(univ1, univ2, labels = "auto", nrow = 2)
ggsave("index/figures/ch4_univlog.png", width = 7.5, height = 5)

```

```

# density plot of continuous covariates
cov_cont <- comb_log |>
  select(age, bmi) |>
  pivot_longer(cols = 1:2) |>
  ggplot(aes(x = value)) +
  geom_density() +
  facet_wrap(~name, scales = "free", ncol = 1)

# create new dataset for dist. of categorical covariates
df_forcovcat <- comb_log |>
  select(smoke, race) |>
  mutate(smoke = ifelse(smoke == 0, "Never-exposed", "Ever-exposed"),
    race = case_when(
      race == 1 ~ "Non-Hisp. white",
      race == 2 ~ "Non-Hisp. black",
      race == 3 ~ "Non-Hisp. other",
      race == 4 ~ "Hispanic born\nin US",
      race == 5 ~ "Hispanic born\noutside US"
    )) |>
  pivot_longer(cols = 1:2) |>
  mutate(value = factor(
    value, levels = rev(c("Never-exposed", "Ever-exposed",
      "Non-Hisp. white", "Non-Hisp. black", "Non-Hisp. other",
      "Hispanic born\nin US", "Hispanic born\noutside US")))
  ))

# bar plot of categorical covariates
cov_cat <- df_forcovcat |>
  ggplot(aes(x = value)) +
  geom_bar(stat = "count", fill = "gray") +
  geom_text(aes(label = after_stat(count)), stat = "count",
    size = 3, hjust = 1, nudge_y = -2) +
  facet_wrap(~name, scales = "free", ncol = 1) +
  coord_flip() +
  labs(x = NULL)

# plot and save
cowplot::plot_grid(cov_cont, cov_cat, labels = "auto", nrow = 1,
  rel_widths = c(0.4, 0.6))
ggsave("index/figures/ch4_covdist.png", width = 6, height = 4)

```

```

#look at association between race and chemicals
name_order <- c("As", "Cd", "Co", "Hg", "Ni", "Tl", "Pb", "Mo", "Sb", "Sn")
comb_log |>
  select(c(6, 10:19)) |>
  pivot_longer(cols = 2:11, names_to = "key", values_to = "value") |>
  mutate(key = factor(key, levels = name_order)) |>
  mutate(race = as.factor(race)) |>
  ggplot(aes(x = race, y = value, color = race)) +
  geom_boxplot() +
  scale_color_discrete(
    name = "Race by ethnicity\nand birth place",
    labels = c("Non-Hisp. white", "Non-Hisp. black", "Non-Hisp. other",
      "Hispanic born\nin US", "Hispanic born\noutside US")) +
  theme(legend.spacing.y = unit(0.25, 'cm')) +
  guides(color = guide_legend(byrow = TRUE)) +
  labs(x = "Race, coded", y = "Log concentration") +
  facet_wrap(~key, scales = "free_y")

# save
ggsave("index/figures/ch4_race_exp.png", width = 7, height = 3.5)

```

```

#####
# look at simulated data, smaller size
#####

# read smaller size simulation back in
out1 <- read_rds("sim/sim_preds_sm.RDS")
comb_sim1 <- bind_rows(out1)

# density plots for exposures
name_order <- c("As", "Cd", "Co", "Hg", "Ni", "Tl", "Pb", "Mo", "Sb", "Sn")
comb_sim1 |>
  mutate(sim = as.factor(sim)) |>
  select(5:15) |>
  pivot_longer(cols = 1:10) |>
  mutate(name = factor(name, levels = name_order)) |>
  ggplot(aes(x = value, group = sim)) +
  geom_line(stat = "density", color = "grey10", alpha = 0.01) +
  # reference density from observed data
  geom_density(
    data = comb_log |> select(10:19) |> pivot_longer(cols = 1:10) |>
      mutate(name = factor(name, levels = name_order)),
    mapping = aes(x = value),
    color = "deepskyblue", linewidth = 0.75, inherit.aes = FALSE
  ) +
  facet_wrap(~name, scales = "free")
# save
ggsave("index/figures/ch4_univ_exp_sim.png", width = 6, height = 4)

# density plot for continuous covariates
cov_sim_p <- comb_sim1 |>
  mutate(sim = as.factor(sim)) |>
  select(age, bmi, sim) |>
  pivot_longer(cols = 1:2) |>
  ggplot(aes(x = value, group = sim)) +
  geom_line(stat = "density", color = "grey10", alpha = 0.01) +
  geom_density(
    data = comb_log |> select(age, bmi) |> pivot_longer(cols = 1:2),
    mapping = aes(x = value),
    color = "deepskyblue", linewidth = 0.75, inherit.aes = FALSE
  ) +
  facet_wrap(~name, scales = "free", ncol = 1)

# bar + violin plot for categorical covariates
cov_sim_q <- comb_sim1 |>
  mutate(sim = as.factor(sim)) |>
  select(sim, smoke, race) |>
  mutate(smoke = ifelse(smoke == 0, "Never-exposed", "Ever-exposed"),
    race = case_when(
      race == 1 ~ "Non-Hisp. white",
      race == 2 ~ "Non-Hisp. black",
      race == 3 ~ "Non-Hisp. other",
      race == 4 ~ "Hispanic born\nin US",
      race == 5 ~ "Hispanic born\noutside US"
    )) |>
  pivot_longer(cols = 2:3) |>
  group_by(sim, name, value) |>
  summarize(count = n()) |>
  mutate(value = factor(
    value, levels = rev(c("Never-exposed", "Ever-exposed",
      "Non-Hisp. white", "Non-Hisp. black", "Non-Hisp. other",
      "Hispanic born\nin US", "Hispanic born\noutside US")))
  )) |>
  ggplot(aes(x = value, y = count)) +

```

```

geom_bar(data = df_forcovcat, aes(x = value), inherit.aes = FALSE,
         stat = "count", fill = "skyblue") +
geom_violin(color = "gray30", fill = "gray", alpha = 0.25) +
facet_wrap(~name, scales = "free", ncol = 1) +
coord_flip() +
labs(x = NULL)

# plot in grid and save
cowplot::plot_grid(cov_sim_p, cov_sim_q, labels = "auto", nrow = 1,
                    rel_widths = c(0.4, 0.6))

ggsave("index/figures/ch4_univ_cov_sim.png", width = 6, height = 4)

# look at correlation structure

# extract correlation structure from simulated data
cors <- out1 |>
  purrr::map_df(\(x) {
    cor_mat <- cor(x[, 5:14], method = "spearman")
    cor_mat[lower.tri(cor_mat)] <- NA
    melt_cor <- reshape2::melt(cor_mat) |>
      mutate(value = ifelse(value == 1, NA, value)) |>
      na.omit() |>
      mutate(sim = x$sim[1])
    return(melt_cor)
  })

# correlation heatmap of average correlation in simulated data
cor_sim <- cors |>
  group_by(Var1, Var2) |>
  summarize(value = mean(value)) |>
  mutate(label = round(value, 2)) |>
  ggplot(aes(x = Var1, y = Var2, fill = value)) +
  geom_tile() +
  geom_text(aes(label = label), size = 3.5) +
  scale_fill_gradient2(
    limit = c(-0.6, 0.6), breaks = c(-0.6, -0.3, 0, 0.3, 0.6),
    low = "deepskyblue3", mid = "white", high = "darkorange",
    na.value = NA) +
  coord_fixed() +
  labs(x = NULL, y = NULL, fill = TeX(r"( Mean Spearman's $\rho$ )")) +
  theme(
    panel.grid.major.x = element_line(color = "grey85",
                                         linewidth = 0.25,
                                         linetype = 2),
    panel.border = element_blank(),
    legend.justification = c(1, 0),
    legend.position = c(0.9, 0.1),
    legend.direction = "horizontal")+
  guides(fill = guide_colorbar(barwidth = 7, barheight = 1,
                               title.position = "top", title.hjust = 0.5))

# plot and save
cor_sim
ggsave("index/figures/ch4_corr_avg_sim.png", width = 5, height = 5)

# put original and simulated correlation heatmaps together
top_row <- cowplot::plot_grid(cor_orig, cor_sim, labels = "auto", label_size = 16,
                               nrow = 1, scale = 0.95)
top_row
ggsave("index/figures/ch4_corr_sim+orig.png", width = 10, height = 5)

```

B.2.3 Code for Chapter 4.2.3:

Next, we simulate the response data. We use the `rslurm` package in this section.

This code was run on the Amherst HPC RStudio server.

```
# load packages
library(tidyverse)
library(rslurm)

#####
# create functions for various response variables
#####

# base case, no interactions
base_case <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# HgxNi, mult, small
am1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.35*Hg*Ni +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# HgxNi, mult, large
am2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.7*Hg*Ni +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# HgxNi, poly, small
ap1 <- function(df) {
```

```

    mutate(df, y =
      Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
      0.13*Hg*((Ni-1)^2) +
      age + 0.5*bmi +
      case_when(race == 1 ~ 1,
                race == 2 ~ 1.5,
                race == 3 ~ 1,
                race == 4 ~ 1,
                race == 5 ~ 1.5) +
      ifelse(smoke == 1, -1, 0.5) +
      rnorm(nrow(df), 0, 5))
  }

# HgxNi, poly, large
ap2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.26*Hg*((Ni-1)^2) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# CdxAs, mult, small
bm1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.35*Cd*As +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# CdxAs, mult, large
bm2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.7*Cd*As +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# CdxAs, poly, small
bp1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.125*Cd*((As-1)^2) +
    age + 0.5*bmi +

```

```

    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# CdxAs, poly, large
bp2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.25*Cd*((As-1)^2) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# HgxCo, mult, small
cm1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.3*Hg*Co +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# HgxCo, mult, large
cm2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.6*Hg*Co +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# HgxCo, poly, small
cp1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.15*Hg*((Co-1)^2) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

```

```

        race == 5 ~ 1.5) +
  ifelse(smoke == 1, -1, 0.5) +
  rnorm(nrow(df), 0, 5))
}

# HgxCe, poly, large
cp2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.3*Hg*((Co-1)^2) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# three-way, multi, small
dm1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.3*Hg*Ni*Tl +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# three-way, multi, large
dm2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.6*Hg*Ni*Tl +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# three-way, poly, small
dp1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.09*Hg*((Ni-1)^2)*Tl +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

```

```

# three-way, poly, large
dp2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    0.18*Hg*((Ni-1)^2)*Tl +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

#####
# create response variables for exposure-exposure interxn
#####

# read output back in, size 252
out1 <- read_rds("sim/sim_preds_sm.RDS")

# create function for responses at size 252
run_resp1 <- function() {
  set.seed(0)
  out1_resp1 <- out1 |>
    purrr::map(~(x) {
      # get dataset number
      no <- x$sim[1]
      x <- x |>
        # scale log-transformed exposures and covariates
        mutate(across(age:Sn, -c(scale(.))))
      df <- case_when(
        no <= 100 ~ base_case(x),
        no <= 200 ~ am1(x),
        no <= 300 ~ am2(x),
        no <= 400 ~ ap1(x),
        no <= 500 ~ ap2(x),
        no <= 600 ~ bm1(x),
        no <= 700 ~ bm2(x),
        no <= 800 ~ bp1(x),
        no <= 900 ~ bp2(x),
        no <= 1000 ~ cm1(x),
        no <= 1100 ~ cm2(x),
        no <= 1200 ~ cp1(x),
        no <= 1300 ~ cp2(x),
        no <= 1400 ~ dm1(x),
        no <= 1500 ~ dm2(x),
        no <= 1600 ~ dp1(x),
        no <= 1700 ~ dp2(x),
        .default = x #note 1701 - 2100 is for cov-exp interxn
      )
    }) |>
    purrr::set_names(nm = c(
      rep("_base", 100),
      rep("am1", 100),
      rep("am2", 100),
      rep("ap1", 100),
      rep("ap2", 100),
      rep("bm1", 100),
      rep("bm2", 100),
      rep("bp1", 100),
      rep("bp2", 100),

```

```

        rep("cm1", 100),
        rep("cm2", 100),
        rep("cp1", 100),
        rep("cp2", 100),
        rep("dm1", 100),
        rep("dm2", 100),
        rep("dp1", 100),
        rep("dp2", 100),
        rep("unset", 400)
    ))
    return(out1_resp1)
}

# run to hpc
runrespsm <- slurm_call(
    run_resp1,
    global_objects = c('out1', 'base_case',
                       'am1', 'am2', 'ap1', 'ap2',
                       'bm1', 'bm2', 'bp1', 'bp2',
                       'cm1', 'cm2', 'cp1', 'cp2',
                       'dm1', 'dm2', 'dp1', 'dp2'),
    jobname = 'sim_resp1')

# get output
out1_resp1 <- get_slurm_out(runrespsm)
# only save for exp-exp interxns
out1_resp1 <- out1_resp1[1:1700]
write_rds(out1_resp1, "sim/sim_resp_sm_a.RDS")

# read output back in, size 1000
out2 <- read_rds("sim/sim_preds_lg.RDS")

# create function for response at size 1000
run_resp2 <- function() {
    set.seed(0)
    out2_resp1 <- out2 |>
        purrr::map((x) {
            # get dataset number
            no <- x$sim[1]
            x <- x |>
                mutate(across(age:Sn, ~c(scale(.))))
            df <- case_when(
                no <= 100 ~ base_case(x),
                no <= 200 ~ am1(x),
                no <= 300 ~ am2(x),
                no <= 400 ~ ap1(x),
                no <= 500 ~ ap2(x),
                no <= 600 ~ bm1(x),
                no <= 700 ~ bm2(x),
                no <= 800 ~ bp1(x),
                no <= 900 ~ bp2(x),
                no <= 1000 ~ cm1(x),
                no <= 1100 ~ cm2(x),
                no <= 1200 ~ cp1(x),
                no <= 1300 ~ cp2(x),
                no <= 1400 ~ dm1(x),
                no <= 1500 ~ dm2(x),
                no <= 1600 ~ dp1(x),
                no <= 1700 ~ dp2(x),
                .default = x #note 1701 - 2100 is for cov-exp interxn
            )
        }) |>
        purrr::set_names(nm = c(
            rep("_base", 100),

```

```

    rep("am1", 100),
    rep("am2", 100),
    rep("ap1", 100),
    rep("ap2", 100),
    rep("bm1", 100),
    rep("bm2", 100),
    rep("bp1", 100),
    rep("bp2", 100),
    rep("cm1", 100),
    rep("cm2", 100),
    rep("cp1", 100),
    rep("cp2", 100),
    rep("dm1", 100),
    rep("dm2", 100),
    rep("dp1", 100),
    rep("dp2", 100),
    rep("unset", 400)
  )))
  return(out2_resp1)
}

# send to HPC
runresplg <- slurm_call(
  run_resp2,
  global_objects = c('out2', 'base_case',
                     'am1', 'am2', 'ap1', 'ap2',
                     'bm1', 'bm2', 'bp1', 'bp2',
                     'cm1', 'cm2', 'cp1', 'cp2',
                     'dm1', 'dm2', 'dp1', 'dp2'),
  jobname = 'sim_resp2')

# get output
out2_resp1 <- get_slurm_out(runresplg)
# only save output for exp-exp interxns for now
out2_resp1 <- out2_resp1[1:1700]
write_rds(out2_resp1, "sim/sim_resp_lg_a.RDS")

#####
# create response variables for exposure-covariate interxn
#####

# functions for creating response
# interxn in smaller group, smaller effect size
em1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5 + 0.5*Hg, # 1.5x in group 2
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# interxn in smaller group, larger effect size
em2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5 + Hg, # double in group 2
              race == 3 ~ 1.5 + 0.5*Hg,
              race == 4 ~ 1.5 + 0.5*Hg,
              race == 5 ~ 1.5 + 0.5*Hg))
}

```

