SELECTIVE INference FOR EFFECT MODIFICATION VIA THE LASSO

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Abstract. Effect modification occurs when the effect of the treatment on an outcome varies according to the level of other covariates and often has important implications in decision making. When there are tens or hundreds of covariates, it becomes necessary to use the observed data to select a simpler model for effect modification and then make valid statistical inference. We propose a two stage procedure to solve this problem. First, we use Robinson’s transformation to decouple the nuisance parameters from the treatment effect of interest and use machine learning algorithms to estimate the nuisance parameters. Next, after plugging in the estimates of the nuisance parameters, we use the Lasso to choose a low-complexity model for effect modification. Compared to a full model consisting of all the covariates, the selected model is much more interpretable. Compared to the univariate subgroup analyses, the selected model greatly reduces the number of false discoveries. We show that the conditional selective inference for the selected model is asymptotically valid given the rate assumptions in classical semiparametric regression. Extensive simulation studies are conducted to verify the asymptotic results and an epidemiological application is used to demonstrate the method.

1. Introduction

When analyzing the causal effect of an intervention, effect modification (or treatment effect heterogeneity) occurs when the magnitude of the causal effect varies as a function of other observed covariates. Much of the causal inference literature focuses on statistical inference about the average causal effect in a population of interest. However, in many applications, it is also important to study how the causal effect varies in different subpopulations, i.e., effect modification, for reasons including personalizing treatments in precision medicine (Murphy, 2003 [Ashley, 2015], generalizing the causal finding to different populations (Stuart et al., 2011), better understanding of the causal mechanism (Grobbee and Hoes, 2009 page 96), and making inference less sensitive to unmeasured confounding bias (Hsu et al., 2013 [Ertefaie et al., 2017]).

A natural way of identifying effect modification is subgroup analysis, in which observations are stratified based on the covariates. More generally, one can study effect modification by including interaction terms between the treatment and the covariates in an outcome regression. Depending on whether the subgroups or interactions are chosen before or after any examination of the data, the statistical analysis can be a priori or post hoc (Wang et al., 2007). A priori subgroup analyses are free of selection bias and are frequently used in clinical trials and other observational studies. They do discover some effect modification, often convincingly, from the data, but since the potential effect modifiers are determined a priori rather than using the data, many real effect modifiers may remain undetected.

With the enormous amount of data and covariates being collected nowadays, discovering effect modification by post hoc analyses has become a common interest in several applied fields, including precision medicine (Lee et al., 2016b [Pickkers and Kox, 2017], Jiang et al., 2018), education (Schochet, 2017).
et al., 2014), political science (Imai and Ratkovic, 2013; Grimmer et al., 2017), economics (Angrist, 2004), and online digital experiments (Taddy et al., 2016). Post hoc analysis was originally treated as a multiple comparisons problem in the works of Tukey (1949) and Scheffé (1953), where a single categorical effect modifier is considered. However, modern applications can easily have tens or hundreds of potential effect modifiers. In this case, it is impractical to consider the subgroups exhaustively (for example, there are $2^{30} > 10^9$ distinct subgroups with just 30 binary covariates). Therefore, there has been an increasing demand for more sophisticated post hoc methods that can discover effect modification from the data.

Tukey (1991) discussed thoroughly about the difference between a priori and post hoc analyses and why they are both important. In page 103, he wrote:

> Exploration—which some might term “data dredging”—is quite different from “exogenous selection of a few comparisons”. Both have their place. We need to be prepared to deal with either.

For Tukey, data dredging (post hoc subgroup analyses in our context) seems to mean a full exploration of the data, so it can only give interesting hints rather than confident conclusions. In this paper we will present an effort based on the recently developed selective inference framework (Taylor and Tibshirani, 2015) to partially explore the data and then make confident conclusions about the interesting hints. Such an approach was perhaps not envisioned by Tukey, but he did point out that the degree of exploration can impact the inference, which is a fundamental idea for selective inference. In fact, confidence intervals using his studentized range (Tukey, 1949) are tighter than Scheffé’s method because fewer (but more important, as he argued) comparisons are made.

### 1.1. Defining the effect modification problem

Depending on the goal of the particular application, there are several ways to set up the inferential problem of effect modification. One way to phrase this problem is that we would like an optimal or near-optimal treatment assignment rule for future experimental objects (e.g. patients). Thus the statistical problem is to estimate the probability that a certain treatment outperforms other treatment(s) given characteristics of the objects and quantify its uncertainty. This optimal treatment regimes problem has been studied extensively by Murphy (2003), Robins (2004), Manski (2004), Hirano and Porter (2009), Zhao et al. (2012), Zhang et al. (2012), Ertefaie (2014), Luedtke and van der Laan (2016), Athey and Wager (2017) among many others. A closely related but less direct formulation is to estimate the conditional average treatment effect and provide confidence/credible intervals, see Robins et al. (2008), Hill (2011), Balzer et al. (2016), Athey et al. (2018) for some recent references.

A third way to define the effect modification problem, which is the formulation we will take in this paper, is to post questions like: Is covariate A an effect modifier? What are the other potential effect modifiers and how certain are we about them? These questions are frequently raised in practice to test existing scientific hypotheses, generate new hypotheses, and gather information for intelligent decision making.

Unfortunately, the previous two approaches are not designed to answer these questions directly. Although there exist several proposals of discovering (in Tukey’s language, interesting hints about) effect modifying covariates or subgroups (Imai and Ratkovic, 2013; Tian et al., 2014; Athey and Imbens, 2016), little attention has been given to providing inference such as confidence interval or statistical significance for the selected covariates or subgroups (in Tukey’s language, making confident conclusions).

When giving inference after model selection, the naive inference ignoring the data dredging is generally over-confident, but not all applied researchers are mindful to this danger. For example, in a book on testing and interpreting interactions in social sciences, Aiken et al. (1991, page 105) recommended to drop insignificant interactions from the regression model especially if they are not expected by the investigator, but the authors did not mention that the subsequent statistical inference would be corrupted. Such a suggestion can also be found in another highly cited book by Cohen et al. (2003, page 361):
We then use the products of these main effects collectively to test the significance of the interaction, . . . . If the interaction term turns out to be significant, then the regression coefficients from the full model including the interaction should be reported.

Empirical studies that ignore the danger of cherry-picking the interaction model can be found even in top medical journals (e.g. Sumithran et al., 2011, Zatzick et al., 2013). Other books such as Weisberg (2005) Section 10.3.1 and Vittinghoff et al. (2011) Section 5.3.3 warned that “significance (in the selected model by the naive inference) is overstated” and “exploratory analyses are susceptible to false-positive findings”, but no practical solution was given. A temporary fix used in practice is to test each potential interaction separately with all the main effects (e.g. Ohman et al., 2017), but this method may find too many inconsequential covariates which are merely correlated with the actual effect modifiers.

To fill this gap, we propose a method that combines classical semiparametric regression (c.f. Robinson, 1988; van der Vaart, 2000; Li and Racine, 2007) with recent advances in post-selection inference for high-dimensional regression (c.f. Berk et al., 2013; Lee et al., 2016a; Fithian et al., 2014; Tian and Taylor, 2018; Rinaldo et al., 2016). The basic idea is that the semiparametric regression is used to remove confounding and increase the power of discovering treatment effect variation, and the post-selection inferential tools are then used to ascertain the discovered effect modifiers. Although this idea is generally applicable to other selective inference methods, in this paper we will focus on the selective inference framework developed in Lee et al. (2016a) where the effect modification model is selected by the lasso (Tibshirani, 1996).

Our method can also be used in non-causal regression problems when the interest is on the interaction terms between some low-dimensional primary variables (not necessarily a treatment) and some high-dimensional covariates. Examples include gene-environment interaction (Crossa et al., 2010; Biswas et al., 2014), interaction between species traits and environment in ecology (Brown et al., 2014), and subgroup-specific reactions to political issues when modeling electoral choices (Mauerer et al., 2015). In these examples, the applied researchers often want to make statistical inference for a selected interaction model.