```

        race == 3 ~ 1,
        race == 4 ~ 1,
        race == 5 ~ 1.5) +
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# interxn in larger group, smaller effect size
ep1 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5 + 0.5*Hg) + # 1.5x in group 5
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# interxn in larger group, larger effect size
ep2 <- function(df) {
  mutate(df, y =
    Hg + 3/(1+exp(-4*Ni)) - (Sb^2) + 0.5*Sb + 1.5/(1+exp(-4*Sn)) +
    age + 0.5*bmi +
    case_when(race == 1 ~ 1,
              race == 2 ~ 1.5,
              race == 3 ~ 1,
              race == 4 ~ 1,
              race == 5 ~ 1.5 + Hg) + # double in group 5
    ifelse(smoke == 1, -1, 0.5) +
    rnorm(nrow(df), 0, 5))
}

# read output back in, size 252
out1 <- read_rds("sim/sim_preds_sm.RDS")

# create function to simulate response for smaller size
run_resp1_re <- function() {
  set.seed(0)
  out1_resp1 <- out1 |>
    purrr::map(\(x) {
      # get dataset number
      no <- x$sim[1]
      x <- x |>
        mutate(across(age:Sn, ~c(scale(.))))
      df <- case_when(
        no <= 1700 ~ x, #note 1 - 1700 are chemchem
        no <= 1800 ~ em1(x),
        no <= 1900 ~ em2(x),
        no <= 2000 ~ ep1(x),
        no <= 2100 ~ ep2(x),
        .default = x
      )
    }) |>
    purrr::set_names(nm = c(
      rep("unset", 1700),
      rep("em1", 100),
      rep("em2", 100),
      rep("ep1", 100),
      rep("ep2", 100)
    ))
  return(out1_resp1)
}

```

```

}

# send to HPC
runrespdm_re <- slurm_call(
  run_resp1_re,
  global_objects = c('out1',
                     'em1', 'em2', 'ep1', 'ep2'),
  jobname = 'sim_resp1_re')

# get output
out1_resp1_re <- get_slurm_out(runrespdm_re)
out1_resp1_re <- out1_resp1_re[1701:2100]
write_rds(out1_resp1_re, "sim/sim_resp_sm_re.RDS")

# read output back in, size 1000
out2 <- read_rds("sim/sim_preds_lg.RDS")

# create function to simulate response for larger size
run_resp2_re <- function() {
  set.seed(0)
  out2_resp1 <- out2 |>
    purrr::map(\(x) {
      # get dataset number
      no <- x$sim[1]
      x <- x |>
        mutate(across(age:Sn, ~c(scale(.))))
      df <- case_when(
        no <= 1700 ~ x, #note 1 - 1700 are chemxchem
        no <= 1800 ~ em1(x),
        no <= 1900 ~ em2(x),
        no <= 2000 ~ ep1(x),
        no <= 2100 ~ ep2(x),
        .default = x
      )
    }) |>
    purrr::set_names(nm = c(
      rep("unset", 1700),
      rep("em1", 100),
      rep("em2", 100),
      rep("ep1", 100),
      rep("ep2", 100)
    ))
  return(out2_resp1)
}

# send to HPC
runresplg_re <- slurm_call(
  run_resp2_re,
  global_objects = c('out2',
                     'em1', 'em2', 'ep1', 'ep2'),
  jobname = 'sim_resp2_re')

# get output
out2_resp1_re <- get_slurm_out(runresplg_re)
out2_resp1_re <- out2_resp1_re[1701:2100]
write_rds(out2_resp1_re, "sim/sim_resp_lg_re.RDS")

```

B.2.4 Code for Chapter 4.2.4:

Here, we fit the models to our simulated data. We use the `rslurm`, `bkmr`, and `NLinteraction` packages in this section. This code was run on the Amherst HPC RStudio server.

```
# load packages
library(tidyverse)
library(bkmr)
library(NLinteraction)
```

First, we fit the naive and oracle MLRs.

```
#####
# naive and oracle MLRs
#####

### smaller size

# read in simulated data
out1_resp1 <- read_rds("sim/sim_resp_sm_a.RDS")

run_mlr_sm <- function() {
  # initialize vectors
  mlrs <- vector(mode='list', length = 1700)
  names(mlrs) <- names(out1_resp1)
  mlrtimes <- vector(mode = 'list', length = 1700)
  names(mlrtimes) <- names(out1_resp1)

  oracles <- vector(mode='list', length = 1700)
  names(oracles) <- names(out1_resp1)
  oracletimes <- vector(mode = 'list', length = 1700)
  names(oracletimes) <- names(out1_resp1)

  for(i in 1:1700) {
    df <- out1_resp1[[i]] |>
      mutate(race = as.factor(race), smoke = as.factor(smoke)) |>
      select(-sim)

    start.time <- Sys.time()
    mlrs[[i]] <- lm(y ~ ., data = df)
    end.time <- Sys.time()
    mlrtimes[[i]] <- end.time - start.time

    if(i <= 100) {
      start.time <- Sys.time()
      oracles[[i]] <- lm(y ~ Hg + Sb +
        I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
        age + bmi + race + smoke, data = df)
      end.time <- Sys.time()
      oracletimes[[i]] <- end.time - start.time
    } else if (i <= 300) {
      start.time <- Sys.time()
      oracles[[i]] <- lm(y ~ Hg + Sb +
        I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
        Hg*Ni +
```

```

            age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 500) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Hg*((Ni-1)^2)) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 700) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
Cd*As +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 900) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Cd*((As-1)^2)) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 1100) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
Ni*Co +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 1300) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Ni*((Co-1)^2)) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 1500) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
Hg:Ni:Tl +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
} else if (i <= 1700) {
start.time <- Sys.time()
oracles[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Hg*((Ni-1)^2)*Tl) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimes[[i]] <- end.time - start.time
}
}

return(list(mlrs, mlrtimes, oracles, oracletimes))
}

```



```

            age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
} else if (i <= 700) {
start.time <- Sys.time()
oracle[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
Cd*As +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
} else if (i <= 900) {
start.time <- Sys.time()
oracle[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Cd*((As-1)^2)) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
} else if (i <= 1100) {
start.time <- Sys.time()
oracle[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
Ni*Co +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
} else if (i <= 1300) {
start.time <- Sys.time()
oracle[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Ni*((Co-1)^2)) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
} else if (i <= 1500) {
start.time <- Sys.time()
oracle[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
Hg:Ni:Tl +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
} else if (i <= 1700) {
start.time <- Sys.time()
oracle[[i]] <- lm(y ~ Hg + Sb +
I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
I(Hg*((Ni-1)^2)*Tl) +
age + bmi + race + smoke, data = df)
end.time <- Sys.time()
oracletimel[[i]] <- end.time - start.time
}
}
return(list(mlrl, mlrtimel, oracle, oracletimel))
}

# send to hpc
sjob6 <- slurm_call(
  run_mlrl,
  global_objects = c('out2_resp1'),
  jobname = 'mlrl'
)

# get output
mlrl <- get_slurm_out(sjob6)

```

```

mlr_modl <- mlr_lg[[1]]
mlr_timel <- mlr_lg[[2]]
oracle_modl <- mlr_lg[[3]]
oracle_timel <- mlr_lg[[4]]
write_rds(mlr_modl, "sim/mlr_mods_lg.RDS")
write_rds(mlr_timel, "sim/mlr_mods_lg_times.RDS")
write_rds(oracle_modl, "sim/oracle_mods_lg.RDS")
write_rds(oracle_timel, "sim/oracle_mods_lg_times.RDS")

```

Next, we fit BKMR and BSR models with the base case and with interactions between chemicals.

```

#####
# run bkmr
#####

### smaller sample size

out1_resp1 <- read_rds("sim/sim_resp_sm_a.RDS")

run_bkmr_sm <- function(vector) {
  # initiate vector of times
  bkmr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output
  if(!dir.exists("mods")) {
    dir.create("mods")
  }
  if(!dir.exists("times")) {
    dir.create("times")
  }

  # for each simulated dataset...
  for(i in vector) {
    print(paste0("----- run ", i, "-----"))

    # prepare data
    df <- out1_resp1[[i]]
    Z <- df |>
      select(As:Sn)
    X <- df |>
      bind_cols(
        data.frame(model.matrix(~ race-1, data =
          mutate(df, race = as.factor(race))))
    ) |>
      select(race2:race5, smoke:bmi)
    y <- df$y

    # fit model and save time
    set.seed(0)
    start.time <- Sys.time()
    mod <- kmbayes(y = y, Z = Z, X = X,
                  iter = 50000, verbose = FALSE, varsel = TRUE)
    end.time <- Sys.time()
    bkmr_times[[i]] <- end.time - start.time

    # save model and remove from memory
    write_rds(mod, file = paste0("mods/bkmr_sm_", names(out1_resp1)[i], "_", i, ".RDS"))
    write_rds(bkmr_times[[i]], file =
      paste0("times/bkmr_sm_", names(out1_resp1)[i], "_", i, ".RDS"))
  }
}

```

```

    rm(mod)
}
# save times
write_rds(bkmr_times, file = "bkmr_sm_times.RDS")
}

# send all simulated datasets to hpc
for(i in seq(1, 1601, by = 100)) {
  slurm_call(
    run_bkmr_sm,
    params = list(vector = i:(i+99)),
    global_objects = c('out1_resp1'),
    jobname = paste0("bkmr_sm", str_pad(ceiling(i/100), 2, pad = "0")),
    slurm_options = list(mem = '8G')
  )
}

### larger sample size
out2_resp1 <- read_rds("sim/sim_resp_lg_a.RDS")

run_bkmr_lg <- function(vector) {
  # initiate vector of times
  bkmr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output
  if(!dir.exists("mods")) {
    dir.create("mods")
  }
  if(!dir.exists("times")) {
    dir.create("times")
  }

  # sometimes this code would stop prematurely...
  # so this chunk finds the index of the last model that was run
  list_files <- list.files("mods", full.names = TRUE)
  nums <- as.numeric(sub(".*_(_\\d+)\\.RDS", "\\\\1", list_files))
  print(nums)
  if(length(nums) == 0) {
    final <- 0; starting <- min(vector)
  } else {
    final <- max(nums); starting <- final + 1
  }
  # keep note of when the loop was stopped and re-started
  if(file.exists("final.txt")) {
    write(paste0("final ran = ", final, ", starting at ", starting), "final.txt", append = T)
  } else {
    writeLines(paste0("final ran = ", final, ", starting at ", starting), "final.txt")
  }

  # for each simulated dataset...
  for(i in starting:max(vector)) {
    print(paste0("----- run ", i, "-----"))

    # prepare data
    df <- out2_resp1[[i]]
    Z <- df |>
      select(As:Sn)
    X <- df |>
      bind_cols(
        data.frame(model.matrix(~ race-1, data =
          mutate(df, race = as.factor(race))))
    ) |>
      select(race2:race5, smoke:bmi)
  }
}

```

```

y <- df$y
knots <- fields::cover.design(Z, nd = 100)$design

# fit model and save time
set.seed(0)
start.time <- Sys.time()
mod <- kmbayes(y = y, Z = Z, X = X, knots = knots,
                 iter = 50000, verbose = FALSE, varsel = TRUE)
end.time <- Sys.time()
bkmr_times[[i]] <- end.time - start.time

# save model and remove from memory
write_rds(mod, file = paste0("mods/bkmr_lg_", names(out2_resp1)[i], "_", i, ".RDS"))
write_rds(bkmr_times[[i]], file =
            paste0("times/bkmr_lg_", names(out2_resp1)[i], "_", i, ".RDS"))
rm(mod)
}

# save times
write_rds(bkmr_times, file = "bkmr_lg_times.RDS")
}

# send all simulated datasets to hpc
for(i in seq(1, 1601, by = 100)) {
  slurm_call(
    run_bkmr_lg,
    params = list(vector = i:(i+99)),
    global_objects = c('out2_resp1'),
    jobname = paste0("bkmr_lg", str_pad(ceiling(i/100), 2, pad = "0")),
    slurm_options = list(mem = '8G')
  )
}
}

```

```

#####
## run bsr
#####

### smaller sample size

out1_resp1 <- read_rds("sim/sim_resp_sm_a.RDS")

run_bsr_sm <- function(vector) {
  bsr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output
  if(!dir.exists("mods")) {
    dir.create("mods")
  }
  if(!dir.exists("times")) {
    dir.create("times")
  }

  # sometimes this code would stop prematurely...
  # so this chunk finds the index of the last model that was run
  list_files <- list.files("mods", full.names = TRUE)
  nums <- as.numeric(sub(".+_(_).d.+", "\\\\"1", list_files))
  if(length(nums) == 0) {
    final <- 0; starting <- min(vector)
  } else {
    final <- max(nums); starting <- final + 1
  }
  if(file.exists("final.txt")) {
    write(paste0("final ran = ", final, ", starting at ", starting), "final.txt", append = T)
  } else {

```

```

    writeLines(paste0("final ran = ", final, ", starting at ", starting), "final.txt")
}

# for each simulated dataset...
for(i in starting:max(vector)) {
  print(paste0("----- run ", i, " -----"))

  # prepare data
  df <- out1_resp1[[i]]
  X <- df |>
    select(As:Sn) |>
    as.matrix.data.frame()
  C <- df |>
    bind_cols(
      data.frame(model.matrix(~ race-1, data =
        mutate(df, race = as.factor(race))))
    ) |>
    select(race2:race5, smoke:bmi) |>
    as.matrix.data.frame()
  Y <- df$y

  # fit model for d = {1, 2, 3, 4, 5} and save time
  list_times <- vector(mode = "list", length = 2)

  set.seed(0)
  start.time <- Sys.time()
  mod1 <- NLInt(Y = Y, X = X, C = C,
                 nIter = 5000, nBurn = 2500, ns = 1)
  mod2 <- NLInt(Y = Y, X = X, C = C,
                 nIter = 5000, nBurn = 2500, ns = 2)
  mod3 <- NLInt(Y = Y, X = X, C = C,
                 nIter = 5000, nBurn = 2500, ns = 3)
  mod4 <- NLInt(Y = Y, X = X, C = C,
                 nIter = 5000, nBurn = 2500, ns = 4)
  end.time <- Sys.time()
  list_times[[1]] <- end.time - start.time

  ind <- which.min(c(mod1$waic, mod2$waic, mod3$waic, mod4$waic))

  print(paste0("----- chose ", ind, " -----"))

  # fit with selected d from waic
  start.time <- Sys.time()
  mod <- NLInt(Y = Y, X = X, C = C,
                nIter = 50000, nBurn = 25000, ns = ind)
  end.time <- Sys.time()
  list_times[[2]] <- end.time - start.time

  bsr_times[[i]] <- list_times

  # save model and remove from memory
  write_rds(mod, file =
    paste0("mods/bsr_sm_", names(out1_resp1)[i], "_",
          "df", ind, ".RDS"))
  write_rds(list_times, file =
    paste0("times/bsr_sm_", names(out1_resp1)[i], "_",
          "df", ind, ".RDS"))
  rm(mod1, mod2, mod3, mod4, mod)
}

write_rds(bsr_times, file = "bsr_smf_times.RDS")
return(bsr_times)
}

```

```

# send all simulated datasets to hpc
for(i in seq(1, 1601, by = 100)) {
  slurm_call(
    run_bsr_lg,
    params = list(vector = i:(i+99)),
    global_objects = c('out1_resp1'),
    jobname = paste0("bsr_sm", str_pad(ceiling(i/100), 2, pad = "0")),
    slurm_options = list(mem = '8G')
  )
}

### larger sample size

out2_resp1 <- read_rds("sim/sim_resp_lg_a.RDS")

run_bsr_lg <- function(vector) {
  bsr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output
  if(!dir.exists("mods")) {
    dir.create("mods")
  }
  if(!dir.exists("times")) {
    dir.create("times")
  }

  # sometimes this code would stop prematurely...
  # so this chunk finds the index of the last model that was run
  list_files <- list.files("mods", full.names = TRUE)
  nums <- as.numeric(sub(".+_(_.+)d.+", "\\\1", list_files))
  if(length(nums) == 0) {
    final <- 0; starting <- min(vector)
  } else {
    final <- max(nums); starting <- final + 1
  }
  if(file.exists("final.txt")) {
    write(paste0("final ran = ", final, ", starting at ", starting), "final.txt", append = T)
  } else {
    writeLines(paste0("final ran = ", final, ", starting at ", starting), "final.txt")
  }

  for(i in starting:max(vector)) {
    print(paste0("----- run ", i, "-----"))

    # prepare data
    df <- out2_resp1[[i]]
    X <- df |>
      select(As:Sn) |>
      as.matrix.data.frame()
    C <- df |>
      bind_cols(
        data.frame(model.matrix(~ race-1, data =
          mutate(df, race = as.factor(race))))
      ) |>
      select(race2:race5, smoke:bmi) |>
      as.matrix.data.frame()
    Y <- df$y

    # fit model for d = {1, 2, 3, 4, 5} and save time
    list_times <- vector(mode = "list", length = 2)

    set.seed(0)
    start.time <- Sys.time()
  }
}

```

```

mod1 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 1)
mod2 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 2)
mod3 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 3)
mod4 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 4)
end.time <- Sys.time()
list_times[[1]] <- end.time - start.time

ind <- which.min(c(mod1$waic, mod2$waic, mod3$waic, mod4$waic))

print(paste0("----- chose ", ind, " -----"))

start.time <- Sys.time()
mod <- NLint(Y = Y, X = X, C = C,
                nIter = 50000, nBurn = 25000, ns = ind)
end.time <- Sys.time()
list_times[[2]] <- end.time - start.time

bsr_times[[i]] <- list_times

# save model and remove from memory
write_rds(mod, file =
            paste0("mods/bsr_lgf_", names(out2_resp1)[i], "_", i,
                   ".RDS"))
write_rds(list_times, file =
            paste0("times/bsr_lgf_", names(out2_resp1)[i], "_", i,
                   ".RDS"))

rm(mod1, mod2, mod3, mod4, mod)
}

write_rds(bsr_times, file = "bsr_lgf_times.RDS")
# return(bsr_times)
}

# send all simulated datasets to hpc
for(i in seq(1, 1601, by = 100)) {
  slurm_call(
    run_bsr_sm,
    params = list(vector = i:(i+99)),
    global_objects = c('out2_resp1'),
    jobname = paste0("bsr_lg", str_pad(ceiling(i/100), 2, pad = "0")),
    slurm_options = list(mem = '8G')
  )
}

```

Next, we fit stratified models with an interaction between the categorical race variable and a chemical.

```

#####
# stratified bkmr, smaller size
#####

out1_resp1_re <- read_rds("sim/sim_resp_sm_re.RDS")

run_bkmr_sm_re <- function(vector) {
  bkmr_times <- vector(mode = "list", length = length(vector))

```

```

# create folder for model output
if(!dir.exists("mods")) {
  dir.create("mods")
}
if(!dir.exists("times")) {
  dir.create("times")
}

for(i in vector) {
  print(paste0("----- run ", i, "-----"))

  # prepare data
  df_full <- out1_resp1_re[[i]]

  # for each race level, run bmkr
  list_times <- vector(mod = "list", length = 6)
  list_mods <- vector(mod = "list", length = 6)

  set.seed(0)
  for(j in 1:5) {
    df <- df_full[df_full$race == j, ]
    Z <- df |>
      select(As:Sn)
    X <- df |>
      select(smoke:bmi)
    y <- df$y

    # fit model and save time
    start.time <- Sys.time()
    mod <- tryCatch({
      kmbayes(y = y, Z = Z, X = X,
              iter = 50000, verbose = FALSE, varsel = TRUE)
    }, error = function(e) {
      NA
    })
    end.time <- Sys.time()
    list_times[[j]] <- end.time - start.time
    list_mods[[j]] <- mod
  }

  # combine 1-3 r/e
  df <- df_full[df_full$race %in% c(1, 2, 3), ]
  Z <- df |>
    select(As:Sn)
  X <- df |>
    select(smoke:bmi)
  y <- df$y

  # fit model and save time
  start.time <- Sys.time()
  mod <- tryCatch({
    kmbayes(y = y, Z = Z, X = X,
            iter = 50000, verbose = FALSE, varsel = TRUE)
  }, error = function(e) {
    NA
  })
  end.time <- Sys.time()
  list_times[[6]] <- end.time - start.time
  list_mods[[6]] <- mod

  bkmr_times[[i]] <- list_times
  # save model and remove from memory
  write_rds(list_mods, file =

```

```

        paste0("mods/bkmr_sm_", names(out1_resp1_re)[i], "_", i, ".RDS"))
write_rds(list_times, file =
            paste0("times/bkmr_smf_", names(out1_resp1_re)[i], "_", i, ".RDS"))
rm(mod)
}
# write_rds(bkmr_times, file = "bkmr_sm_times.RDS")
return(bkmr_times)
}

# send to hpc
ujob01 <- slurm_call(
  run_bkmr_sm_re, params = list(vector = 1:100),
  global_objects = c('out1_resp1_re'),
  jobname = 'ksmre01',
  slurm_options = list(mem = '8G'))

ujob02 <- slurm_call(
  run_bkmr_sm_re, params = list(vector = 101:200),
  global_objects = c('out1_resp1_re'),
  jobname = 'ksmre02',
  slurm_options = list(mem = '8G'))

ujob03 <- slurm_call(
  run_bkmr_sm_re, params = list(vector = 201:300),
  global_objects = c('out1_resp1_re'),
  jobname = 'ksmre03',
  slurm_options = list(mem = '8G'))

ujob04 <- slurm_call(
  run_bkmr_sm_re, params = list(vector = 301:400),
  global_objects = c('out1_resp1_re'),
  jobname = 'ksmre04',
  slurm_options = list(mem = '8G'))

```

```

#####
# stratified bkmr, larger size
#####

out2_resp1_re <- read_rds("sim/sim_resp_lg_re.RDS")

run_bkmr_lg_re <- function(vector) {
  bkmr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output
  if(!dir.exists("mods")) {
    dir.create("mods")
  }
  if(!dir.exists("times")) {
    dir.create("times")
  }

  for(i in vector) {
    print(paste0("----- run ", i, "-----"))

    # prepare data
    df_full <- out2_resp1_re[[i]]

    # for each race level, run bmkr
    list_times <- vector(mod = "list", length = 5)
    list_mods <- vector(mod = "list", length = 5)

    set.seed(0)
    for(j in 1:5) {

```

```

df <- df_full[df_full$race == j, ]
Z <- df |>
  select(As:Sn)
X <- df |>
  select(smoke:bmi)
y <- df$y

# fit model and save time
start.time <- Sys.time()
mod <- kmbayes(y = y, Z = Z, X = X,
                 iter = 50000, verbose = FALSE, varsel = TRUE)
end.time <- Sys.time()
list_times[[j]] <- end.time - start.time
list_mods[[j]] <- mod
}

bkmr_times[[i]] <- list_times
# save model and remove from memory
write_rds(list_mods, file =
  paste0("mods/bkmr_lg_", names(out2_resp1_re)[i], "_", i, ".RDS"))
write_rds(list_times, file =
  paste0("times/bkmr_lgf_", names(out2_resp1_re)[i], "_", i, ".RDS"))
rm(mod)
}
# write_rds(bkmr_times, file = "bkmr_lg_times_re.RDS")
return(bkmr_times)
}

# send to hpc
tjob01 <- slurm_call(
  run_bkmr_lg_re, params = list(vector = 1:100),
  global_objects = c('out2_resp1_re'),
  jobname = 'klgre01',
  slurm_options = list(mem = '8G'))

tjob02 <- slurm_call(
  run_bkmr_lg_re, params = list(vector = 101:200),
  global_objects = c('out2_resp1_re'),
  jobname = 'klgre02',
  slurm_options = list(mem = '8G'))

tjob03 <- slurm_call(
  run_bkmr_lg_re, params = list(vector = 201:300),
  global_objects = c('out2_resp1_re'),
  jobname = 'klgre03',
  slurm_options = list(mem = '8G'))

tjob04 <- slurm_call(
  run_bkmr_lg_re, params = list(vector = 301:400),
  global_objects = c('out2_resp1_re'),
  jobname = 'klgre04',
  slurm_options = list(mem = '8G'))

#####
## stratified bsr, smaller size
#####

out1_resp1_re <- read_rds("sim/sim_resp_sm_re.RDS")

run_bsr_sm_re <- function(vector) {
  bsr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output

```

```

if(!dir.exists("mods")) {
  dir.create("mods")
}
if(!dir.exists("times")) {
  dir.create("times")
}

# sometimes bsr would stop prematurely...
# so this code finds the index of the last model run
list_files <- list.files("mods", full.names = TRUE)
nums <- as.numeric(sub(".+_(.+)d.+", "\\\\"1", list_files))
if(length(nums) == 0) {
  final <- 0
  starting <- min(vector)
} else {
  final <- max(nums)
  starting <- final + 1
}
if(file.exists("final.txt")) {
  write(paste0("final ran = ", final, ", starting at ", starting), "final.txt", append = T)
} else {
  writeLines(paste0("final ran = ", final, ", starting at ", starting), "final.txt")
}

for(i in starting:max(vector)) {
  print(paste0("----- run ", i, "-----"))

  # prepare data
  df_full <- out1_resp1_re[[i]]

  # for each race level, run bsr
  list_times <- vector(mod = "list", length = 6)
  list_mods <- vector(mod = "list", length = 6)

  set.seed(0)
  for(j in 1:5) {
    df <- df_full[df_full$race == j, ]
    X <- df |>
      select(As:Sn) |>
      as.matrix.data.frame()
    C <- df |>
      select(smoke:bmi) |>
      as.matrix.data.frame()
    Y <- df$y

    # waic for choosing df
    list_times_small <- vector(mode = "list", length = 2)

    start.time <- Sys.time()
    mod1 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 1)
    mod2 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 2)
    mod3 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 3)
    mod4 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 4)
    end.time <- Sys.time()
    list_times_small[[1]] <- end.time - start.time

    ind <- which.min(c(mod1$waic, mod2$waic, mod3$waic, mod4$waic))

    # fit model and save time
  }
}

```

```

start.time <- Sys.time()
mod <- tryCatch({
  NLint(Y = Y, X = X, C = C,
    nIter = 50000, nBurn = 25000, ns = ind)
}, error = function(e) {
  NA
})
end.time <- Sys.time()
list_times_small[[2]] <- end.time - start.time

bsr_times[[j]] <- list_times_small
list_mods[[j]] <- mod
}

# combine 1-3 r/e
df <- df_full[df_full$race %in% c(1, 2, 3), ]
X <- df |>
  select(As:Sn) |>
  as.matrix.data.frame()
C <- df |>
  select(smoke:bmi) |>
  as.matrix.data.frame()
Y <- df$y

# waic for choosing df
list_times_small <- vector(mode = "list", length = 2)

start.time <- Sys.time()
mod1 <- NLint(Y = Y, X = X, C = C,
  nIter = 5000, nBurn = 2500, ns = 1)
mod2 <- NLint(Y = Y, X = X, C = C,
  nIter = 5000, nBurn = 2500, ns = 2)
mod3 <- NLint(Y = Y, X = X, C = C,
  nIter = 5000, nBurn = 2500, ns = 3)
mod4 <- NLint(Y = Y, X = X, C = C,
  nIter = 5000, nBurn = 2500, ns = 4)
end.time <- Sys.time()
list_times_small[[1]] <- end.time - start.time

ind <- which.min(c(mod1$waic, mod2$waic, mod3$waic, mod4$waic))

# fit model and save time
start.time <- Sys.time()
mod <- tryCatch({
  NLint(Y = Y, X = X, C = C,
    nIter = 50000, nBurn = 25000, ns = ind)
}, error = function(e) {
  NA
})
end.time <- Sys.time()
list_times_small[[2]] <- end.time - start.time

list_times[[6]] <- list_times_small
list_mods[[6]] <- mod

# save model and remove from memory
write_rds(list_mods, file =
  paste0("mods/bsr_sm_", names(out1_resp1_re)[i], "_",
    "df", ind, ".RDS"))
write_rds(list_times, file =
  paste0("times/bsr_sm_", names(out1_resp1_re)[i], "_",
    "df", ind, ".RDS"))

rm(mod1, mod2, mod3, mod4, mod)

```

```

}

return(bsr_times)
}

# send to hpc
vjob01 <- slurm_call(
  run_bsr_sm_re, params = list(vector = 1:100),
  global_objects = c('out1_resp1_re'),
  jobname = 'ssmre01',
  slurm_options = list(mem = '8G'))

vjob02 <- slurm_call(
  run_bsr_sm_re, params = list(vector = 101:200),
  global_objects = c('out1_resp1_re'),
  jobname = 'ssmre02',
  slurm_options = list(mem = '8G'))

vjob03 <- slurm_call(
  run_bsr_sm_re, params = list(vector = 201:300),
  global_objects = c('out1_resp1_re'),
  jobname = 'ssmre03',
  slurm_options = list(mem = '8G'))

vjob04 <- slurm_call(
  run_bsr_sm_re, params = list(vector = 301:400),
  global_objects = c('out1_resp1_re'),
  jobname = 'ssmre04',
  slurm_options = list(mem = '8G'))

#####
# stratified bsr, larger size
#####

out2_resp1_re <- read_rds("sim/sim_resp_lg_re.RDS")

run_bsr_lg_re <- function(vector) {
  bsr_times <- vector(mode = "list", length = length(vector))

  # create folder for model output
  if(!dir.exists("mods")) {
    dir.create("mods")
  }
  if(!dir.exists("times")) {
    dir.create("times")
  }

  # sometimes bsr would stop prematurely...
  # so this code finds the index of the last model run
  list_files <- list.files("mods", full.names = TRUE)
  nums <- as.numeric(sub(".+_(.+)d.+", "\\\\"1", list_files))
  if(length(nums) == 0) {
    final <- 0
    starting <- min(vector)
  } else {
    final <- max(nums)
    starting <- final + 1
  }
  if(file.exists("final.txt")) {
    write(paste0("final ran = ", final, ", starting at ", starting), "final.txt", append = T)
  } else {
    writeLines(paste0("final ran = ", final, ", starting at ", starting), "final.txt")
  }
}

```

```

for(i in starting:max(vector)) {
  print(paste0("----- run ", i, "-----"))

  # prepare data
  df_full <- out2_resp1_re[[i]]

  # for each race level, run bsr
  list_times <- vector(mod = "list", length = 6)
  list_mods <- vector(mod = "list", length = 6)

  set.seed(0)
  for(j in 1:5) {
    df <- df_full[df_full$race == j, ]
    X <- df |>
      select(As:Sn) |>
      as.matrix.data.frame()
    C <- df |>
      select(smoke:bmi) |>
      as.matrix.data.frame()
    Y <- df$y

    # waic for choosing df
    list_times_small <- vector(mode = "list", length = 2)

    start.time <- Sys.time()
    mod1 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 1)
    mod2 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 2)
    mod3 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 3)
    mod4 <- NLint(Y = Y, X = X, C = C,
                  nIter = 5000, nBurn = 2500, ns = 4)
    end.time <- Sys.time()
    list_times_small[[1]] <- end.time - start.time

    ind <- which.min(c(mod1$waic, mod2$waic, mod3$waic, mod4$waic))

    # fit model and save time
    start.time <- Sys.time()
    mod <- tryCatch({
      NLint(Y = Y, X = X, C = C,
            nIter = 50000, nBurn = 25000, ns = ind)
    }, error = function(e) {
      NA
    })
    end.time <- Sys.time()
    list_times_small[[2]] <- end.time - start.time

    bsr_times[[j]] <- list_times_small
    list_mods[[j]] <- mod
  }

  # combine 1-3 r/e
  df <- df_full[df_full$race %in% c(1, 2, 3), ]
  X <- df |>
    select(As:Sn) |>
    as.matrix.data.frame()
  C <- df |>
    select(smoke:bmi) |>
    as.matrix.data.frame()
  Y <- df$y
}

```