In the rest of the Introduction, we shall give a brief overview of our proposal with minimal mathematical details. Since our proposal of combining Robinson’s transformation and selective inference is very straightforward, a practitioner should be able to implement this procedure after reading the Introduction and may skip the theoretical details in the next few Sections until the applied example in Section 6.

1.2. Causal model and the tradeoff between accuracy and interpretability. We first describe the causal model used in this paper. Suppose we observe i.i.d. variables \{X_i, T_i, Y_i\}_{i=1}^n where the vector $X_i \in X \subset \mathbb{R}^p$ contains covariates measured before the treatment, $T_i \in \mathcal{T}$ is the treatment assignment, and $Y_i \in \mathbb{R}$ is the observed continuous response. Let $Y_i(t)$ be the potential outcome (or counterfactual) of $Y_i$ if the treatment is set to $t \in \mathcal{T}$. Throughout this paper we shall assume $Y_i = Y_i(T_i)$ (consistency of the observed outcome) and the usual unconfoundedness and positivity assumptions in causal inference; see Section 3 for more detail. We allow our dataset to come from a randomized experiment (where the distribution $T_i|X_i = x$ is known) or an observational study (where the distribution $T_i|X_i = x$ must be estimated from the data).

We assume a nonparametric model for the potential outcomes,

$$Y_i(t) = \eta(X_i) + t \cdot \Delta(X_i) + \epsilon_i(t), \quad i = 1, \ldots, n.$$  

Here $\eta$ and $\Delta$ are functions defined on $X$ and $\mathbb{E}[\epsilon_i(t)|X_i] = 0$. Our model (1) is very general. It is in fact saturated if the treatment $T_i$ is binary, i.e. $\mathcal{T} = \{0, 1\}$. In this case, $\Delta(x) = \mathbb{E}[Y_i(1) - Y_i(0)|X_i = x]$ is commonly referred to as the conditional average treatment effect (CATE). When the treatment is continuous, i.e. $\mathcal{T} \subseteq \mathbb{R}$ (for example dosage), model (1) assumes the interactions between the treatment and the covariates are linear in the treatment but possibly nonlinear in the covariates. In causal inference, $\Delta(x)$ is the parameter of interest (for example, $\mathbb{E}[\Delta(X)]$ is the average treatment...
effect), whereas \( \eta(x) \) is regarded as an infinite-dimensional nuisance parameter. We say there is effect modification if the function \( \Delta(x) \) is not a constant.

When the dimension of \( X \) is high, there is a fundamental tradeoff between estimation accuracy and interpretability of \( \Delta(x) \). On one extreme (the rightmost column in Table 1), one could use flexible machine learning methods to estimate \( \Delta(x) \), which is important when the goal is accurate prediction (e.g. for the purpose of personalizing the treatment). However, such models are generally very difficult to interpret (see e.g. Zhao and Hastie, 2017). For example, in random forests it is challenging to even define a good notion of variable importance (Strobl et al., 2007). The full linear model \( \Delta(x) \approx \alpha + x^T \beta \) suffers from the same interpretability problem when the dimension of \( x \) is more than just a few. Moreover, important effect modifiers may be masked by noise covariates.

On the other extreme (the leftmost column in Table 1), one could run marginal regressions to test if (estimated) \( \Delta(x) \) is correlated with each covariate. However, this method usually discovers too many false positive covariates in the sense that they are no longer associated with \( \Delta(x) \) after conditioning on the actual effect modifiers. For example, in our example in Section 6, the most probable effect modifiers are gender and age. However, univariate regressions also find several other covariates significant, including marital status and whether the person had arthritis, heart attack, stroke, and gout. This is most likely due to their strong correlation with age.

Following the ideas in Berk et al. (2013) and Lee et al. (2016a), in this paper we propose to use a linear submodel to approximate the treatment effect, \( \Delta(x) \approx \alpha_{\mathcal{M}} + x^T_{\mathcal{M}} \beta_{\mathcal{M}} \), where the subset \( \mathcal{M} \subseteq \{1, \ldots, p\} \) is selected using the data. We argue that a low-dimensional linear model often yields the desirable tradeoff between accuracy and interpretability by selecting important effect modifiers, especially if the goal is to discover a few effect modifiers for further investigation or to select covariates to personalize the treatment. In our applied example Section 6 that considers the effect of being overweight on systematic inflammation, our method selected the linear submodel with gender, age, stroke, and gout to approximate \( \Delta(x) \). After adjusting for model selection, stroke and gout become non-significant in the submodel. Table 1 gives a comparison of the strengths and weaknesses of using different statistical models to approximate \( \Delta(x) \).

### Table 1. Tradeoff of accuracy and interpretability of different models of effect modification.

In the case of high-dimensional covariates, machine learning and full linear model approximate \( \Delta(x) \) more accurately but are difficult to interpret. Univariate regressions find the covariates correlated with \( \Delta(x) \) but may end up with false positives that are no longer correlated with \( \Delta(x) \) after conditioning on other covariates. The selected submodel approach proposed in this paper is an attractive trade-off between accuracy and interpretability. See Section 7.1 for more discussion.

1.3. **Our proposal.** In this paper we will select the linear submodel of effect modification using the lasso (Tibshirani, 1996), which has been shown to be very effective at selecting relevant variables in high-dimensional regression (Zhao and Yu, 2006, Hastie et al., 2009, Buhlmann and van de Geer, 2011). To illustrate the proposal, for a moment let’s assume \( \eta(x) = 0 \) for all \( x \in X \) and \( T_i = 1 \), so (1) becomes a conditional mean model:

\[
Y_i = \Delta(X_i) + \epsilon_i, \quad i = 1, \ldots, n.
\]
We can select a small linear submodel by running the following lasso regression with a prespecified regularization parameter $\lambda$,

\[
\text{(3) minimize } \sum_{i=1}^{n} (Y_i - \alpha - X_i^T \beta)^2 + \lambda \| \beta \|_1.
\]

Let the selected model $\hat{M} \subset \{1, \ldots, p\}$ be the positions of non-zero entries in the solution to the above problem. Lee et al. (2016a) derived an exact inference of the regression parameter $\beta^*_{M}$ where $\alpha^*_M + X_i^T \beta^*_M$ is the “best submodel approximation” of $\Delta(X_i)$ in Euclidean distance, assuming the design matrix is fixed. Thus the parameter $\beta^*_M$ here depends on the randomness in $X$ in a random design setting. Furthermore, $\beta^*_M$ also depends on the selected model $\hat{M}$ and thus inherits the randomness in the model selection procedure (Berk et al., 2013).

Based on a pivotal statistic obtained by Lee et al. (2016a) and by conditioning on the selection event, it is possible to form valid confidence intervals for the entries of $\beta^*_M$ that satisfies

\[
\text{(4) } P\left((\beta^*_M)_j \in [D^-_j, D^+_j] \mid \hat{M} = M\right) = 1 - q.
\]

An important consequence is that this guarantees the control of false coverage rate (FCR), that is

\[
\text{(5) } E \left[ \frac{\# \{ 1 \leq j \leq |\hat{M}| : (\beta^*_M)_j \notin [D^-_j, D^+_j] \} }{\max(|\hat{M}|, 1)} \right] \leq q.
\]

FCR is the average proportion of non-covering confidence intervals and extends the concept of false discovery rate to estimation (Benjamini and Yekutieli, 2005). Notice that (4) directly implies (5) given $M = \hat{M}$, and (5) can then be proven by marginalizing over $\hat{M}$. See Lee et al. (2016a) Lemma 2.1 and Fithian et al. (2014).