```

# waic for choosing df
list_times_small <- vector(mode = "list", length = 2)

start.time <- Sys.time()
mod1 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 1)
mod2 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 2)
mod3 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 3)
mod4 <- NLint(Y = Y, X = X, C = C,
                nIter = 5000, nBurn = 2500, ns = 4)
end.time <- Sys.time()
list_times_small[[1]] <- end.time - start.time

ind <- which.min(c(mod1$waic, mod2$waic, mod3$waic, mod4$waic))

# fit model and save time
start.time <- Sys.time()
mod <- tryCatch({
  NLint(Y = Y, X = X, C = C,
        nIter = 50000, nBurn = 25000, ns = ind)
}, error = function(e) {
  NA
})
end.time <- Sys.time()
list_times_small[[2]] <- end.time - start.time

list_times[[6]] <- list_times_small
list_mods[[6]] <- mod

# save model and remove from memory
write_rds(list_mods, file =
  paste0("mods/bsr_lg_", names(out2_resp1_re)[i], "_", i,
         "df", ind, ".RDS"))
write_rds(list_times, file =
  paste0("times/bsr_lg_", names(out2_resp1_re)[i], "_", i,
         "df", ind, ".RDS"))

rm(mod1, mod2, mod3, mod4, mod)
}

# write_rds(bsr_times, file = "bsr_lgf_times.RDS")
return(bsr_times)
}

# send to hpc
wjob01 <- slurm_call(
  run_bsr_lg_re, params = list(vector = 1:100),
  global_objects = c('out2_resp1_re'),
  jobname = 'slgre01',
  slurm_options = list(mem = '8G'))

wjob02 <- slurm_call(
  run_bsr_lg_re, params = list(vector = 101:200),
  global_objects = c('out2_resp1_re'),
  jobname = 'slgre02',
  slurm_options = list(mem = '8G'))

wjob03 <- slurm_call(
  run_bsr_lg_re, params = list(vector = 201:300),
  global_objects = c('out2_resp1_re'),
  jobname = 'slgre03',
  slurm_options = list(mem = '8G'))

```

```
wjob04 <- slurm_call(
  run_bsr_lg_re, params = list(vector = 301:400),
  global_objects = c('out2_resp1_re'),
  jobname = 'slgre04',
  slurm_options = list(mem = '8G'))
```

B.2.5 Code for Chapter 4.3:

Extracting results

Here, we extract results from our simulation. We use the `rslurm`, `bkmr`, and `NLInteraction` packages in this section. This code was run on the Amherst HPC RStudio server.

First, we extract p-values from the multiple linear regression models.

```
# naive small, chemxchem models
mlr_sm <- read_rds("sim/mlr_mods_sm.RDS")

mlrsm_pval <- 1:1700 |>
  map_df(\(x) {
    mod <- mlr_sm[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(mlrsm_pval, "sim/_mlr/pvals_sm.csv")

# naive large, chemxchem models
mlr_lg <- read_rds("sim/mlr_mods_lg.RDS")

mlrlg_pval <- 1:1700 |>
  map_df(\(x) {
    mod <- mlr_lg[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(mlrlg_pval, "sim/_mlr/pval_lg.csv")

# oracle small, chemxchem models
orac_sm <- read_rds("sim/oracle_mods_sm.RDS")

oracsm_pval <- 1:1700 |>
  map_df(\(x) {
    mod <- orac_sm[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(oracsm_pval, "sim/_oracle/pvals_sm.csv")
```

```

# oracle large, chemxchem models
orac_lg <- read_rds("sim/oracle_mods_lg.RDS")

oraclg_pval <- 1:1700 |>
  map_df(\(x) {
    mod <- orac_lg[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(oraclg_pval, "sim/_oracle/pvallg.csv")

# naive small, chemxcov models
mlr_sm_re <- read_rds("sim/mlr_mods_sm_re.RDS")

mlrsmre_pval <- 1:400 |>
  map_df(\(x) {
    mod <- mlr_sm_re[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(mlrsmre_pval, "sim/_mlr/pvalsmpre.csv")

# naive large, chemxcov models
mlr_lg_re <- read_rds("sim/mlr_mods_lg_re.RDS")

mlrlgre_pval <- 1:400 |>
  map_df(\(x) {
    mod <- mlr_lg_re[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(mlrlgre_pval, "sim/_mlr/pvallgre.csv")

# oracle small, chemxcov models
orac_sm_re <- read_rds("sim/oracle_mods_sm_re.RDS")

oracsmre_pval <- 1:400 |>
  map_df(\(x) {
    mod <- orac_sm_re[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(oracsmre_pval, "sim/_oracle/pvalsmpre.csv")

# oracle large, chemxcov models
orac_lg_re <- read_rds("sim/oracle_mods_lg_re.RDS")

oraclgre_pval <- 1:400 |>
  map_df(\(x) {
    mod <- orac_lg_re[[x]]
    data.frame(summary(mod)$coefficients) |>
      rownames_to_column(var = "var") |>
      select(var, p = 5) |>
      mutate(case = x)
  })
write_csv(oraclgre_pval, "sim/_oracle/pvallgre.csv")

```

Now, we write some functions to extract output from BKMR and BSR models.

```
bivarinter_bkmr <- function(fit, z1, z2, qs.diff = c(0.25, 0.75),
                           qs.fixed = c(0.25, 0.75), q.rest = 0.5) {
  #' fit = bkmr model
  #' z1 = index of chemical 1
  #' z2 = index of chemical 2
  #' qs.diff = quantiles to calculate response diff for
  #' qs.fixed = quantiles to fix other chemical at
  #' q.rest = quantile to fix rest of chemicals at
  #
  #' note that order of z1 and z2 don't matter

  # extract fit
  y <- fit$y
  Z <- fit$Z
  X <- fit$X

  # fix all chems at q.rest
  point1 <- apply(Z[, z1], 2, quantile, q.rest)
  # fix z2 at lower
  point1[z2] <- quantile(Z[, z2], qs.fixed[1])
  # fix z1 at lower and upper
  point1[z1] <- quantile(Z[, z1], qs.diff[2])
  point1[z1] <- quantile(Z[, z1], qs.diff[1])
  newz.q1 <- rbind(point1, point1) # has all lower quantiles of z2
  # fix all chems at q.rest
  point2 <- apply(Z[, z2], 2, quantile, q.rest)
  # fix z2 at higher
  point2[z2] <- quantile(Z[, z2], qs.fixed[2])
  # fix z1 at lower and upper
  point2[z1] <- quantile(Z[, z1], qs.diff[2])
  point2[z1] <- quantile(Z[, z1], qs.diff[1])
  newz.q2 <- rbind(point2, point2) # has all upper quantiles of z2

  # prepare
  cc <- c(-1 * c(-1, 1), c(-1, 1))
  newz <- rbind(newz.q1, newz.q2)

  # default to using approximate calculation
  preds <- ComputePostmeanHnew(fit = fit, y = y, Z = Z, X = X, Znew = newz)

  # extract intervals
  int <- drop(cc %*% preds$postmean)
  int.se <- drop(sqrt(cc %*% preds$postvar %*% cc))
  ints <- c(est = int, sd = int.se)

  return(data.frame(z1 = colnames(Z)[z1], z2 = colnames(Z)[z2],
                    est = ints["est"], sd = ints["sd"], row.names = NULL))
}

trivarinter_bkmr <- function(fit, z1, z2, z3, qs.diff = c(0.25, 0.75),
                               qs.fixed = c(0.25, 0.75), q.rest = 0.5) {
  #' fit = bkmr model
  #' z1 = index of chemical 1
  #' z2 = index of chemical 2
  #' z3 = index of chemical 3
  #' qs.diff = quantiles to calculate response diff for
  #' qs.fixed = quantiles to fix other chemical at
  #' q.rest = quantile to fix rest of chemicals at
```

```

#'
#' note that order of z1, z2, z3 don't matter

# extract fit
y <- fit$y
Z <- fit$Z
X <- fit$X

df <- purrr::map_df(1:3, \(\text{x}\) {
  if(\text{x} == 1) {
    c1 <- z1; c2 <- z2; c3 <- z3
  } else if (\text{x} == 2) {
    c1 <- z2; c2 <- z3; c3 <- z1
  } else {
    c1 <- z3; c2 <- z1; c3 <- z2
  }

  # fix all chems at q.rest
  point1 <- point1 <- apply(Z, 2, quantile, q.rest)
  # fix c2 at lower
  point1[c2] <- point1[c2] <- quantile(Z[, c2], qs.fixed[1])
  # fix c3 at lower
  point1[c3] <- point1[c3] <- quantile(Z[, c3], qs.fixed[1])
  # fix c1 at lower and upper
  point1[c1] <- quantile(Z[, c1], qs.diff[2])
  point1[c1] <- quantile(Z[, c1], qs.diff[1])
  newz.q1 <- rbind(point1, point2) # has all lower quantiles of c2, c3
  # fix all chems at q.rest
  point2 <- point2 <- apply(Z, 2, quantile, q.rest)
  # fix c2 at higher
  point2[c2] <- point2[c2] <- quantile(Z[, c2], qs.fixed[2])
  # fix c3 at higher
  point2[c3] <- point2[c3] <- quantile(Z[, c3], qs.fixed[2])
  # fix c1 at lower and upper
  point2[c1] <- quantile(Z[, c1], qs.diff[2])
  point2[c1] <- quantile(Z[, c1], qs.diff[1])
  newz.q2 <- rbind(point1, point2) # has all upper quantiles of c2, c3

  # prepare
  cc <- c(-1 * c(-1, 1), c(-1, 1))
  newz <- rbind(newz.q1, newz.q2)

  # default to using approximate calculation
  preds <- ComputePostmeanHnew(fit = fit, y = y, Z = Z, X = X, Znew = newz)

  # extract intervals
  int <- drop(cc %*% preds$postmean)
  int.se <- drop(sqrt(cc %*% preds$postvar %*% cc))
  ints <- c(est = int, sd = int.se)

  return(data.frame(variable = colnames(Z)[c1], fixedat1 = colnames(Z)[c2],
                     fixedat2 = colnames(Z)[c3],
                     est = ints["est"], sd = ints["sd"], row.names = NULL))
})

return(df)
}

trivarsurf_bkmr <- function(fit, z1, z2, z3, qs.diff = c(0.1, 0.5, 0.9),
                           q.fixed = 0.5, ngrid = 50) {
  #' fit = bkmr model
  #' z1 = index of chemical 1
  #' z2 = index of chemical 2
  #' z3 = index of chemical 3
}

```

```

#' qs.diff = quantiles to calculate response diff for
#' q.fixed = quantiles to fix rest of chemicals at
#'
#' note that order of z1, z2, z3 don't matter

# call from fit
y <- fit$y
Z <- fit$Z
X <- fit$X
z.names <- colnames(Z)

df <- purrr::map_df(1:3, \x) {
  if(x == 1) {
    c1 <- z1; c2 <- z2; c3 <- z3
  } else if (x == 2) {
    c1 <- z2; c2 <- z3; c3 <- z1
  } else {
    c1 <- z3; c2 <- z1; c3 <- z2
  }

  # create new ordering
  ord <- c(c1, c2, c3, setdiff(1:ncol(Z), c(c1, c2, c3)))

  # create grid of z-values to evaluate at
  z1.grid <- seq(min(Z[, ord[1]]), max(Z[, ord[1]]), length = ngrid)
  z2.grid <- quantile(Z[, ord[2]], probs = qs.diff)
  z3.grid <- quantile(Z[, ord[3]], probs = qs.diff)
  z.all <- c(list(z1.grid), list(z2.grid), list(c(-99)))
  if (ncol(Z) > 3) {
    z.others <- lapply(4:ncol(Z), function(x) quantile(Z[, ord[x]], q.fixed))
    z.all <- c(z.all, z.others)
  }
  newz.grid <- expand.grid(z.all)
  newz.grid[, 3] <- rep(z3.grid, each = ngrid)
  z1save <- newz.grid[, 1]
  colnames(newz.grid) <- colnames(Z)[ord]
  newz.grid <- newz.grid[, colnames(Z)]

  # evaluate prediction, assume approx fit
  preds <- ComputePostmeanHnew(fit = fit, y = y, Z = Z, X = X, Znew = newz.grid)
  preds.mean <- preds$postmean
  preds.se <- sqrt(diag(preds$postvar))

  # return
  return(data.frame(z1_val = z1save,
                    z23_q = rep(qs.diff, each = ngrid),
                    est = preds.mean,
                    se = preds.se,
                    z1_name = rep(colnames(Z)[c1], length(z1save)),
                    z2_name = rep(colnames(Z)[c2], length(z1save)),
                    z3_name = rep(colnames(Z)[c3], length(z1save))))
}

return(df)
}

bivarsurf_bsr <- function(NLmod, X, C, j1, j2, gridLength = 50,
                           quantile_j2 = c(0.1, 0.5, 0.9), quantile_rest = 0.5) {
  #' NLmod = bsr model
  #' X = matrix or dataframe of chemical values used to fit model
  #' C = matrix or dataframe of covariate values used to fit model
  #' gridLength = number of points to estimate response at
  #' j1 = index of first chemical
  #' j2 = index of second chemical

```

```

#' quantile_j2 = vector of quantiles to fix second chemical at
#' quantile_rest = quantile to fix other chemicals at
#'
##' NOTE order of j1 and j2 doesn't matter

# define parameters
n <- dim(X)[1]
ns <- NLmod$ns
k <- NLmod$k
p <- dim(X)[2]
Xstar <- array(NA, dim = c(n, p, ns + 1))
Xstar[, , 1] <- 1
for (j in 1:p) {
  Xstar[, j, 2:(ns + 1)] <- scale(splines::ns(X[, j], df = ns))
}

# define posteriors
zetaPost <- NLmod$posterior$zeta
betaList <- NLmod$posterior$beta
betaCPost <- NLmod$posterior$betaC
totalScans <- dim(NLmod$posterior$betaC)[2]
nChains <- dim(NLmod$posterior$betaC)[1]

# create design of covariates
pc <- dim(C)[2]
NewDesignC <- matrix(NA, gridLength, pc + 1)
NewDesignC[, 1] <- 1
for (jc in 1:pc) {
  NewDesignC[, jc + 1] <- mean(C[, jc])
}

# for each quantile of j2
df <- purrr::map_df(quantile_j2, \(\text{quantile\_j2}\) {
  # create design of chemicals
  n <- dim(X)[1]
  NewDesignMat <- matrix(NA, gridLength, p)
  for (j in 1:p) {
    NewDesignMat[, j] <- quantile(X[, j], quantile_rest)
  }
  NewDesignMat[, j1] <- seq(quantile(X[, j1], 0.025),
                            quantile(X[, j1], 0.975), length = gridLength)
  NewDesignMat[, j2] <- quantile(X[, j2], quantile_j2)
  NewDesign <- array(NA, dim = c(gridLength, p, ns + 1))
  NewDesign[, , 1] <- 1
  for (j in 1:p) {
    temp_ns_object <- splines::ns(X[, j], df = ns)
    temp_sds <- apply(temp_ns_object, 2, sd)
    temp_means <- apply(temp_ns_object, 2, mean)
    NewDesign[, j, 2:(ns + 1)] <- t((t(predict(temp_ns_object,
                                                NewDesignMat[, j])) - temp_means)/temp_sds)
  }
}

# generate predictions
predictions <- NLinteraction:::PredictionsMixture(
  XstarOld = Xstar, XstarNew = NewDesign,
  designC = NewDesignC, totalScans = totalScans, nChains = nChains,
  zetaPost = zetaPost, betaList = betaList, betaCPost = betaCPost,
  k = k, ns = ns)

# get surface
return(data.frame(
  j1val = NewDesignMat[, j1],
  j2quant = rep(quantile_j2, gridLength),
  est = apply(predictions$PredictedPost, 3, mean),

```

```

        lower = apply(predictions$PredictedPost, 3, quantile, 0.025),
        upper = apply(predictions$PredictedPost, 3, quantile, 0.975)
    ))
}
return(df)
}

trivarsurf_bsr <- function(NLmod, X, C, j1, j2, j3, gridLength = 50,
                           quantile_j23 = c(0.1, 0.5, 0.9), quantile_rest = 0.5) {
  #' NLmod = bsr model
  #' X = matrix or dataframe of chemical values used to fit model
  #' C = matrix or dataframe of covariate values used to fit model
  #' gridLength = number of points to estimate response at
  #' j1 = index of first chemical, chemical used as primary predictor
  #' j2 = index of second chemical
  #' j3 = index of third chemical
  #' quantile_j23 = vector of quantiles to fix second and third chemicals at
  #' quantile_rest = quantile to fix other chemicals at
  #
  #' NOTE order of j1, j2, j3 matters

  # define parameters
  n <- dim(X)[1]
  ns <- NLmod$ns
  k <- NLmod$k
  p <- dim(X)[2]
  Xstar <- array(NA, dim = c(n, p, ns + 1))
  Xstar[, , 1] <- 1
  for (j in 1:p) {
    Xstar[, j, 2:(ns + 1)] <- scale(splines::ns(X[, j], df = ns))
  }

  # define posteriors
  zetaPost <- NLmod$posterior$zeta
  betaList <- NLmod$posterior$beta
  betaCPost <- NLmod$posterior$betaC
  totalScans <- dim(NLmod$posterior$betaC)[2]
  nChains <- dim(NLmod$posterior$betaC)[1]

  # create design of covariates
  pc <- dim(C)[2]
  NewDesignC <- matrix(NA, gridLength, pc + 1)
  NewDesignC[, 1] <- 1
  for (jc in 1:pc) {
    NewDesignC[, jc + 1] <- mean(C[, jc])
  }

  # for each quantile of j2, j3
  df <- purrr::map_df(quantile_j23, \(\text{quantile\_j23}\) {
    # create design of chemicals
    n <- dim(X)[1]
    NewDesignMat <- matrix(NA, gridLength, p)
    for (j in 1:p) {
      NewDesignMat[, j] <- quantile(X[, j], quantile_rest)
    }
    NewDesignMat[, j1] <- seq(quantile(X[, j1], 0.025),
                               quantile(X[, j1], 0.975), length = gridLength)
    NewDesignMat[, j2] <- quantile(X[, j2], quantile_j23)
    NewDesignMat[, j3] <- quantile(X[, j3], quantile_j23)
    NewDesign <- array(NA, dim = c(gridLength, p, ns + 1))
    NewDesign[, , 1] <- 1
    for (j in 1:p) {
      temp_ns_object <- splines::ns(X[, j], df = ns)
      temp_sds <- apply(temp_ns_object, 2, sd)
    }
  })
}

```

```

    temp_means <- apply(temp_ns_object, 2, mean)
    NewDesign[, j, 2:(ns + 1)] <- t((t(predict(temp_ns_object,
                                                NewDesignMat[, j])) - temp_means)/temp_sds)
}

# generate predictions
predictions <- NLinteraction:::PredictionsMixture(
  XstarOld = Xstar, XstarNew = NewDesign,
  designC = NewDesignC, totalScans = totalScans, nChains = nChains,
  zetaPost = zetaPost, betaList = betaList, betaCPost = betaCPost,
  k = k, ns = ns)

# get surface
return(data.frame(
  j1val = NewDesignMat[, j1],
  j23quant = rep(quantile_j23, gridLength),
  est = apply(predictions$PredictedPost, 3, mean),
  lower = apply(predictions$PredictedPost, 3, quantile, 0.025),
  upper = apply(predictions$PredictedPost, 3, quantile, 0.975)
))
})
return(df)
}

```

Next, we extract output from BKMR models run on smaller and larger size simulated datasets, including the base case and models with interactions between chemicals.

```

# load packages
library(tidyverse)
library(bkmr)

#####
# extract bkmr smalls!
#####

# get file paths of models
list_files <- list.dirs(".", full.names = FALSE, recursive = FALSE)
list_ksm <- list_files[grep("_rslurm_bkmr_sm", list_files)]

ksm_subf <- list.dirs(list_ksm, full.names = TRUE, recursive = TRUE)
ksm_mod <- ksm_subf[grep("mods", ksm_subf)]

ksm_labels <- gsub("\\D", "", ksm_mod)
ksm_labels <- ifelse(ksm_labels == "", 1, as.numeric(ksm_labels))

# get paths
ksm_paths <- ksm_mod |>
  purrr::map(\(x) {
    list.files(x, full.names = TRUE)
  }) |>
  setNames(nm = ksm_labels)

# extract PIP's
ksm_pips <- names(ksm_paths) |>
  purrr::map_df(\(x) {
    ksm_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
      })
  })

```

```

    result <- data.frame(
      ExtractPIPs(bkmr)
    ) |>
      mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\"1", y)))
    rm(bkmr)
    return(result)
  }) |>
  mutate(case = x)
}
write_csv(ksm_pips, "sim/bkmr_sm/pips.csv")

# extract univariate relationships
ksm_univ <- names(ksm_paths) |>
  purrr::map_df(\(x) {
    ksm_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
        result <- data.frame(
          PredictorResponseUnivar(bkmr)
        ) |>
          mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\"1", y)))
        rm(bkmr)
        return(result)
      }) |>
      mutate(case = x)
  })
write_csv(ksm_univ, "sim/bkmr_sm/univ_exresp.csv")

# extract bivariate relationships
ksm_biv <- names(ksm_paths)[2:13] |> # only for 2-way interaction
purrr::map_df(\(x) {
  indices <- case_when(
    x %in% 2:5 ~ c(4, 5), # Hg and Ni
    x %in% 6:9 ~ c(1, 2), # Cd and As
    x %in% 10:13 ~ c(3, 5) # Co and Ni
  )
  ksm_paths[[x]] |>
    purrr::map_df(\(y) {
      bkmr <- read_rds(y)
      bivar <- PredictorResponseBivar(bkmr,
                                      z.pairs = rbind(indices), verbose = FALSE)
      result <- data.frame(
        PredictorResponseBivarLevels(
          pred.resp.df = bivar,
          Z = bkmr$Z, qs = c(0.1, 0.5, 0.9))
      ) |>
        mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\"1", y)))
      rm(bkmr)
      return(result)
    }) |>
    mutate(case = x)
  })
ksm_biv_nona <- na.omit(ksm_biv)
write_csv(ksm_biv_nona, "sim/bkmr_sm/biv_exresp.csv")

# load in fxn
source("extract_fxns.R")

# extract trivariate relationships
ksm_triv <- names(ksm_paths)[14:17] |> # only for 3-way
purrr::map_df(\(x) {
  message("starting ", x)
  ksm_paths[[x]] |>

```

```

purrr::map_df(\(y) {
  bkmr <- read_rds(y)
  result <- trivarsurf_bkmr(bkmr, 4, 5, 6,
    qs.diff = c(0.1, 0.5, 0.9),
    q.fixed = 0.5, ngrid = 50) |>
    mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\$1", y)))
  return(result)
}) |>
  mutate(case = x)
})
write_csv(ksm_triv, "sim/bkmr_sm/triv_exresp.csv")

# extract one vs. rest bivariate interactions
ksm_ints <- names(ksm_paths)[2:17] |>
  purrr::map_df(\(x) {
    print(paste0("starting ", x))
    indices <- case_when(
      x %in% 2:5 ~ list(c(4, 5)), # Hg and Ni
      x %in% 6:9 ~ list(c(1, 2)), # Cd and As
      x %in% 10:13 ~ list(c(3, 5)), # Co and Ni
      x %in% 14:17 ~ list(c(4, 5, 6)) # Hg, Ni, Tl
    )
    ksm_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
        ints <- SingVarIntSummaries(bkmr,
          which.z = indices[[1]],
          qs.diff = c(0.25, 0.75),
          qs.fixed = c(0.25, 0.75),
          method = "approx")
        result <- data.frame(ints) |>
          mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\$1", y)))
        rm(bkmr)
        return(result)
      }) |>
      mutate(case = x)
    })
  write_csv(ksm_ints, "sim/bkmr_sm/int.csv")

# load in fns
source("extract_fxns.R")

# extract one vs. other bivariate interactions
ksm_intb <- names(ksm_paths)[2:13] |> # only for two-way
  purrr::map_df(\(x) {
    print(paste0("starting ", x))
    indices <- case_when(
      x %in% 2:5 ~ list(c(4, 5)), # Hg and Ni
      x %in% 6:9 ~ list(c(1, 2)), # Cd and As
      x %in% 10:13 ~ list(c(3, 5)) # Co and Ni
    )
    ksm_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
        ints <- bivarinter_bkmr(bkmr,
          z1 = indices[[1]][1],
          z2 = indices[[1]][2],
          qs.diff = c(0.25, 0.75),
          qs.fixed = c(0.25, 0.75),
          q.rest = 0.5)
        result <- data.frame(ints) |>
          mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\$1", y)))
        rm(bkmr)
        return(result)
      })
  })

```

```

    }) |>
    mutate(case = x)
  })
write_csv(ksm_intb, "sim/bkmr_sm/int_bivar.csv")

# extract one vs. 2 others trivariate interactions
ksm_intt <- names(ksm_paths)[14:17] |> # only for three-way
purrr::map_df(\(x) {
  print(paste0("starting ", x))
  ksm_paths[[x]] |>
    purrr::map_df(\(y) {
      bkmr <- read_rds(y)
      ints <- trivarinter_bkmr(bkmr,
        z1 = 4, z2 = 5, z3 = 6,
        qs.diff = c(0.25, 0.75),
        qs.fixed = c(0.25, 0.75),
        q.rest = 0.5)
      result <- data.frame(ints) |>
        mutate(trial = as.numeric(sub(".*_(_\\d+)\\.RDS", "\\\\1", y)))
      rm(bkmr)
      return(result)
    }) |>
    mutate(case = x)
  })
write_csv(ksm_intt, "sim/bkmr_sm/int_trivar.csv")

#####
# extract bkmr larges!
#####

list_files <- list.dirs(".", full.names = FALSE, recursive = FALSE)
list_klg <- list_files[grep("rslurm_bkmr_lg", list_files)]

klg_subbf <- list.dirs(list_klg, full.names = TRUE, recursive = TRUE)
klg_mod <- klg_subbf[grep("mods", klg_subbf)]

klg_labels <- gsub("\\D", "", klg_mod)
klg_labels <- ifelse(klg_labels == "", 1, as.numeric(klg_labels))

# get paths
klg_paths <- klg_mod |>
  purrr::map(\(x) {
    list.files(x, full.names = TRUE)
  }) |>
  setNames(nm = klg_labels)

# extract PIP's
klg_pips <- names(klg_paths) |>
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    klg_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
        result <- data.frame(
          ExtractPIPs(bkmr)
        ) |>
          mutate(trial = as.numeric(sub(".*_(_\\d+)\\.RDS", "\\\\1", y)))
        rm(bkmr)
        return(result)
      }) |>
      mutate(case = x)
  })
write_csv(klg_pips, "sim/bkmr_lg/pips.csv")

```

```

# extract univariate relationships
klg_univ <- names(klg_paths) |>
  purrr::map_df(\(x) {
    klg_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
        result <- data.frame(
          PredictorResponseUnivar(bkmr)
        ) |>
          mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\'1", y)))
        rm(bkmr)
        return(result)
      }) |>
        mutate(case = x)
  })
write_csv(klg_univ, "sim/bkmr_lg/univ_exresp.csv")

# extract bivariate relationships
klg_biv <- names(klg_paths)[2:13] |> # only for 2-way interaction
purrr::map_df(\(x) {
  print(paste0("starting at ", x))
  indices <- case_when(
    x %in% 2:5 ~ c(4, 5), # Hg and Ni
    x %in% 6:9 ~ c(1, 2), # Cd and As
    x %in% 10:13 ~ c(3, 5) # Co and Ni
  )
  klg_paths[[x]] |>
    purrr::map_df(\(y) {
      bkmr <- read_rds(y)
      bivar <- PredictorResponseBivar(bkmr,
                                      .pairs = rbind(indices), verbose = FALSE)
      result <- data.frame(
        PredictorResponseBivarLevels(
          pred.resp.df = bivar,
          Z = bkmr$Z, qs = c(0.1, 0.5, 0.9))
      ) |>
        mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\'1", y)))
      rm(bkmr)
      return(result)
    }) |>
      mutate(case = x)
  })
# write_csv(klg_biv, "sim/bkmr_lg/biv_exresp.csv")
# write_rds(klg_biv, "sim/bkmr_lg/biv_exresp.rds")
klg_biv_nona <- na.omit(klg_biv)
write_csv(klg_biv_nona, "sim/bkmr_lg/biv_exresp.csv")

# load in fns
source("extract_fxns.R")

# extract trivariate relationships
klg_triv <- names(klg_paths)[14:17] |> # only for 3-way
purrr::map_df(\(x) {
  message("starting ", x)
  klg_paths[[x]] |>
    purrr::map_df(\(y) {
      bkmr <- read_rds(y)
      result <- trivarsurf_bkmr(bkmr, 4, 5, 6,
                                 qs.diff = c(0.1, 0.5, 0.9),
                                 q.fixed = 0.5, ngrid = 50) |>
        mutate(trial = as.numeric(sub(".*_(\\d+)\\.RDS", "\\\\'1", y)))
      return(result)
    }) |>
})

```

```

        mutate(case = x)
    })
write_csv(klg_triv, "sim/bkmr_lg/triv_exresp.csv")

# extract one vs. rest bivariate interactions
klg_ints <- names(klg_paths)[2:17] |>
  purrr::map_df(\(x) {
    print(paste0("starting ", x))
    indices <- case_when(
      x %in% 2:5 ~ list(c(4, 5)), # Hg and Ni
      x %in% 6:9 ~ list(c(1, 2)), # Cd and As
      x %in% 10:13 ~ list(c(3, 5)), # Co and Ni
      x %in% 14:17 ~ list(c(4, 5, 6)) # Hg, Ni, Tl
    )
    klg_paths[[x]] |>
      purrr::map_df(\(y) {
        bkmr <- read_rds(y)
        ints <- SingVarIntSummaries(bkmr,
                                      which.z = indices[[1]],
                                      qs.diff = c(0.25, 0.75),
                                      qs.fixed = c(0.25, 0.75),
                                      method = "approx")
        result <- data.frame(ints) |>
          mutate(trial = as.numeric(sub(".*_(<\d+)>.RDS", "\\\\"1", y)))
        rm(bkmr)
        return(result)
      }) |>
      mutate(case = x)
    })
write_csv(klg_ints, "sim/bkmr_lg/intns.csv")

# load in fxa
source("extract_fxns.R")

# extract one vs. other bivariate interactions
klg_intb <- names(klg_paths)[2:13] |> # only for two-way
purrr::map_df(\(x) {
  print(paste0("starting ", x))
  indices <- case_when(
    x %in% 2:5 ~ list(c(4, 5)), # Hg and Ni
    x %in% 6:9 ~ list(c(1, 2)), # Cd and As
    x %in% 10:13 ~ list(c(3, 5)) # Co and Ni
  )
  klg_paths[[x]] |>
    purrr::map_df(\(y) {
      bkmr <- read_rds(y)
      ints <- bivarinter_bkmr(bkmr,
                                z1 = indices[[1]][1],
                                z2 = indices[[1]][2],
                                qs.diff = c(0.25, 0.75),
                                qs.fixed = c(0.25, 0.75),
                                q.rest = 0.5)
      result <- data.frame(ints) |>
        mutate(trial = as.numeric(sub(".*_(<\d+)>.RDS", "\\\\"1", y)))
      rm(bkmr)
      return(result)
    }) |>
    mutate(case = x)
  })
write_csv(klg_intb, "sim/bkmr_lg/int_bivar.csv")

# extract one vs. 2 others trivariate interactions
klg_intt <- names(klg_paths)[14:17] |> # only for three-way
purrr::map_df(\(x) {

```

```

print(paste0("starting ", x))
klg_paths[[x]] |>
  purrr::map_df(\(y) {
    bkmr <- read_rds(y)
    ints <- trivarinter_bkmr(bkmr,
                               z1 = 4, z2 = 5, z3 = 6,
                               qs.diff = c(0.25, 0.75),
                               qs.fixed = c(0.25, 0.75),
                               q.rest = 0.5)
    result <- data.frame(ints) |>
      mutate(trial = as.numeric(sub(".*_(_\\d+)_\\.RDS", "\\\\1", y)))
    rm(bkmr)
    return(result)
  }) |>
  mutate(case = x)
})
write_csv(klg_intt, "sim/bkmr_lg/int_trivar.csv")

```

Next, we extract output from BSR models run on smaller and larger size simulated datasets, including the base case and models with interactions between chemicals.