The main challenge to directly applying selective inference to the effect modification problem is the nuisance parameter $\eta(x)$. In this paper we propose to use the technique in Robinson (1988) to eliminate this nuisance parameter. Our proposal is a two-stage procedure. In the first stage, we introduce two nuisance parameters: $\mu_y(x) = E[Y_i | X_i = x]$ and $\mu_t(x) = E[T_i | X_i = x]$, so $\mu_y(x) = \eta(x) + \mu_t(x) \Delta(x)$ by (1) and unconfoundedness. The nonparametric model (1) can be rewritten as

\[
\text{(6) } Y_i - \mu_y(X_i) = [T_i - \mu_t(X_i)] \cdot \Delta(X_i) + \epsilon_i, \ i = 1, \ldots, n.
\]

We have eliminated $\eta(x)$ from the model but introduced two more nuisance parameters, $\mu_t(x)$ and $\mu_y(x)$. Fortunately, these two nuisance functions can be directly estimated by regression using the pooled data, preferably using some machine learning methods with good prediction performance as advocated by van der Laan and Rose (2011) and Chernozhukov et al. (2018a) (see Section 7.2 for more discussion). In the numerical examples, we will use the random forests (Breiman, 2001) as they usually have very competitive prediction accuracy and there is great off-the-shelf software (Liaw and Wiener, 2002; Athey et al., 2018). A common technique to control the remainder terms in semiparametric estimation is cross-fitting (i.e. sample splitting), where the predicted value (of the nuisance functions) for the $i$-th data point is fitted using a subsample of the data that does not contain the $i$-th data point (Schick, 1986; Chernozhukov et al., 2018a; Athey and Wager, 2017; Newey and Robins, 2018). For example, we can split the data into two halves and for the $i$-th data point, $\mu_y(X_i)$ and $\mu_t(X_i)$ will be estimated using the other half of the data. This technique will be used in our theoretical investigation. Let the estimated nuisance functions at the $i$-th data point be $\hat{\mu}_y^{(-i)}(X_i)$ and $\hat{\mu}_t^{(-i)}(X_i)$. For notational simplicity, we suppress the dependence on the subsample used to train these models and simply denote them as $\hat{\mu}_y(X_i)$ and $\hat{\mu}_t(X_i)$ below.
In the second stage, we plug in these estimates in (6) and select a model for effect modification by solving

\[ \hat{\beta}_M(\lambda) = \arg\min_{\alpha, \beta_M} \sum_{i=1}^{n} \left\{ [Y_i - \hat{\mu}_y(X_i)] - [T_i - \hat{\mu}_t(X_i)] \cdot (\alpha + X_{i,M}^T \beta_M) \right\}^2 + \lambda \| \beta_M \|_1 \]

with \( M = \{1, \ldots, p\} \) being the full model in this step. Let the selected model \( \hat{M} \) be the nonzero entries of \( \hat{\beta}_{\{1, \ldots, p\}}(\lambda) \). Consider the unpenalized least squares solution \( \hat{\beta}_M = \hat{\beta}_M(0) \) using the selected model \( \hat{M} \), which belongs to the “relaxed lasso” class of estimator \( \beta_{\hat{M}}(\lambda) \) indexed by \( \lambda \) (Meinshausen, 2007). Naturally, \( \hat{\beta} \) estimates the following (weighted) projection of \( \Delta(x) \) to the submodel spanned by \( X_{-M} \),

\[ \beta_M^* = \beta_{M}^*(T, X) = \arg\min_{\alpha, \beta_M} \sum_{i=1}^{n} [T_i - \mu_t(X_i)]^2 [\Delta(X_i) - \alpha - X_{i,M}^T \beta_M]^2. \]

This can be interpreted as the best linear approximation of \( \Delta(x) \) in the observed sample if observation \( i \) is weighted by \( [T_i - \mu_t(X_i)]^2 \). However, since the submodel \( \hat{M} \) is selected using the data, we must adjust for this fact to obtain the selective distribution of \( \hat{\beta}_M^* \). Our main theoretical contribution in this paper is to show that the pivotal statistic obtained by Lee et al. (2016a) is asymptotically valid under the standard rate assumptions in semiparametric regression (e.g. Robinson, 1988). The main challenge is that the estimation error in \( \mu_y(x) \) and \( \mu_t(x) \) further complicates the model selection event and the pivotal statistics.

For practitioners, our proposal can be easily implemented by using \( Y_i - \hat{\mu}_y(X_i) \) as the response and \( (T_i - \hat{\mu}_t(X_i)) \cdot X_i \) as the regressors in existing softwares for selective inference (Tibshirani et al., 2017b). Notice that it is not necessary to use the same set of covariates to remove confounding (estimate \( \mu_t(x) \) and \( \mu_y(x) \)) and make selective inference for effect modification. Thus the practitioner can simply run selective inference using \( Y_i - \hat{\mu}_y(X_i) \) as the response and \( (T_i - \hat{\mu}_t(X_i)) \cdot Z_i \) as the regressors, where \( Z_i \) are user-specified potential effect modifiers. For notational simplicity, we will assume \( Z_i = X_i \) from this point forward.

The rest of this paper is organized as follows. Section 2 reviews the selective inference in the linear model (2) and Section 3 reviews the asymptotics of the semiparametric regression estimator \( \hat{\beta}_M(0) \) with fixed model \( M \) and no regularization. Section 4 presents our main result. Section 5 verifies the asymptotic results through simulations and studies the performance of the selective confidence intervals in finite sample and high dimensional settings. Readers who are not interested in the technical details can skip these Sections and directly go to Section 6 where we discuss an application of the proposed method to an epidemiological study. Section 7 concludes the paper with some further discussion.

2. Review of selective inference in linear models

We briefly review selective inference for linear models using the lasso in Lee et al. (2016a). This corresponds to the simplified version (2) of our problem where \( \eta(x) = 0 \) for all \( x \in \mathcal{X} \) and \( T \equiv 1 \). First we follow Berk et al. (2013) and Lee et al. (2016a) and define the inferential target rigorously. For simplicity, we assume \( Y \) and every column of \( X \) are centered so their sample mean is 0. For any submodel \( M \subseteq \{1, \ldots, p\} \), we are interested in the parameter \( \beta_M \) such that \( X_{\hat{M}}^T \beta_M \) is the overall best approximation to the true mean of \( Y_i, \Delta(X_i) \), in the sense that

\[ \beta_M \ = \ \arg\min_{\beta_M \in \mathbb{R}^{\|M\|}} \sum_{i=1}^{n} \left( \Delta(X_i) - X_{\hat{M}}^T \beta_M \right)^2. \]

We do not need to consider the intercept term because the data are centered. Let

\[ X_{\hat{M}} = (X_{\hat{M}}^T X_{\hat{M}})^{-1} X_{\hat{M}}^T \]
be the pseudo-inverse of the matrix $X_{\mathcal{M}}$ (the submatrix of $X$ with columns in $\mathcal{M}$), so $\beta^*_\mathcal{M} = X_{\mathcal{M}}^\dagger \Delta$

where $\Delta = (\Delta(X_1), \ldots, \Delta(X_n))^T$.

We are interested in making inference for $\beta^*_\mathcal{M}$, where $\hat{\mathcal{M}}$ contains all the nonzero entries of the solution to the lasso problem (3). Notice that (3) is the same as (7) and (9) is the same as (8) by taking $\hat{\mu}_i(x) = \bar{\mu}_j(x) = 0$ since $T_i = 1$. We assume the noise $\varepsilon_i$ is i.i.d. normal with variance $\sigma^2$. The normality assumption can be relaxed in large samples (Tian and Taylor, 2017). A natural estimator of $\beta^*_\mathcal{M}$ is the least squares solution $\hat{\beta}_\mathcal{M} = X_{\mathcal{M}}^\dagger Y$ that treats $\mathcal{M}$ as known. However, to obtain the sampling distribution of $\hat{\mathcal{M}}$, the immediate challenge is that the submodel $\mathcal{M}$ is selected using the data, therefore the usual normal distribution of the least squares estimator does not hold.