```

# load packages
library(NLinteraction)
library(tidyverse)

# create indices of chemical names
cnames <- c("As", "Cd", "Co", "Hg", "Ni", "Tl", "Pb", "Mo", "Sb", "Sn")

#####
# extract bsr smalls!
#####

# extracting file names
list_files <- list.dirs(".", full.names = FALSE, recursive = FALSE)
list_ssm <- list_files[grep("_rslurm_bsr_sm", list_files)]

ssm_subf <- list.dirs(list_ssm, full.names = TRUE, recursive = TRUE)
ssm_mod <- ssm_subf[grep("mods", ssm_subf)]

ssm_labels <- gsub("\\D", "", ssm_mod)
ssm_labels <- ifelse(ssm_labels == "", 1, as.numeric(ssm_labels))

# get paths
ssm_paths <- ssm_mod |>
  purrr::map(\(x) {
    list.files(x, full.names = TRUE)
  }) |>
  setNames(nm = ssm_labels)

# extract PIPs
ssm_pips <- names(ssm_paths) |>
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    ssm_paths[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- data.frame(variable = cnames, PIP = bsr$MainPIP) |>
          mutate(trial = as.numeric(sub(".+_(_\\d+)_\\.RDS", "\\\\1", y)),
                 df = bsr$ns)
        rm(bsr)
      })
  })

```

```

        return(result)
    }) |>
    mutate(case = x)
})
write_csv(ssm_pips, "sim/bsr_sm/pips.csv")

# extract bivariate pip's
ssm_pip_biv <- names(ssm_paths) |>
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    ssm_paths[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- reshape2::melt(bsr$InteractionPIP,
                               na.rm = TRUE,
                               value.name = "PIP") |>
          mutate(trial = as.numeric(sub(".+_(_.+)d.+", "\\\\"1", y)),
                 df = bsr$ns)
        rm(bsr)
        return(result)
    }) |>
    mutate(case = x)
})
write_csv(ssm_pip_biv, "sim/bsr_sm/pip_biv.csv")

# extract trivariate pip's
ssm_pip_triv <- names(ssm_paths)[14:17] |> # trivariate only
purrr::map_df(\(x) {
  print(paste0("starting at ", x))
  ssm_paths[[x]] |>
    purrr::map_df(\(y) {
      bsr <- read_rds(y)
      result <- data.frame(
        PIP = InteractionProb(NLmod = bsr, Xsub = c(4, 5, 6)),
        trial = as.numeric(sub(".+_(_.+)d.+", "\\\\"1", y)),
        df = bsr$ns
      )
      rm(bsr)
      return(result)
    }) |>
    mutate(case = x)
})
write_csv(ssm_pip_triv, "sim/bsr_sm/pip_triv.csv")

# read back in data
out1_resp1 <- read_rds("sim/sim_resp_sm_a.RDS")
source("extract_fxns.R")

# extract bivariate relationships
ssm_biv <- names(ssm_paths)[2:13] |> # bivariate only
purrr::map_df(\(x) {
  print(paste0("starting at ", x))
  indices <- case_when(
    x %in% 2:5 ~ c(4, 5), # Hg and Ni
    x %in% 6:9 ~ c(1, 2), # Cd and As
    x %in% 10:13 ~ c(3, 5) # Co and Ni
  )
  ssm_paths[[x]] |>
    purrr::map_df(\(y) {
      trial <- as.numeric(sub(".+_(_.+)d.+", "\\\\"1", y))
      if(trial %% 5 == 0) print(paste0("index ", y))
      df <- out1_resp1[[trial]]
      X <- df |>
        select(As:Sn) |>

```

```

    as.matrix.data.frame()
C <- df |>
  bind_cols(
    data.frame(model.matrix(~ race-1, data =
      mutate(df, race = as.factor(race))))
  ) |>
  select(race2:race5, smoke:bmi) |>
  as.matrix.data.frame()
Y <- df$y

bsr <- read_rds(y)

result1 <- bivarsurf_bsr(bsr, X = X, C = C, j1 = indices[1], j2 = indices[2],
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+)d.+", "\\\\"1", y)),
         df = bsr$ns,
         j1 = cnames[indices[1]],
         j2 = cnames[indices[2]])
result2 <- bivarsurf_bsr(bsr, X = X, C = C, j1 = indices[2], j2 = indices[1],
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+)d.+", "\\\\"1", y)),
         df = bsr$ns,
         j1 = cnames[indices[2]],
         j2 = cnames[indices[1]])

rm(bsr)
return(bind_rows(result1, result2))
}) |>
  mutate(case = x)
}
write_csv(ssm_biv, "sim-bsr_sm/biv_exresp.csv")

# extract trivariate relationships
ssm_triv <- names(ssm_paths)[14:17] |> # trivariate only
purrr::map_df(\(x) {
  message("starting ", x)
  ssm_paths[[x]] |>
    purrr::map_df(\(y) {
      trial <- as.numeric(sub(".+_(.+)d.+", "\\\\"1", y))
      if(trial %% 5 == 0) message("  index ", trial)
      df <- out1_resp1[[trial]]
      X <- df |>
        select(As:Sn) |>
        as.matrix.data.frame()
      C <- df |>
        bind_cols(
          data.frame(model.matrix(~ race-1, data =
            mutate(df, race = as.factor(race))))
        ) |>
        select(race2:race5, smoke:bmi) |>
        as.matrix.data.frame()
      Y <- df$y

      bsr <- read_rds(y)

      result1 <- trivarsurf_bsr(bsr, X = X, C = C, j1 = 4, j2 = 5, j3 = 6,
                                 gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                                 quantile_rest = 0.5) |>
        mutate(trial = as.numeric(sub(".+_(.+)d.+", "\\\\"1", y)),
               df = bsr$ns,
               j1 = cnames[4],
               j2 = cnames[5],
               j3 = cnames[6])
    })
})

```

```

        j3 = cnames[6])
result2 <- trivarsurf_bsr(bsr, X = X, C = C, j1 = 5, j2 = 6, j3 = 4,
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+d.+", "\\\\"1", y))),
         df = bsr$ns,
         j1 = cnames[5],
         j2 = cnames[6],
         j3 = cnames[4])
result3 <- trivarsurf_bsr(bsr, X = X, C = C, j1 = 6, j2 = 4, j3 = 5,
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+d.+", "\\\\"1", y))),
         df = bsr$ns,
         j1 = cnames[6],
         j2 = cnames[4],
         j3 = cnames[5])

rm(bsr)
return(bind_rows(result1, result2, result3))
}) |>
  mutate(case = x)
})
write_csv(ssm_triv, "sim-bsr_sm/triv_exresp.csv")

#####
# extract bsr larges!
#####

# extracting file names

list_files <- list.dirs(".", full.names = FALSE, recursive = FALSE)
list_slg <- list_files[grep("rslurm_bsr_lg", list_files)] 

slg_subf <- list.dirs(list_slg, full.names = TRUE, recursive = TRUE)
slg_mod <- slg_subf[grep("mods", slg_subf)] 

slg_labels <- gsub("\\D", "", slg_mod)
slg_labels <- ifelse(slg_labels == "", 1, as.numeric(slg_labels))

# get paths
slg_paths <- slg_mod |>
  purrr::map(\(x) {
    list.files(x, full.names = TRUE)
  }) |>
  setNames(nm = slg_labels)

# extract PIPs
slg_pips <- names(slg_paths) |>
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    slg_paths[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- data.frame(variable = cnames, PIP = bsr>MainPIP) |>
          mutate(trial = as.numeric(sub(".+_(.+d.+", "\\\\"1", y))),
                 df = bsr$ns)
        rm(bsr)
        return(result)
      }) |>
      mutate(case = x)
  })
write_csv(slg_pips, "sim-bsr_lg/pips.csv")

```

```

# extract bivariate pip's
slg_pip_biv <- names(slg_paths) |>
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    slg_paths[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- reshape2::melt(bsr$InteractionPIP,
                                 na.rm = TRUE,
                                 value.name = "PIP") |>
          mutate(trial = as.numeric(sub(".+_(.+d.+", "\\\\"1", y)),
                                     df = bsr$ns)
        rm(bsr)
        return(result)
      }) |>
      mutate(case = x)
    })
  write_csv(slg_pip_biv, "sim/bsr_lg/pip_biv.csv")

# extract trivariate pip's
slg_pip_triv <- names(slg_paths)[14:17] |> # trivariate only
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    slg_paths[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- data.frame(
          PIP = InteractionProb(NLmod = bsr, Xsub = c(4, 5, 6)),
          trial = as.numeric(sub(".+_(.+d.+", "\\\\"1", y)),
                             df = bsr$ns
        )
        rm(bsr)
        return(result)
      }) |>
      mutate(case = x)
    })
  write_csv(slg_pip_triv, "sim/bsr_lg/pip_triv.csv")

# read back in data
out2_resp1 <- read_rds("sim/sim_resp_lg_a.RDS")
source("extract_fxns.R")

# extract bivariate relationships
slg_biv <- names(slg_paths)[2:13] |> # bivariate only
  purrr::map_df(\(x) {
    print(paste0("starting at ", x))
    indices <- case_when(
      x %in% 2:5 ~ c(4, 5), # Hg and Ni
      x %in% 6:9 ~ c(1, 2), # Cd and As
      x %in% 10:13 ~ c(3, 5) # Co and Ni
    )
    slg_paths[[x]] |>
      purrr::map_df(\(y) {
        trial <- as.numeric(sub(".+_(.+d.+", "\\\\"1", y))
        if(trial %% 5 == 0) print(paste0("index ", y))
        df <- out2_resp1[[trial]]
        X <- df |>
          select(As:Sn) |>
          as.matrix.data.frame()
        C <- df |>
          bind_cols(
            data.frame(model.matrix(~ race-1, data =
                                      mutate(df, race = as.factor(race))))
        ) |>

```

```

    select(race2:race5, smoke:bmi) |>
      as.matrix.data.frame()
Y <- df$y

bsr <- read_rds(y)

result1 <- bivarsurf_bsr(bsr, X = X, C = C, j1 = indices[1], j2 = indices[2],
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+).+", "\\\\"1", y)),
         df = bsr$ns,
         j1 = cnames[indices[1]],
         j2 = cnames[indices[2]])
result2 <- bivarsurf_bsr(bsr, X = X, C = C, j1 = indices[2], j2 = indices[1],
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+).+", "\\\\"1", y)),
         df = bsr$ns,
         j1 = cnames[indices[2]],
         j2 = cnames[indices[1]])

rm(bsr)
return(bind_rows(result1, result2))
}) |>
  mutate(case = x)
})
write_csv(slg_biv, "sim/bsr_lg/biv_expresp.csv")

# extract trivariate relationships
slg_triv <- names(slg_paths)[14:17] |> # trivariate only
purrr::map_df(\(x) {
  message("starting ", x)
  slg_paths[[x]] |>
    purrr::map_df(\(y) {
      trial <- as.numeric(sub(".+_(.+).+", "\\\\"1", y))
      if(trial %% 5 == 0) message("  index ", trial)
      df <- out2_resp1[[trial]]
      X <- df |>
        select(As:Sn) |>
        as.matrix.data.frame()
      C <- df |>
        bind_cols(
          data.frame(model.matrix(~ race-1, data =
            mutate(df, race = as.factor(race))))
        ) |>
        select(race2:race5, smoke:bmi) |>
        as.matrix.data.frame()
      Y <- df$y

      bsr <- read_rds(y)

      result1 <- trivarsurf_bsr(bsr, X = X, C = C, j1 = 4, j2 = 5, j3 = 6,
                                  gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                                  quantile_rest = 0.5) |>
        mutate(trial = as.numeric(sub(".+_(.+).+", "\\\\"1", y)),
               df = bsr$ns,
               j1 = cnames[4],
               j2 = cnames[5],
               j3 = cnames[6])
      result2 <- trivarsurf_bsr(bsr, X = X, C = C, j1 = 5, j2 = 6, j3 = 4,
                                  gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                                  quantile_rest = 0.5) |>
        mutate(trial = as.numeric(sub(".+_(.+).+", "\\\\"1", y)),
               df = bsr$ns,
               j1 = cnames[5],
               j2 = cnames[6],
               j3 = cnames[4])
    })
  })
}

```

```

j1 = cnames[5],
j2 = cnames[6],
j3 = cnames[4])
result3 <- trivarsurf_bsr(bsr, X = X, C = C, j1 = 6, j2 = 4, j3 = 5,
                           gridLength = 50, quantile_j2 = c(0.1, 0.5, 0.9),
                           quantile_rest = 0.5) |>
  mutate(trial = as.numeric(sub(".+_(.+)d.+", "\\\\"1", y)),
         df = bsr$ns,
         j1 = cnames[6],
         j2 = cnames[4],
         j3 = cnames[5])

rm(bsr)
return(bind_rows(result1, result2, result3))
}) |>
  mutate(case = x)
}
write_csv(slg_triv, "sim-bsr_lg/triv_exresp.csv")

```

Next, we extract output from stratified models.

Finally, we extract information on run-times.

Present results

Here, we present results

- create tables
- keep track of which results are actually going into the appendix

Get some specific stats that are reported in results

```
# significance of As, naive mlr large, case 9
naive_sens |> filter(case == 9, size == "Large", var == "Cd")
```

Here, we visualize and summarize results from model output.

B.3 Code for Appendix A:

Here, we create the supplemental output that is included in Appendix A.

First, we visualize relationships between significant univariate exposures and the response.

```

library(tidyverse)

p1 <- ggplot(NULL) +
  geom_function(fun = function(x) x,
                color = "darkorchid1") +
  xlim(-2, 2) +
  labs(x = "Hg")

p2 <- ggplot(NULL) +
  geom_function(fun = function(x) 3/(1+exp(-4*x)),
                color = "deepskyblue3") +
  xlim(-2, 2) +
  labs(x = "Ni")

p3 <- ggplot(NULL) +
  geom_function(fun = function(x) 1.5/(1+exp(-4*x)),
                color = "darkorange") +
  xlim(-2, 2) +
  labs(x = "Sn")

p4 <- ggplot(NULL) +
  geom_function(fun = function(x) (x^2) + 0.5*x,
                color = "coral1") +
  xlim(-2, 2) +
  labs(x = "Sb")

cowplot::plot_grid(p1, p2, p3, p4)
ggsave("index/figures/univariatelines.png", width = 6, height = 4)

```

Next, we visualize 3D surfaces for pair-wise interactions between exposures.