To solve this problem, Lee et al. (2016a) proposed to use the conditional distribution $\hat{\beta}_\mathcal{M} | \hat{\mathcal{M}} = \mathcal{M}$ to construct a pivotal statistic for $\beta^*_\mathcal{M}$. Let $\hat{s}$ be the sign of the solution to the lasso problem (3). They found that the event $\{\hat{\mathcal{M}} = \mathcal{M}\}$ can be written as the union of some linear constraints on the response $Y$,

$$\{\hat{\mathcal{M}} = \mathcal{M}\} = \bigcup_{s} \{\mathcal{M} = \mathcal{M}, \hat{s} = s\} = \bigcup_{s} \{A(M, s)Y \leq b(M, s)\}.$$  (10)

The constraints are given by $A(M, s) = (A_0(M, s)^T, A_1(M, s)^T)^T$, $b(M, s) = (b_0(M, s)^T, b_1(M, s)^T)^T$, where $A_0$ satisfies $A_0X_{\mathcal{M}} = 0$ (the exact expressions for $A_0$ and $b_0$ can be found in Lee et al. (2016a)), and

$$A_1(M, s) = -\text{diag}(s)X_{\mathcal{M}}^\dagger, \quad b_1(M, s) = -\lambda \text{diag}(s)(X_{\mathcal{M}}^\dagger X_{\mathcal{M}})^{-1}s.$$

Suppose we are interested in the $j$-th component of $\beta^*_\mathcal{M}$. Let $\eta_M = (X_{\mathcal{M}}^\dagger)^T e_j$ where $e_j$ is the unit vector for the $j$-th coordinate, so $(\hat{\beta}^*_\mathcal{M})_j = \eta_M^T \Delta$ and $(\hat{\beta}_\mathcal{M})_j = \eta_M^T Y$. In a nutshell, the main result of Lee et al. (2016a) states that $(\hat{\beta}_\mathcal{M})_j | \hat{\mathcal{M}} = \mathcal{M}$ follows a truncated normal distribution. More precisely, let $F(y; \mu, \sigma^2, l, u)$ denote the CDF of normal variable $N(\mu, \sigma^2)$ truncated to the interval $[l, u]$, that is,

$$F(y; \mu, \sigma^2, l, u) = \frac{\Phi((y - \mu)/\sigma) - \Phi((l - \mu)/\sigma)}{\Phi((u - \mu)/\sigma) - \Phi((l - \mu)/\sigma)}.$$  (11)

Lee et al. (2016a) Theorem 5.2 showed that

**Lemma 1.** (Selective inference for the lasso) If the noise $\varepsilon_i$ are i.i.d. $N(0, \sigma^2)$, then

$$F((\hat{\beta}^*_\mathcal{M})_j; (\hat{\beta}^*_\mathcal{M})_j, \sigma^2 \eta_M^T \eta_M, L, U) \mid \hat{\mathcal{M}} = \mathcal{M}, \hat{s} = s \sim \text{Unif}(0, 1),$$

where

$$L = L(Y; \mathcal{M}, s) = \eta_M^T Y + \max_{\varepsilon_k \leq 0} b_k - A(M)k,$$

$$U = U(Y; \mathcal{M}, s) = \eta_M^T Y + \max_{\varepsilon_k \geq 0} b_k - A(M)k.$$  (12)

Since $A_0X_{\mathcal{M}} = 0$, we have $A_0 \eta_M = 0$. Therefore the interval $[L, U]$ only depends on $A_1$, which corresponds to the set of constraints on the active variables.

To construct the selective confidence interval for $(\hat{\beta}^*_\mathcal{M})_j$, one can invert the pivotal statistic (12) by finding values $D^-_j$ and $D^+_j$ such that

$$F((\hat{\beta}^*_\mathcal{M})_j; D^-_j, \sigma^2 \eta_M^T \eta_M, L, U) = 1 - q/2, \quad F((\hat{\beta}^*_\mathcal{M})_j; D^+_j, \sigma^2 \eta_M^T \eta_M, L, U) = q/2.$$  (13)

Then by (12) it is easy to show that the confidence interval $[D^-_j, D^+_j]$ controls the selective type I error (4) (if further conditioning on the event $(\hat{s} = s)$) and hence the false coverage rate (5). One can further improve the power of selective inference by marginalizing over the coefficient signs $s$, see Lee et al. (2016a) Section 5.2 for more detail.
3. Inference for a fixed model of effect modification

We now turn to the causal model (1) without the simplifying assumption that \( \eta(x) \equiv 0 \) and \( T \equiv 1 \). As explained in Section 1.3, the submodel parameter \( \beta^*_{\mathcal{M}} \) is defined by the weighted projection (8) instead of (6). First, we state the fundamental assumptions that are necessary for statistical inference for the conditional average treatment effect \( \Delta(x) \).

Assumption 1. (Fundamental assumptions in causal inference) For \( i = 1, \ldots, n \),

1. Consistency of the observed outcome: \( Y_i = Y_i(T_i) \);
2. Unconfoundedness of the treatment assignment: \( T_i \perp \!\!\!\perp Y_i(t)|X_i, \forall t \in T \);
3. Positivity (or Overlap) of the treatment assignment: \( T_i|X_i \) has a positive density with respect to a dominating measure on \( T \). In particular, we assume \( \text{Var}(T_i|X_i) \) exists and is between \( 1/C \) and \( C \) for some constant \( C > 1 \) and all \( X_i \in \mathcal{X} \).

Assumption 1A connects the observed outcome with the potential outcomes and states that there is no interference between the observations. Assumption 1B assumes that there is no unmeasured confounding variable and is crucial to identify the causal effect of \( T \) on \( Y \). This assumption is trivially satisfied in a randomized experiment \( (T_i \perp X_i) \). Assumption 1C ensures that statistical inference of the treatment effect is possible. All the assumptions are essential and commonly found in causal inference, see Rosenbaum and Rubin (1983), Hernan and Robins (2017).

In this section we consider the case of a fixed model of effect modification, where we want to approximate \( \Delta(X_i) \) with \( X_{i,\mathcal{M}}\beta_{\mathcal{M}} \) in the sense that it is the best linear approximation to the data generating model in (6). Formally, the inferential target is defined by (8) (replacing \( \hat{\beta} \) by \( \beta_{\mathcal{M}} \)). This is slightly different from the parameter in the linear model defined (6) because the outcome regression also involves the treatment variable. Similar to Section 3 we assume the response \( Y_i - \hat{\mu}_y(X_i) \) and the design \( (T_i - \hat{\mu}_t(X_i))X_i, i = 1, \ldots, n \), are all centered, so we will ignore the intercept term in the theoretical analysis below.

As described in Section 1, a natural estimator of \( \beta^*_{\mathcal{M}} \) is the least squares estimator \( \hat{\beta} = \hat{\beta}_{\mathcal{M}}(0) \) defined in (7) with the plug-in nuisance estimates \( \hat{\mu}_t(x) \) and \( \hat{\mu}_y(y) \) and no regularization. The problem is: how accurate do \( \hat{\mu}_t(x) \) and \( \hat{\mu}_y(y) \) need to be so that \( \hat{\beta}_{\mathcal{M}}(0) \) is consistent and asymptotically normal? One challenge of the theoretical analysis is that both the regressors and the responses in (7) involve the estimated regression functions. Our analysis hinges on the following modification of \( \beta_{\mathcal{M}} \):

\[
\hat{\beta}_{\mathcal{M}}(T, X) = \arg \min_{\beta_{\mathcal{M}} \in \mathbb{R}^{|\mathcal{M}|}} \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_t(X_i))^2 (\Delta(X_i) - X_{i,\mathcal{M}}\beta_{\mathcal{M}})^2.
\]

We use tilde in this paper to indicate that the quantity also depends on \( \hat{\mu}_t(\cdot) \) and/or \( \hat{\mu}_y(\cdot) \). The next Lemma shows that \( \hat{\beta}_{\mathcal{M}} \) is very close to the target parameter \( \beta^*_{\mathcal{M}} \) when the treatment model is sufficiently accurate.

Assumption 2. (Accuracy of treatment model) \( \|\hat{\mu}_t - \mu_t\|_2^2 = (1/n) \sum_{i=1}^{n} (\hat{\mu}_t(X_i) - \mu_t(X_i))^2 = o_p(n^{-1/2}) \).

Assumption 3. The support of \( X \) is uniformly bounded, i.e. \( \mathcal{X} \subseteq [-C, C]^p \) for some constant \( C \). The conditional treatment effect \( \Delta(X) \) is also bounded by \( C \).

Lemma 2. Suppose Assumptions 1 to 3 are satisfied. For a fixed model \( \mathcal{M} \) such that \( E[X_{i,\mathcal{M}}X_{i,\mathcal{M}}^T] \geq (1/C)I_{|\mathcal{M}|} \), we have \( \|\hat{\beta}_{\mathcal{M}} - \beta^*_{\mathcal{M}}\|_\infty = o_p(n^{-1/2}) \).

Assumption 4. (Accuracy of outcome model) \( \|\hat{\mu}_y - \mu_y\|_2 = o_p(1) \) and \( \|\hat{\mu}_t - \mu_t\|_2 \cdot \|\hat{\mu}_y - \mu_y\|_2 = o_p(n^{-1/2}) \).

The last assumption is a doubly-robust type assumption (Chernozhukov et al., 2018a). Double robustness is the property that the causal effect estimate is consistent if at least one of the two nuisance estimates are consistent (Bang and Robins, 2005). To make asymptotic normal inference, we
Assumption 6. (Sparse eigenvalue assumption) For all model definite, so the regressors are not collinear in any selected model.

Lemma 3. Under the assumptions in Lemma 2 and additionally Assumptions 5 and 6, \( \beta \) (Size of the selected model) For some constant \( C \) and let the selected model \( \hat{M} \) be the positions of the non-zero entries in the solution \( \beta_{\{1,\ldots,p\}}(\lambda) \). We want to make valid inference for the parameter \( \beta_{\hat{M}}^* \) defined in (8) given the fact that \( \hat{M} \) is selected using the data.

Compared to the selective inference in linear models described in Section 2, the challenge here is that the nuisance parameters \( \mu_\parallel(x) \) and \( \mu_\perp(x) \) must be estimated by the data. This means that in the regression model (6), the response \( Y_i - \mu_\parallel(X_i) \) and the regressors (in the approximate linear model) \( (T_i - \mu_\parallel(X_i))X_i \), are not observed exactly. Similar to Section 4, the estimation error \( \|\hat{\mu}_\parallel - \mu_\parallel\|_2 \) and \( \|\hat{\mu}_\perp - \mu_\perp\|_2 \) must be sufficiently small to make the asymptotic theory go through. Our main technical result is that with some additional assumptions on the selection event, the same rate assumptions in the fixed model case (Assumptions 2 and 4) holds trivially. Assumption 4 is reduced to the very weak condition that \( \hat{\mu}_\parallel(x) \) is consistent. It is easily satisfied by standard nonparametric regressions or the random forests (Biau, 2012, Scornet et al., 2015).

4. Selective inference for effect modification

As argued in Section 1, it is often desirable to use a simple model to approximately describe the effect modification when the dimension of \( X \) is high. One way to do this is to solve the lasso problem (9) and let the selected model \( M = \hat{M}, \) be the positions of the non-zero entries in the solution \( \beta_{\{1,\ldots,p\}}(\lambda) \). We want to make valid inference for the parameter \( \beta_{\hat{M}}^* \) defined in (8) given the fact that \( \hat{M} \) is selected using the data.

Similarly to Lemma 2, we assume the covariance matrices of the design \( X \) are uniformly positive definite, so the regressors are not collinear in any selected model.

Assumption 6. (Sparse eigenvalue assumption) For all model \( M \) such that \( \|M\| \leq m \), \( E[X_{i:M}X_{i:M}^T] \geq (1/C)I_{|M|} \).

These additional assumptions ensure the modified parameter \( \tilde{\beta}_{\hat{M}} \) is not too far from the target parameter \( \beta_{\hat{M}}^* \) when the treatment model is sufficiently accurate.

Lemma 3. Under the assumptions in Lemma 2 and additionally Assumptions 3 and 6, \( \|\beta_{\hat{M}}^*\|_\infty = O_p(1) \) and \( \|\beta_{\hat{M}} - \beta_{\hat{M}}^*\|_\infty = o_p(n^{-1/2}) \).
Let $\hat{X}_{i,M} = (T_i - \hat{\mu}_t(X_i))X_{i,M}$ be the transformed design (tilde indicates dependence on $\hat{\mu}_t$) and $\hat{\eta}_M = (\hat{X}_{1,M})^T \mathbf{e}_j$ be the linear transformation we are interested in. In other words, $(\hat{\beta}_M)_j = \hat{\eta}_M^T Y$ where $Y = Y - \hat{\mu}_y$ and $\hat{\mu}_y$ is the vector of fitted values of the $Y$ versus $X$ regression, $\hat{\mu}_y = (\hat{\mu}_y(X_1), \ldots, \hat{\mu}_y(X_n))^T$. The model selection event $(10)$ can be obtained analogously by substituting $X$ with the estimated transformed design $\hat{X}$ in the definition of the matrices $A(M, s)$ and vectors $b(M, s)$.

Next we state the extra technical assumptions for our main Theorem.

**Assumption 7.** (Truncation threshold) The truncation thresholds $L$ and $U$ (computed using the transformed design $\hat{X}$) satisfy

$$P\left(\frac{U(Y - \hat{\mu}_y) - L(Y - \hat{\mu}_y)}{\sigma \|\hat{\eta}_M\|} \geq 1/C\right) \to 1.$$  

**Assumption 8.** (Lasso solution) $P\left(||\hat{\beta}_{1,\ldots,p}(\lambda)||_1 \geq 1/(C\sqrt{n}), \forall k \in \hat{M}\right) \to 1$.

Assumption 7 assumes the truncation points $L$ and $U$ are not too close (i.e., the conditioning event is not too small), so a small perturbation does not change the denominator of (11) a lot. Assumption 8 assumes the lasso solution does not have a small coefficient. This is true with high probability if the truth is a sparse linear model and the true nonzero coefficients are not too small; see Negahban et al. (2012). However, Assumption 8 does not require the true model is sparse and must be selected consistently. Together these two assumptions mean the selected model is not a small probability event and is stable to small perturbations. Notice that both these assumptions can be verified empirically.

Finally we state our main Theorem. Note that we assume the noise is homoskedastic and Gaussian in this Theorem, but it is possible to relax this assumption. See Section 7.2 for more discussion about all the assumptions in this paper.

**Theorem 2.** Suppose cross-fitting is used to estimate the nuisance functions and the noise $\epsilon_i$ are i.i.d. $N(0, \sigma^2)$. Under Assumptions 4 to 8 the pivotal statistic in (12) is asymptotically valid. More specifically, for any $M$ such that $P(M = \hat{M}, \hat{s} = s) > 0$,  

$$P(\frac{F\left( (\hat{\beta}_M)_{j, \hat{\beta}^*_{M}} \right) - (\beta^*_{M})_{j, \hat{\beta}^*_{M}}}{\sigma \|\hat{\eta}_M\|} \geq 1/C) \to 1.$$  

The main challenge in proving Theorem 2 is that the CDF $F$ is a ratio (defined in Equation (11)), so it is necessary to bound the error in both the numerator and the denominator. Also, the truncation limits $L$ and $U$ involve taking maxi-ima over many constraints, which lead to additional complications. Notice that our proof of Theorem 2 can be easily extended to other variable selection methods such as forward stepwise regression as long as the selection event $\{M = \hat{M}\}$ can be characterized as linear constraints of $Y$ (Loftus and Taylor, 2014; Taylor and Tibshirani, 2015). In this case, Assumption 8 needs to be replaced by the condition that these linear constraints are satisfied with at least $O(1/\sqrt{n})$ margin. See Lemma 8 in the Appendix.