```

# load packages
library(tidyverse)
library(plotly)
# use reticulate to save plotly 3d plots
if(!require(reticulate)) {
  install.packages('reticulate')
  reticulate::install_miniconda()
  reticulate::conda_install('r-reticulate', 'python-kaleido')
  reticulate::conda_install('r-reticulate', 'plotly', channel = 'plotly')
  Sys.setenv(RETICULATE_PYTHON =
    '/Users/elizabethzhang/Library/r-miniconda-arm64/envs/r-reticulate/bin/python')
  reticulate::use_miniconda('r-reticulate')
}

```

```

# load in observed data
comb_small <- read_csv("madres_data/base_data.csv")

# log-transform and scale target data
comb_scale <- comb_small |>
  mutate(across(10:19, ~scale(log(.)))) 

# check ranges of scaled predictors
range(comb_scale$Hg)
range(comb_scale$Ni)
range(comb_scale$Cd)
range(comb_scale$As)
range(comb_scale$Co)

# generate data covering 2d predictor surface

```

```

data <- expand.grid(x1 = seq(-3, 3, by = 0.1),
                     x2 = seq(-3, 3, by = 0.1))
x1 <- data$x1
x2 <- data$x2

# function to create plot
create_plot <- function(xax, yax, Y, xname = NA, yname = NA) {
  plot_ly(x = ~xax, y = ~yax, z = ~Y, intensity = ~Y) |>
    add_trace(type = "mesh3d") |>
    layout(scene = list(
      xaxis = list(rangemode = "normal",
                   showgrid = FALSE,
                   showline = TRUE,
                   mirror = TRUE,
                   ticks = "outside",
                   title = xname),
      yaxis = list(rangemode = "normal",
                   showgrid = FALSE,
                   showline = TRUE,
                   mirror = TRUE,
                   ticks = "outside",
                   title = yname),
      zaxis = list(rangemode = "normal",
                   showgrid = FALSE,
                   showline = TRUE,
                   mirror = TRUE,
                   ticks = "outside",
                   title = "Y"),
      aspectmode = "cube"
    ))
}

#####
# marginally significant (Hg and Ni)
#####

# no interaction
y00 <- with(data, x1 + 3/(1+exp(-4*x2)))
fig00 <- create_plot(x1, x2, y00, "Hg", "Ni") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = 0.1))))
fig00
save_image(fig00, "index/figures/surfaces/p00.png",
           width = 720, height = 480, scale = 3)

# multiplicative interaction, smaller effect size
yam1 <- with(data, x1 + 3/(1+exp(-4*x2)) + 0.35*x1*x2)
figam1 <- create_plot(x1, x2, yam1, "Hg", "Ni") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = .1))))
figam1
save_image(figam1, "index/figures/surfaces/am1.png",
           width = 720, height = 480, scale = 3)

# multiplicative interaction, larger effect size
yam2 <- with(data, x1 + 3/(1+exp(-4*x2)) + 0.75*x1*x2)
figam2 <- create_plot(x1, x2, yam2, "Hg", "Ni") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = .1))))
figam2
save_image(figam2, "index/figures/surfaces/am2.png",
           width = 720, height = 480, scale = 3)

# polynomial interaction, smaller effect size
yap1 <- with(data, x1 + 3/(1+exp(-4*x2)) + 0.13*x1*((x2-1)^2))
figap1 <- create_plot(x1, x2, yap1, "Hg", "Ni") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = .1))))

```

```

figap1
save_image(figap1, "index/figures/surfaces/ap1.png",
           width = 720, height = 480, scale = 3)

# polynomial interaction, larger effect size
yap2 <- with(data, x1 + 3/(1+exp(-4*x2)) + 0.26*x1*((x2-1)^2))
figap2 <- create_plot(x1, x2, yap2, "Hg", "Ni") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = .1))))
figap2
save_image(figap2, "index/figures/surfaces/ap2.png",
           width = 720, height = 480, scale = 3)

#####
# marginally insignificant (Cd and As)
#####

# multiplicative interaction, smaller effect size
ybm1 <- with(data, 0.35*x1*x2)
figbm1 <- create_plot(x1, x2, ybm1, "Cd", "As") |>
  layout(scene = list(camera = list(eye = list(x = 1.4, y = 1.4, z = 1.2))))
figbm1
save_image(figbm1, "index/figures/surfaces/bm1.png",
           width = 720, height = 480, scale = 3)

# multiplicative interaction, larger effect size
ybm2 <- with(data, 0.7*x1*x2)
figbm2 <- create_plot(x1, x2, ybm2, "Cd", "As") |>
  layout(scene = list(camera = list(eye = list(x = 1.4, y = 1.4, z = 1.2))))
figbm2
save_image(figbm2, "index/figures/surfaces/bm2.png",
           width = 720, height = 480, scale = 3)

# polynomial interaction, smaller effect size
ybp1 <- with(data, 0.125*x1*((x2-1)^2))
figbp1 <- create_plot(x1, x2, ybp1, "Cd", "As") |>
  layout(scene = list(camera = list(eye = list(x = 1.4, y = 1.4, z = 1.2))))
figbp1
save_image(figbp1, "index/figures/surfaces/bp1.png",
           width = 720, height = 480, scale = 3)

# polynomial interaction, larger effect size
ybp2 <- with(data, 0.25*x1*((x2-1)^2))
figbp2 <- create_plot(x1, x2, ybp2, "Cd", "As") |>
  layout(scene = list(camera = list(eye = list(x = 1.4, y = 1.4, z = 1.2))))
figbp2
save_image(figbp2, "index/figures/surfaces/bp2.png",
           width = 720, height = 480, scale = 3)

#####
# highly correlated (Ni and Co)
#####

# multiplicative interaction, smaller effect size
ycm1 <- with(data, 3/(1+exp(-4*x2)) + 0.3*x1*x2)
figcm1 <- create_plot(x1, x2, ycm1, "Ni", "Co") |>
  layout(scene = list(camera = list(eye = list(x = 1.2, y = 1.2, z = 1.5))))
figcm1
save_image(figcm1, "index/figures/surfaces/cm1.png",
           width = 720, height = 480, scale = 3)

# multiplicative interaction, larger effect size
ycm2 <- with(data, 3/(1+exp(-4*x2)) + 0.6*x1*x2)
figcm2 <- create_plot(x1, x2, ycm2, "Ni", "Co") |>
  layout(scene = list(camera = list(eye = list(x = 1.2, y = 1.2, z = 1.5))))

```

```

figcm2
save_image(figcm2, "index/figures/surfaces/cm2.png",
           width = 720, height = 480, scale = 3)

# polynomial interaction, smaller effect size
ycp1 <- with(data, 3/(1+exp(-4*x2)) + 0.1*x1*((x2-1)^2))
figcp1 <- create_plot(x1, x2, ycp1, "Ni", "Co") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = .1))))
figcp1
save_image(figcp1, "index/figures/surfaces/cp1.png",
           width = 720, height = 480, scale = 3)

# polynomial interaction, larger effect size
ycp2 <- with(data, 3/(1+exp(-4*x2)) + 0.2*x1*((x2-1)^2))
figcp2 <- create_plot(x1, x2, ycp2, "Ni", "Co") |>
  layout(scene = list(camera = list(eye = list(x = 1.5, y = 1.5, z = .1))))
figcp2
save_image(figcp2, "index/figures/surfaces/cp2.png",
           width = 720, height = 480, scale = 3)

```

Next, we look at simulated exposure and covariate data for the larger size dataset.

We also create the grid of density plots for Spearman's correlation values between exposures in the simulated smaller size datasets.

```

# create density plot of correlation for smaller size dataset
# read small size back in
out1 <- read_rds("sim/sim_preds_sm.RDS")

# extract correlation
cors <- out1 |>
  purrr::map_df(\(x) {
    cor_mat <- cor(x[, 5:14], method = "spearman")
    cor_mat[lower.tri(cor_mat)] <- NA
    melt_cor <- reshape2::melt(cor_mat) |>
      mutate(value = ifelse(value == 1, NA, value)) |>
      na.omit() |>
      mutate(sim = x$sim[1])
    return(melt_cor)
  })

# function for plotting x-axis
newbreaks <- function(lims) {
  range <- diff(lims)
  return(c(lims[1] + range/5, mean(lims), lims[2] - range/5))
}

# create grid of density plots
cors_dens <- cors |>
  group_by(Var1, Var2) |>
  mutate(mean = mean(value)) |>
  ungroup() |>
  ggplot(aes(x = value, fill = mean)) +
  geom_density() +
  scale_x_continuous(breaks = newbreaks,
                     labels = ~round(.x, 2)) +
  scale_y_continuous(position = "right") +
  scale_fill_gradient2(
    limit = c(-0.6, 0.6), breaks = c(-0.6, -0.3, 0, 0.3, 0.6),
    low = "deepskyblue3", mid = "white", high = "darkorange",

```

```

na.value = NA) +
ggh4x::facet_grid2(fct_rev(Var2) ~ Var1, scales = "free", independent = "x",
                    render_empty = FALSE, switch = "both") +
labs(x = TeX(r"( Spearman's $\rho$ )")) +
theme(strip.placement = "outside",
      strip.text.y.left = element_text(angle = 0),
      legend.justification = c(1, 0),
      legend.position = c(0.9, 0.1),
      legend.direction = "horizontal") +
guides(fill = guide_colorbar(barwidth = 7, barheight = 1,
                             title.position = "top", title.hjust = 0.5))
cors_dens

ggsave("index/figures/ch4_corr_sim.png", width = 10, height = 7)

```

```

#####
# look at simulated data, larger size
#####

# read larger size data back in
out2 <- read_rds("sim/sim_preds_lg.RDS")
comb_sim2 <- bind_rows(out2)

```

```

# density plots for exposures
name_order <- c("As", "Cd", "Co", "Hg", "Ni", "Tl", "Pb", "Mo", "Sb", "Sn")
comb_sim2 |>
  mutate(sim = as.factor(sim)) |>
  select(5:15) |>
  pivot_longer(cols = 1:10) |>
  mutate(name = factor(name, levels = name_order)) |>
  ggplot(aes(x = value, group = sim)) +
  geom_line(stat = "density", color = "grey10", alpha = 0.01) +
  # reference observed densities
  geom_density(
    data = comb_log |> select(10:19) |> pivot_longer(cols = 1:10) |>
      mutate(name = factor(name, levels = name_order)),
    mapping = aes(x = value),
    color = "deepskyblue", linewidth = 0.75, inherit.aes = FALSE
  ) +
  facet_wrap(~name, scales = "free")
# save
ggsave("index/figures/ch4_univ_exp_sim_lg.png", width = 6, height = 4)

```

```

# density plot for continuous covariates
cov_sim_p2 <- comb_sim2 |>
  mutate(sim = as.factor(sim)) |>
  select(age, bmi, sim) |>
  pivot_longer(cols = 1:2) |>
  ggplot(aes(x = value, group = sim)) +
  geom_line(stat = "density", color = "grey10", alpha = 0.01) +
  geom_density(
    data = comb_log |> select(age, bmi) |> pivot_longer(cols = 1:2),
    mapping = aes(x = value),
    color = "deepskyblue", linewidth = 0.75, inherit.aes = FALSE
  ) +
  facet_wrap(~name, scales = "free", ncol = 1)

# bar + violin plot for continuous covariates
cov_sim_q2 <- comb_sim2 |>
  mutate(sim = as.factor(sim)) |>

```

```

select(sim, smoke, race) |>
mutate(smoke = ifelse(smoke == 0, "Never-exposed", "Ever-exposed"),
       race = case_when(
         race == 1 ~ "Non-Hisp. white",
         race == 2 ~ "Non-Hisp. black",
         race == 3 ~ "Non-Hisp. other",
         race == 4 ~ "Hispanic born\nin US",
         race == 5 ~ "Hispanic born\noutside US"
       )) |>
pivot_longer(cols = 2:3) |>
group_by(sim, name, value) |>
summarize(prop = n()/1000) |>
mutate(value = factor(
  value, levels = rev(c("Never-exposed", "Ever-exposed",
                        "Non-Hisp. white", "Non-Hisp. black", "Non-Hisp. other",
                        "Hispanic born\nin US", "Hispanic born\noutside US")))
)) |>
ggplot(aes(x = value, y = prop)) +
  geom_bar(data = df_forcovcat, aes(x = value, y = after_stat(prop), group = 1),
           inherit.aes = FALSE, stat = "count", fill = "skyblue") +
  geom_violin(color = "gray30", fill = "gray", alpha = 0.25) +
  facet_wrap(~name, scales = "free", ncol = 1) +
  coord_flip() +
  labs(x = NULL, y = "proportion")

# plot in grid and save
cowplot:::plot_grid(cov_sim_p2, cov_sim_q2, labels = "auto", nrow = 1,
                     rel_widths = c(0.4, 0.6))
ggsave("index/figures/ch4_univ_cov_sim_lg.png", width = 6, height = 4)

```

```

# extract spearman's correlation from large simulated data
corl <- out2 |>
  purrr::map_df(\(x) {
    cor_mat <- cor(x[, 5:14], method = "spearman")
    cor_mat[lower.tri(cor_mat)] <- NA
    melt_cor <- reshape2::melt(cor_mat) |>
      mutate(value = ifelse(value == 1, NA, value)) |>
      na.omit() |>
      mutate(sim = x$sim[1])
    return(melt_cor)
  })

# grid of density plots of correlation in large simulated data
cors_dens2 <- corl |>
  group_by(Var1, Var2) |>
  mutate(mean = mean(value)) |>
  ungroup() |>
  ggplot(aes(x = value, fill = mean)) +
  geom_density() +
  scale_x_continuous(breaks = newbreaks,
                     labels = ~round(.x, 2)) +
  scale_y_continuous(position = "right") +
  scale_fill_gradient2(
    limit = c(-0.6, 0.6), breaks = c(-0.6, -0.3, 0, 0.3, 0.6),
    low = "deepskyblue3", mid = "white", high = "darkorange",
    na.value = NA) +
  ggh4x::facet_grid2(fct_rev(Var2) ~ Var1, scales = "free", independent = "x",
                     render_empty = FALSE, switch = "both") +
  labs(x = TeX(r"( Spearman's $\rho$ )")) +
  theme(strip.placement = "outside",
        strip.text.y.left = element_text(angle = 0),
        legend.justification = c(1, 0),
        legend.position = c(0.9, 0.1),

```

```

    legend.direction = "horizontal") +
  guides(fill = guide_colorbar(barwidth = 7, barheight = 1,
                               title.position = "top", title.hjust = 0.5))

# heatmap of average correlation in large simulated data
cor_sim2 <- corl |>
  group_by(Var1, Var2) |>
  summarize(value = mean(value)) |>
  mutate(label = round(value, 2)) |>
  ggplot(aes(x = Var1, y = Var2, fill = value)) +
  geom_tile() +
  geom_text(aes(label = label), size = 3.5) +
  scale_fill_gradient2(
    limit = c(-0.6, 0.6), breaks = c(-0.6, -0.3, 0, 0.3, 0.6),
    low = "deepskyblue3", mid = "white", high = "darkorange",
    na.value = NA) +
  coord_fixed() +
  labs(x = NULL, y = NULL, fill = TeX(r"( Mean Spearman's  $\rho$  )")) +
  theme(
    panel.grid.major.x = element_line(color = "grey85",
                                       linewidth = 0.25,
                                       linetype = 2),
    panel.border = element_blank(),
    legend.justification = c(1, 0),
    legend.position = c(0.9, 0.1),
    legend.direction = "horizontal") +
  guides(fill = guide_colorbar(barwidth = 7, barheight = 1,
                               title.position = "top", title.hjust = 0.5))

# put original and simulated correlation heatmaps together
top_row2 <- cowplot::plot_grid(cor_orig, cor_sim2, labels = "auto", label_size = 16,
                                nrow = 1, scale = 0.95)
# put original, simulated, and density plots of correlation together
cowplot::plot_grid(top_row2, cors_dens2, labels = c("", "c"), label_size = 16,
                   nrow = 2, rel_heights = c(5, 7), scale = c(1, 0.95))
ggsave("index/figures/ch4_corr_lg_simorigdens.png", width = 10, height = 12)

```

Here, we create the visualization of R^2 values in multiple linear regressions with the true functional form of the chemicals specified, in order to ensure we are achieving a realistic signal-to-noise ratio. This code was run on the Amherst HPC RStudio server.