Similar to the case in Section 3, the pivot in (15) has no unknown parameter (except for $\sigma^2$, which is assumed to be known in the selective inference of Lee et al. (2016a)) and can be inverted as in (13) to obtain the confidence intervals for the coefficients $\beta^*_{M}$.

5. Simulation

5.1. Validity of selective inference for effect modification. We evaluate the method proposed in this paper with data simulated from the causal model (1). We consider a comprehensive simulation design parametrized by the following parameters:

- $s_t$: sparsity of $\mu_t$, either 0 (a randomized experiment), 5, or 25.
- $f_t$: functional form of $\mu_t$, either linear (lin), quadratic (qua), a five-variate function used by Friedman and Silverman (1989) (FS), or a five-variate function used by Friedman, Grosse, and Stuetzle (1983) (FGS); see below for detail.
• $s_y$: sparsity of $\mu_y$, either 5 or 25.
• $f_y$: functional form of $\mu_y$, same options as $f_t$.
• $s_\Delta$: sparsity of $\Delta$, either 5 or 25.
• $f_\Delta$: functional form of $\Delta$, same options as $f_t$.
• $\sigma$: standard deviation of the noise, either 0.25 or 0.5.
• noise: distribution of the noise, either $\sigma \cdot N(0,1)$ or $\sigma \cdot \text{double-exp}(0,1/\sqrt{2})$.

These give us 3072 simulation settings in total. The functional forms are

- Linear: $f(x_1, x_2, x_3, x_4, x_5) = 3x_1 + x_2 + x_3 + x_4 + x_5 - 3.5$;
- Quadratic: $f(x_1, x_2, x_3, x_4, x_5) = 3(x_1 - 0.5)^2 + (x_2 - 0.5)^2 + (x_3 - 0.5)^2 + (x_4 - 0.5)^2 + (x_5 - 0.5)^2 + 3x_1 + x_2 + x_3 + x_4 + x_5 - 4$;
- FS: $f(x_1, x_2, x_3, x_4, x_5) = [0.1 \exp^{4x_1} + 4/(1 + \exp^{-20(x_2 - 0.5)}) + 3x_3 + 2x_4 + x_5 - 6.3]/2.5$;
- FGS: $f(x_1, x_2, x_3, x_4, x_5) = [10 \sin(\pi x_1 x_2) + 20(x_3 - 0.5)^2 + 10x_4 + 5x_5 - 14.3]/4.9$.

In every setting, we generate $n = 1000$ observations and $p = 25$ covariates that are uniformly distributed over $[0, 1]$ and independent. If the sparsity is 5, for example $s_t = 5$, then $\mu_t(x) = f(x_1, x_2, x_3, x_4, x_5)$. If the sparsity is 25, then $\mu_t(x) = f(x_1, x_2, x_3, x_4, x_5)/1^2 + f(x_6, x_7, x_8, x_9, x_{10})/2^2 + \cdots + f(x_{21}, x_{22}, x_{23}, x_{24}, x_{25})/5^2$ and similarly for $\mu_y(x)$ and $\Delta(x)$. To evaluate the performance of selective inference in high-dimensional settings, we also simulate a more challenging setting with $p = 500$ covariates by appending 475 independent covariates to $X$.

After the data are generated, we use the lasso (with cross validation) or random forest to estimate the nuisance functions $\mu_t(x)$ and $\mu_y(x)$. For the lasso we use the R package glmnet (Friedman et al., 2010). For the random forest we use the R package randomForest (Liaw and Wiener, 2002) with all the default tuning parameters except nodesize = 20 and mtry = 25. For $\hat{\mu}_t(x)$ and $\hat{\mu}_y(x)$, we use the out-of-bag (OOB) predictions from the random forests. This may serve as a proxy to cross-fitting. We have also tried to use cross-fitting to estimate the nuisance functions, but that appears to deteriorate the performance of our methods. Thus in all the empirical investigations below, we decide to use the full sample to estimate the nuisance functions. See Section 7.2 for more discussion on cross-fitting.

We select effect modifiers using the lasso regression (7) with $\lambda = 1.1 \times E[\|X\epsilon\|_\infty]$ as recommended by Negahban et al. (2012). The noise variance $\sigma^2$ is estimated by the full linear regression of $Y_t - \hat{\mu}_y(X_i)$ on $[T_i - \hat{\mu}_t(X_i)]X_i$, $i = 1, \ldots, n$. Finally we use the asymptotic pivot in (15) to construct selective 95%-confidence intervals for the selected submodel as implemented in the function fixedLassoInf in the R package selectiveInference (Tibshirani et al., 2017a). In each simulation setting, we run the above procedure for 300 independent realizations. Three error metrics are reported: the false coverage rate (FCR) defined in (9), the selective type I error (STIE) defined in (4), and the false sign rate (FSR)

$$\text{FSR} = E\left[\frac{\#\{j \in M : 0 \notin [D_j^-, D_j^+]\}, (\beta^*_M)_j \cdot D_j^- < 0\}}{\max(|M|,1)}\right]$$

to examine if any significant selective confidence interval has the incorrect sign.

5.1.1. Results in the low-dimensional settings. In Table 2 we report the simulation results in the low-dimensional settings when the true functional forms are all linear and the nuisance functions are estimated by the random forest. The size of the selected model $|M|$ seems to heavily depend on the intrinsic complexity of the nuisance parameter $(s_t, s_y)$ and the noise level $(\sigma)$. The selective type I error and the false coverage rate were controlled at the nominal 5% level even when the noise is non-Gaussian, and no significant confidence interval containing only incorrect signs was found. Similar conclusions can be reached from Table 3 where exactly one of the true functional forms is nonlinear, with the exception that in two simulation settings the false coverage rates (FCR) were greater than 10%. In both cases, the true propensity score $\mu_t(x)$ is generated by the FGS and the biases of the estimated propensity score $\hat{\mu}_t$ were larger than those in the other settings.
Table 2. Performance of the selective confidence intervals in low-dimensional settings where the true $\mu_t(x)$, $\mu_y(x)$, and $\Delta(x)$ are linear in $x$ and the nuisance functions are estimated by the random forest. The false coverage rates (FCR) and selective type I error (STIE) are all close to the nominal 5% level. Columns in this table are: sparsity of $\mu_t$ ($s_t$), functional form of $\mu_t$ ($f_t$), sparsity of $\mu_y$ ($s_y$), functional form of $\mu_y$ ($f_y$), sparsity of $\Delta$ ($s_\Delta$), functional form of $\Delta$ ($f_\Delta$), standard deviation of the noise ($\sigma$), distribution of the noise (noise), average size of selected models ($|\hat{M}|$), average number of significant partial regression coefficients (# sig), false coverage rate (FCR), selective type I error (STIE), false sign rate (FSR), average bias of the estimated propensity score (bias($\hat{\mu}_t$)).

To get a broader picture of the performance of selective inference, Figure 1 shows the FCR versus the average bias of $\hat{\mu}_t$ for all the 3072 simulation settings when $X$ is low-dimensional ($p = 25$). When $s_t = 0$ (randomized experiments), the error rates were well controlled at the nominal 5% level across all settings, regardless of the dimension of $X$. When $s_t > 0$ (observational studies), the rate assumption for $\hat{\mu}_t$ (Assumption 2) could be violated and there is no guarantee that the selective inference is still asymptotically valid. Somewhat surprisingly, the false coverage rates were not too high in most simulation settings. This is especially true when the nuisance functions are estimated by the random forest. The FCR was well controlled except when $f_t$ is FGS, the case that the random forest estimator of $\mu_t$ was clearly biased. The selective inference performed poorly when $\mu_t$ and $\mu_y$ are estimated by lasso, which is not too surprising because some of the functional forms we used are highly nonlinear.

5.1.2. Results in the high-dimensional settings. The coverage of selective CI deteriorated in observational studies when the dimension of $X$ is high ($p = 500$). Figure 3 is the counterpart of Figure 1 in the high dimensional settings. The FCR is usually much higher than the nominal level, though the performance of lasso is better than the random forest. It seems that the “bet on sparsity” principle (Hastie et al., 2009) pays off to some extent here. When both $\mu_t$ and $\mu_y$ are linear or quadratic functions and when they are estimated by the lasso, the FCR were never larger than 10% (this cannot be directly observed from Figure 3).

5.1.3. Coverage of WATE. A somewhat surprising observation from the previous figures is that although our selective inference procedure cannot guarantee selective error control due to estimation error of $\mu_t$ and $\mu_y$, the false coverage rate was not too much larger than the nominal level in many simulation settings. In Figure 3 we compare FCR with coverage error of a weighted average treatment effect (WATE) in all the simulation settings. The WATE is given by solving the optimization problem...
without effect modification, that is,

\[
\text{WATE} = \arg \min_\alpha \sum_{i=1}^n \left[ T_i - \mu_t(X_i) \right]^2 \left[ \Delta(X_i) - \alpha \right]^2 = \frac{\sum_{i=1}^n \left[ T_i - \mu_t(X_i) \right]^2 \Delta(X_i)}{\sum_{i=1}^n \left[ T_i - \mu_t(X_i) \right]^2}.
\]

Notice that as \( n \to \infty \), we have

\[
\text{WATE} \overset{p}{\to} \mathbb{E}[\mu_t(X_i)(1 - \mu_t(X_i))\Delta(X_i)] / \mathbb{E}[\mu_t(X_i)^2(1 - \mu_t(X_i))]
\]

by the law of large numbers. The population limit on the right hand side is known as the optimally weighted average treatment effect (Crump et al., 2006); see also Li et al. (2018), Zhao (2019).

Confidence intervals of the WATE were obtained by a simple linear regression of \( Y_i - \hat{\mu}_y(X_i) \) on \( T_i - \hat{\mu}_t(X_i) \). In randomized settings (\( s_t = 0 \)), both error rates were controlled at the nominal level as expected. In observational settings (\( s_t = 5 \) or 25), coverage of WATE was very poor, sometimes completely missing the target (coverage error is almost 100%). In contrast, although there is also no guarantee of controlling the FCR as we have shown previously, the FCR was always smaller than the coverage error of WATE. This suggests that the selective inference of effect modification may be more robust to estimation error in the nuisance functions than the semiparametric inference of WATE.
5.2. **Necessity and sufficiency of the rate assumptions.** One of the main theoretical conclusions of this paper is that, when the design and the outcome are observed with error, the selective pivotal statistic is still asymptotically valid as long as the classical semiparametric rate assumptions Assumptions 2 and 4 are satisfied. In the next simulation, we verify the sufficiency and necessity of the crucial condition $\|\hat{\mu}_t - \mu_t\|_2 \cdot \|\hat{\mu}_y - \mu_y\|_2 = o_p(n^{-1/2})$ in an idealized setting. In this simulation, the true design and the true outcome were generated by

$$X_i \sim \mathcal{N}(0, I_{30}), \ Y_i \sim \mathcal{N}(X_i^T \beta, 1), \ i = 1, \ldots, n,$$

where $\beta = (1, 1, 1, 0, \ldots, 0)^T \in \mathbb{R}^{30}$. Next, the design and the outcome were perturbed by

$$X_i \rightarrow X_i \cdot (1 + n^{-\gamma} D_{1i}), \ Y_i \rightarrow Y_i + n^{-\gamma} D_{2i},$$

where $D_{1i}$ and $D_{2i}$ are independent standard Gaussian random variables. Since the nuisance parameters $\mu_t$ and $\mu_y$ are always estimated with error in Section 5.1 the $(1 + n^{-\gamma} D_{1i})$ and $n^{-\gamma} D_{2i}$ terms were used to simulate the estimation error. We used five different values of $\gamma$ in this simulation,
Figure 2. False coverage rate (FCR) versus bias of $\hat{\mu}_t$ in the 3072 high-dimensional simulation settings ($p = 500$). When $s_t = 0$ (randomized experiment), the false coverage rate is well controlled. When $s_t > 0$ (observational data), the FCR can be much larger than the nominal 5% level, though FCR is generally smaller when the nuisance functions are estimated by the lasso instead of random forest.

6. Application: Overweight and systemic inflammation

Finally we use an epidemiological study to demonstrate the method proposed in this paper. Visser et al. (1999) studied the effect of being overweight on low-grade systemic inflammation as measured
6.1. Dataset and methods. We obtain a more recent dataset from NHANES 2007–2008 and 2009–2010. We restricted to survey respondents who were not pregnant, at least 21 years old, and whose BMI and CRP levels are not missing. Among the 10679 people left, 969 have missing income, 4 have missing marital status, 15 have missing education, 1 has missing information about frequent vigorous
recreation, and 20 have no current smoking information. To illustrate the method in this paper, we
ignore the entries with missing variables and end up with 9677 observations. The dataset and R
code of our analysis are included in the supplement.

The CRP level in the dataset ranges from 0.01 mg/dL to 20.00 mg/dL and roughly follows a
log-normal distribution (see the supplementary file). Therefore we decided to use \log(\text{CRP}) as the
response in the regression. We use all the confounders identified in Visser et al. (1999), including
gender, age, income, race, marital status, education, vigorous work activity (yes or no), vigorous
recreation activities (yes or no), ever smoked, number of cigarettes smoked in the last month, estrogen
usage, and if the survey respondent had bronchitis, asthma, emphysema, thyroid problem, arthritis,
heart attack, stroke, liver condition, and gout. There are in total 20 variables and some of them are
categorical. Using the R function \texttt{model.matrix}, the design matrix \(X\) we use has 9677 rows and 30
columns. To test the performance of selective inference in higher dimensions, we also consider a bigger
model containing all the main effects and the first-order interactions of \(X\) (365 columns in total). We
refer the reader to the supplementary file for more summary statistics of these variables.

We examine five different statistical analyses of effect modification using this dataset:

1. Naive linear model: both \(\eta(x)\) and \(\Delta(x)\) are modeled by linear functions of \(x\).
2. Full model: in the following four models, the nuisance parameters (\(\mu_y\) and \(\mu_t\)) are estimated
   by the random forest (Breiman, 2001) (as implemented in the R package \texttt{randomForest}). In
   the full model, \(\Delta(x)\) is modeled by the full linear model \(\Delta(x) \approx \alpha + x^T \beta\).
3. Univariate screening: \(\Delta(x)\) is modeled by univariate linear model \(\Delta(x) \approx \alpha + x_j \beta_j\) for each
   \(j = 1, \ldots, p\) (in the analysis we centered each column of \(X\), so the intercept \(\alpha\) is the same).
4. Selected model: \(\Delta(x) \approx \alpha_{\mathcal{M}} + x^T \hat{\beta}_{\mathcal{M}}\) where \(\mathcal{M}\) is selected by solving the lasso problem (7)
   with \(\lambda = 1.1 \times \mathbb{E}[\|X\epsilon\|_\infty]\) where \(\epsilon \sim N(0, \hat{\sigma}^2 I_p)\) as suggested by Negahban et al. (2012). Then
   we used the pivotal statistic in (15) to make selective inference of \(\hat{\beta}_{\mathcal{M}}\). The noise variance \(\sigma^2\)
   is estimated from a full model as suggested by Lee et al. (2016a).
5. Data snooping model: this is the same as selected model except the statistical inference of
   \(\hat{\beta}_{\mathcal{M}}\) ignores the fact that \(\mathcal{M}\) is selected using the data (known as data snooping).