```

### smaller size

# read in simulated datasets
out1_resp1 <- read_rds("sim/sim_resp_sm_a.RDS")
run_co_sm <- function() {
  # initialize vectors
  chems_oracle <- vector(mode = 'list', length = 1700)
  names(chems_oracle) <- names(out1_resp1)

  for(i in 1:1700) {
    df <- out1_resp1[[i]] |>
      mutate(race = as.factor(race), smoke = as.factor(smoke)) |>
      select(-sim)

    if(i <= 100) {

```

```

chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                         I(1/(1+exp(-4*Ni))) + I(Sb^2) +
                         I(1/(1+exp(-4*Sn))), data = df)
} else if (i <= 300) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           Hg*Ni, data = df)
} else if (i <= 500) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           I(Hg*((Ni-1)^2)), data = df)
} else if (i <= 700) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           Cd*As, data = df)
} else if (i <= 900) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           I(Cd*((As-1)^2)), data = df)
} else if (i <= 1100) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           Ni*Co, data = df)
} else if (i <= 1300) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           I(Ni*((Co-1)^2)), data = df)
} else if (i <= 1500) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           Hg:Ni:Tl, data = df)
} else if (i <= 1700) {
  chems_oracle[[i]] <- lm(y ~ Hg + Sb +
                           I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
                           I(Hg*((Ni-1)^2)*Tl), data = df)
}
}
return(chems_oracle)
}

# send to hpc
cosjob <- slurm_call(
  run_mlr_sm,
  global_objects = c('out1_resp1'),
  jobname = 'co_sm')

# get output
chem_oracle <- get_slurm_out(cosjob)
write_rds(chem_oracle, "sim/chem_oracle_sm.RDS")

### larger sample size

# read in simulated datasets
out2_resp1 <- read_rds("sim/sim_resp_lg_a.RDS")

run_co_lg <- function() {
  # initialize vectors
  chems_only1 <- vector(mode = 'list', length = 1700)
  names(chems_only1) <- names(out2_resp1)
  chems_oracle1 <- vector(mode = 'list', length = 1700)
  names(chems_oracle1) <- names(out2_resp1)

  for(i in 1:1700) {
    df <- out2_resp1[[i]] |>

```

```

    mutate(race = as.factor(race), smoke = as.factor(smoke)) |>
    select(-sim)

  if(i <= 100) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) +
      I(1/(1+exp(-4*Sn))), data = df)
  } else if (i <= 300) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      Hg*Ni, data = df)
  } else if (i <= 500) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      I(Hg*((Ni-1)^2)), data = df)
  } else if (i <= 700) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      Cd*As, data = df)
  } else if (i <= 900) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      I(Cd*((As-1)^2)), data = df)
  } else if (i <= 1100) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      Ni*Co, data = df)
  } else if (i <= 1300) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      I(Ni*((Co-1)^2)), data = df)
  } else if (i <= 1500) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      Hg:Ni:Tl, data = df)
  } else if (i <= 1700) {
    chems_oracle[[i]] <- lm(y ~ Hg + Sb +
      I(1/(1+exp(-4*Ni))) + I(Sb^2) + I(1/(1+exp(-4*Sn))) +
      I(Hg*((Ni-1)^2)*Tl), data = df)
  }
}
return(chems_oracle)
}

# send to hpc
coljob <- slurm_call(
  run_co_lg,
  global_objects = c('out2_resp1'),
  jobname = 'co_lg')

# get output
chem_oracle <- get_slurm_out(coljob)
write_rds(chem_oracle, "sim/chem_oracle_lg.RDS")

```

```

# extract rsq from smaller size datasets
chem_mods <- read_rds("sim/mlr/chem_oracle_sm.RDS")
rsq_chem <- chem_mods |>
  purrr::map_df(\(x) {
    data.frame(
      rsq = summary(x)$r.squared
    )
  }) |>
  mutate(name = names(chem_mods))

```

```

# plot for smaller size
rsqsmplot <- rsq_chem |>
  ggplot(aes(x = rsq)) +
  geom_density() +
  facet_wrap(~name,
             labeller = as_labeller(appender1,
                                     default = label_parsed),
             ncol = 4) +
  labs(y = "Density", x = latex2exp::TeX("R$^2$"))

# extract rsq from larger size datasets
chem_modl <- read_rds("sim/mlr/chem_oracle_lg.RDS")
rsq_cheml <- chem_modl |>
  purrr::map_df(\(x) {
    data.frame(
      rsq = summary(x)$r.squared
    )
  }) |>
  mutate(name = names(chem_modl))

# plot for larger size
rsqlgplot <- rsq_cheml |>
  ggplot(aes(x = rsq)) +
  geom_density() +
  facet_wrap(~name,
             labeller = as_labeller(appender1,
                                     default = label_parsed),
             ncol = 4) +
  labs(y = "Density", x = latex2exp::TeX("R$^2$"))

# plot both in grid and save
cowplot::plot_grid(rsqsmplot, rsqlgplot, labels = "auto", nrow = 1)
ggsave("index/figures/chem_rsq.png", width = 12, height = 6)

```

We also look at selecting degrees of freedom in BSR using 5,000 vs. 50,000 MCMC iterations. Refer to the code for fitting BSR on the smaller size datasets for how the models for this test were run.

```

# extract names of files for 50,000 iterations
main_folder <- "sim/bsr_df_sm"
subfolders <- list.dirs(main_folder, full.names = TRUE, recursive = TRUE)
mod_subfolders <- subfolders[grep("mods", subfolders)]
mod_labels <- gsub("\\D", "", mod_subfolders)
mod_labels <- ifelse(mod_labels == "", 1, as.numeric(mod_labels))

mod_paths <- mod_subfolders |>
  purrr::map(\(x) {
    list.files(x, full.names = TRUE)
  }) |>
  setNames(nm = mod_labels)

# extract WAIC values from model output
waic <- names(mod_paths) |>
  purrr::map_df(\(x) {
    mod_paths[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- data.frame(

```

```

    df = c(1, 2, 3, 4, 5),
    waic = c(bsr[[1]]$waic,
              bsr[[2]]$waic,
              bsr[[3]]$waic,
              bsr[[4]]$waic,
              bsr[[5]]$waic),
    trial = rep(substr(y, nchar(y) - 4, nchar(y) - 4))
  )
  rm(bsr)
  return(result)
}) |>
  mutate(case = x)
})

write_csv(waic, "sim/tables/test_waic.csv")

# look at waic values
waic <- read_csv("sim/tables/test_waic.csv")

# select degrees of freedom that minimizes waic
min_waic <- waic |>
  group_by(case, trial) |>
  filter(waic == min(waic)) |>
  arrange(as.numeric(case))

# extract names of files for 5,000 iterations (trial 2)
main_folder2 <- "sim/bsr_df_sm2"
subfolders2 <- list.dirs(main_folder2, full.names = TRUE, recursive = TRUE)
mod_subfolders2 <- subfolders2[grep("mods", subfolders2)]
mod_labels2 <- gsub("\\D", "", substr(mod_subfolders2, 16, nchar(mod_subfolders2)))
mod_labels2 <- ifelse(mod_labels2 == "", 1, as.numeric(mod_labels2))

mod_paths2 <- mod_subfolders2 |>
  purrr::map(\(x) {
    list.files(x, full.names = TRUE)
  }) |>
  setNames(nm = mod_labels2)

# extract waic from model outputs
waic2 <- names(mod_paths2) |>
  purrr::map_df(\(x) {
    mod_paths2[[x]] |>
      purrr::map_df(\(y) {
        bsr <- read_rds(y)
        result <- data.frame(
          df = c(1, 2, 3, 4, 5),
          waic = c(bsr[[1]]$waic,
                    bsr[[2]]$waic,
                    bsr[[3]]$waic,
                    bsr[[4]]$waic,
                    bsr[[5]]$waic),
          trial = rep(substr(y, nchar(y) - 4, nchar(y) - 4))
        )
        rm(bsr)
        return(result)
      }) |>
      mutate(case = x)
  })

write_csv(waic2, "sim/tables/test_waic2.csv")

# compare them
waic <- read_csv("sim/tables/test_waic.csv")
waic2 <- read_csv("sim/tables/test_waic2.csv")

```

```

waic_comb <- waic |>
  mutate(iter = 1) |>
  bind_rows(mutate(waic2, iter = 2))

# create plot
waic_comb |>
  filter(trial <= 5) |>
  mutate(df = as.factor(df),
         iter = factor(ifelse(iter == 1, "F", "P"), levels = c("P", "F"))) |>
  ggplot(aes(x = iter, y = waic, color = df)) +
  geom_point() +
  geom_line(aes(group = df)) +
  ggh4x::facet_grid2(paste0("Trial ", trial) ~ case,
                      scales = "free_y", independent = "y") +
  theme(axis.text.y=element_blank(),
        axis.ticks.y=element_blank(),
        plot.caption = element_text(hjust = 0, size = 7)) +
  labs(y = "WAIC", x = "# MCMC iterations (F = 50,000, P = 5,000)",
       color = "Degrees\nof freedom",
       caption = paste0(
         "Scenarios are labelled in the top strip as follows:\n",
         "1 = base case; 2 = HgNi mult. small; 3 = HgNi mult. large; ",
         "4 = HgNi poly. small; 5 = HgNi poly. large; ",
         "6 = CdAs mult. small; 7 = CdAs mult. large; ",
         "8 = CdAs poly. small; 9 = CdAs poly. large;\n",
         "10 = NiCo mult. small; 11 = NiCo mult. large; ",
         "12 = NiCo poly. small; 13 = NiCo poly. large; ",
         "14 = HgNiTl mult. small; 15 = HgNiTl mult. large; ",
         "16 = HgNiTl poly. small; 17 = HgNiTl poly. large"))

ggsave("index/figures/test_waic2.png", height = 6, width = 9)

# get proportion of correctly selected df's
waic_min <- waic_comb |>
  mutate(iter = ifelse(iter == 1, "full", "partial")) |>
  arrange(iter, case, trial) |>
  filter(trial <= 5) |>
  group_by(iter, trial, case) |>
  filter(waic == min(waic)) |>
  ungroup() |>
  pivot_wider(id_cols = c(trial, case),
              names_from = iter, values_from = df) |>
  mutate(equal = (full == partial))
mean(waic_min$equal)

```

We check convergence using trace plots for a selection of BKMR and BSR models.

```

library(bkmr)
library(NLinteraction)

# bkmr fits
bkmr_sm_am2_203 <- readRDS("testing/bkmr_sm_am2_203.RDS")
bkmr_lg_am2_284 <- readRDS("testing/bkmr_lg_am2_284.RDS")

# bsr fits
bsr_sm_am2_203df2 <- readRDS("testing-bsr_sm_am2_203df2.RDS")
bsr_lgf_am2_284df2 <- readRDS("testing-bsr_lgf_am2_284df2.RDS")

# bkmr sm
png("index/figures/traceplots/bksm_traceplot.png", width = 8, height = 6, units = "in", res = 360)
par(mfrow = c(2, 2))

```

```

TracePlot(fit = bkmr_sm_am2_203, par = "beta") # prior probability
TracePlot(fit = bkmr_sm_am2_203, par = "sigsq.eps") # variance of residuals
TracePlot(fit = bkmr_sm_am2_203, par = "r", comp = 1) # prob of each
TracePlot(fit = bkmr_sm_am2_203, par = "r", comp = 5)
dev.off()

# bkmr lg
png("index/figures/traceplots/bklg_traceplot.png", width = 8, height = 6, units = "in", res = 360)
par(mfrow = c(2, 2))
TracePlot(fit = bkmr_lg_am2_284, par = "beta")
TracePlot(fit = bkmr_lg_am2_284, par = "sigsq.eps")
TracePlot(fit = bkmr_lg_am2_284, par = "r", comp = 1)
TracePlot(fit = bkmr_lg_am2_284, par = "r", comp = 5)

# bsr sm
h <- bsr_sm_am2_203df2$posterior

png("index/figures/traceplots/bssm_traceplot.png", width = 8, height = 6, units = "in", res = 360)
par(mfrow = c(2, 2))
htau <- t(h[["tau"]][, , 1])
plot(htau[, 1], type = "l",
      main = paste0("(tau = ", round(mean(htau[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(htau[, 1]), col = "blue", lwd = 2)

hsigma <- t(h[["sigma"]])
plot(hsigma[, 1], type = "l",
      main = paste0("(sigma = ", round(mean(hsigma[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(hsigma[, 1]), col = "blue", lwd = 2)

hzeta1 <- t(h[["zeta"]][, , 1, 2])
plot(hzeta1[, 1], type = "l",
      main = paste0("(zeta1 = ", round(mean(hzeta1[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(hzeta1[, 1]), col = "blue", lwd = 2)

hzeta5 <- t(h[["zeta"]][, , 5, 2])
plot(hzeta5[, 1], type = "l",
      main = paste0("(zeta5 = ", round(mean(hzeta5[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(hzeta5[, 1]), col = "blue", lwd = 2)
dev.off()

# bsr lg
h <- bsr_lgf_am2_284df2$posterior

png("index/figures/traceplots/bslg_traceplot.png", width = 8, height = 6, units = "in", res = 360)
par(mfrow = c(2, 2))
htau <- t(h[["tau"]][, , 1])
plot(htau[, 1], type = "l",
      main = paste0("(tau = ", round(mean(htau[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(htau[, 1]), col = "blue", lwd = 2)

hsigma <- t(h[["sigma"]])
plot(hsigma[, 1], type = "l",
      main = paste0("(sigma = ", round(mean(hsigma[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(hsigma[, 1]), col = "blue", lwd = 2)

hzeta1 <- t(h[["zeta"]][, , 1, 2])
plot(hzeta1[, 1], type = "l",
      main = paste0("(zeta1 = ", round(mean(hzeta1[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")

```

```

  xlab = "scan", ylab = "parameter value")
abline(h = mean(hzeta1[, 1]), col = "blue", lwd = 2)

hzeta5 <- t(h[["zeta"]][, , 2])
plot(hzeta5[, 1], type = "l",
      main = paste0("zeta5 = ", round(mean(hzeta5[, 1]), 2), ")"),
      xlab = "scan", ylab = "parameter value")
abline(h = mean(hzeta5[, 1]), col = "blue", lwd = 2)
dev.off()

# put all together

library(magick)

# list of input files
file_list <- c("index/figures/traceplots/bksm_traceplot.png",
              "index/figures/traceplots/bklg_traceplot.png",
              "index/figures/traceplots/bssm_traceplot.png",
              "index/figures/traceplots/bslg_traceplot.png")

# output file name
output_file <- "index/figures/traceplots/bksm_traceplotmerged.png"

# merge images
merge_and_save <- function(file_list, output_file) {
  images <- image_read(file_list)

  # two columns
  top_row <- image_append(images[1:2], stack = TRUE)
  bottom_row <- image_append(images[3:4], stack = TRUE)

  # combine columns
  combined_image <- image_append(c(top_row, bottom_row), stack = FALSE)

  # add labels
  combined_image <- image_annotate(combined_image, "a", location = "+30+20",
                                      size = 120, color = "black", font = "Roboto", weight = 700)
  combined_image <- image_annotate(combined_image, "b", location = "+2900+20",
                                      size = 120, color = "black", font = "Roboto", weight = 700)
  combined_image <- image_annotate(combined_image, "c", location = "+30+2110",
                                      size = 120, color = "black", font = "Roboto", weight = 700)
  combined_image <- image_annotate(combined_image, "d", location = "+2900+2110",
                                      size = 120, color = "black", font = "Roboto", weight = 700)

  image_write(combined_image, path = output_file, format = "png")
}

merge_and_save(file_list, output_file)

```

Corrections

A list of corrections after submission to department.

Corrections may be made to the body of the thesis, but every such correction will be acknowledged in a list under the heading “Corrections,” along with the statement “When originally submitted, this honors thesis contained some errors which have been corrected in the current version. Here is a list of the errors that were corrected.” This list will be given on a sheet or sheets to be appended to the thesis. Corrections to spelling, grammar, or typography may be acknowledged by a general statement such as “30 spellings were corrected in various places in the thesis, and the notation for definite integral was changed in approximately 10 places.” However, any correction that affects the meaning of a sentence or paragraph should be described in careful detail. The files samplethesis.tex and samplethesis.pdf show what the “Corrections” section should look like. Questions about what should appear in the “Corrections” should be directed to the Chair.

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