Figure 4. False coverage proportion under different strengths of perturbation and
different sample sizes. Using naive inference that ignores the model is selected using
the data, the false coverage rate is not controlled. Using selective inference, the false
coverage proportion converges to the nominal 10\% level (the dashed horizontal line)
if and only if \(\gamma > 0.25\).
6.2. **Average treatment effect.** We obtain estimates of the weighted average treatment effect (WATE) in (16) using the naive linear model (method 1) and the full model (method 2). Since the last four methods use the same estimated nuisance parameters, their estimates of the WATE are identical. In other words, their only difference is how effect modification is modeled. The two estimates of WATE are quite close: using the naive linear model (nuisance parameters are estimated by linear model), the point estimate is 1.166 with 95% confidence interval [1.088, 1.244]; using the full model (parameters are estimated by the random forest), the point estimate is 1.168 with 95% confidence interval [1.071, 1.220].

6.3. **Effect modification.** The results of the five methods are reported in Tables 4 to 8, respectively. The first three methods do not select a submodel, so the coefficients of all 27 regressors are reported. In the selective inference (method 4), four regressors (Gender, Age, Stroke, Gout) were selected using the lasso when only main effects were used to approximate $\Delta(x)$. The last two regressors are replaced by Age $\times$ Vigorous work and Age $\times$ Stroke in the lasso when interaction terms are allowed. The corresponding partial coefficients are reported for methods 4 and 5.

Next we discuss three observations that the reader may have already noticed when comparing these results. First, although the naive linear model (method 1) and the full model (method 2) generate very similar estimates of the WATE, the coefficients in their effect modification models are notably different (compare Table 4 with Table 5). For example, the estimated coefficient of Gender is 0.654 using method 1 and 0.481 using method 2. In general, the full model is more credible because the nuisance parameters are more accurately estimated.

Second, the univariate screening (method 3) detects many covariates that are very likely not the actual effect modifiers. Besides Gender and Age themselves, all the other significant variables—Marital (Widowed), Marital (Never married), Arthritis, Heart attack, Stroke, and Gout—are strongly correlated with Gender or Age or both (the sample correlations are at least 0.15). When Gender and Age are already in the model (they were the first two active variables in the lasso solution path), these variables are not subsequently selected by the lasso or are not significant after adjusting for model selection.

Third, Stroke and Gout are selected by the lasso and they are not significant using selective inference (method 4) in Table 7a. However, they are significant by using the naive inference that ignores model selection (method 5) in Table 8a. A similar phenomenon happens when interaction terms are also used to model $\Delta(x)$. Age $\times$ Vigorous work and Age $\times$ Stroke are selected by the lasso but were not significant in a selective inference (Table 7b). The data snooping inference that ignores model selection would find them to be significant (Table 8b). In general, non-selective inference (data snooping) does not generate valid $p$-values and confidence intervals. The example here demonstrates the practical importance of selective inference, as stroke and gout would be reported as significant otherwise.

7. **Discussion**

7.1. **When is selective inference a good approach for effect modification?** In Section 6, we have compared accuracy and interpretability of different approaches to modeling effect modification. The machine learning approaches usually approximate the conditional average treatment effect $\Delta(x)$ better but are difficult to interpret. The univariate regressions find significantly covariates correlated with $\Delta(x)$, but that correlation can vanish after conditioning on other covariates as illustrated in the example in Section 6. The selective inference approach provides an appealing tradeoff between accuracy and interpretability and is a good approach for modeling effect modification when interpretability is important in the study, for example, when the goal is to generate new scientific hypotheses or to assist clinicians to make intelligent treatment decisions.

The simulations in Section 5 show that the selective inference for effect modification can be trusted in randomized experiments, but does not guarantee selective error control in observational studies, especially when the dimension of confounders is high. The consoling news is that the selective error
Table 4. Results of the naive linear model (method 1) where $\eta(x)$ and $\Delta(x)$ are modeled by linear functions of $x$. In other words, it is assumed that $Y_i = \gamma_0 + X_i^T\gamma + T_i(\alpha + X_i^T\beta)$ and the reported coefficients are $\beta$. The reported values are the point estimates, $p$-values and confidence intervals (CI) of each entry of $\beta$. In general, the results are less credible because the linear model can be misspecified.

| Estimate | $p$-value | CI low  | CI up  |
|----------|-----------|---------|--------|
| Gender (Female) | 0.654 | 0.000 | 0.488 | 0.821 *** |
| Age | -0.024 | 0.000 | -0.030 | -0.018 *** |
| Income | -0.019 | 0.495 | -0.072 | 0.035 |
| Race (Hispanic) | 0.052 | 0.752 | -0.272 | 0.377 |
| Race (White) | 0.166 | 0.196 | -0.086 | 0.418 |
| Race (Black) | 0.376 | 0.010 | 0.089 | 0.664 ** |
| Race (Other) | 0.038 | 0.842 | -0.337 | 0.141 |
| Marital (Widowed) | -0.083 | 0.593 | -0.389 | 0.223 |
| Marital (Divorced) | 0.161 | 0.202 | -0.086 | 0.409 |
| Marital (Separated) | -0.235 | 0.272 | -0.654 | 0.184 |
| Marital (Never married) | 0.117 | 0.320 | -0.113 | 0.347 |
| Marital (Living with partner) | -0.050 | 0.745 | -0.349 | 0.250 |
| Education (9–11th grade) | 0.259 | 0.100 | -0.049 | 0.566 . |
| Education (High school) | 0.307 | 0.041 | 0.013 | 0.601 * |
| Education (Some college) | 0.296 | 0.052 | -0.002 | 0.593 . |
| Education (College grad.) | 0.316 | 0.054 | -0.006 | 0.638 . |
| Vigorous work | -0.019 | 0.854 | -0.216 | 0.179 |
| Vigorous recreation | -0.323 | 0.001 | -0.521 | -0.125 *** |
| Ever smoked | -0.067 | 0.447 | -0.239 | 0.105 |
| # Cigarettes last month | -0.000 | 0.437 | -0.000 | 0.000 |
| Estrogen | -0.645 | 0.002 | -1.063 | -0.228 ** |
| Bronchitis | -0.092 | 0.725 | -0.603 | 0.420 |
| Asthma | 0.193 | 0.230 | -0.122 | 0.509 |
| Emphysema | 0.045 | 0.862 | -0.464 | 0.554 |
| Thyroid problem | 0.122 | 0.438 | -0.187 | 0.431 |
| Arthritis | -0.046 | 0.644 | -0.240 | 0.148 |
| Heart attack | -0.178 | 0.393 | -0.586 | 0.230 |
| Stroke | -0.364 | 0.090 | -0.785 | 0.057 . |
| Liver condition | -0.332 | 0.311 | -0.973 | 0.310 |
| Gout | -0.584 | 0.012 | -1.040 | -0.129 * |

is often not too much higher than the nominal level, and is usually smaller than the coverage error of the weighted ATE. Thus with observational and high dimensional data, the results of the selective inference of effect modification should be interpreted with caution, although they are usually more reliable than the inference of the weighted ATE.

When the dimension of $X$ is high, an alternative approach to high-dimensional regression inference is the debiased lasso [Zhang and Zhang, 2014, Van de Geer et al., 2014, Javanmard and Montanari, 2014]. Compared to the debiased lasso, the selective inference approach does not require sparsity of the true regression coefficients. Instead, it shifts the inferential target to the best linear approximation using the selected covariates [Berk et al., 2013]. It is also possible to make selective inference for the regression coefficient in the full model [Liu et al., 2018]. Notice that lasso is used for different purposes in these two approaches: the debiased lasso uses the lasso to estimate the regression coefficients, while selective inference only uses the lasso to select a submodel. In principle, we think our method is most useful in randomized experiments or observational studies with a moderate number (e.g. $p = 50$) of...
Table 5. Results of the full model (method 2) where $\mu_y(x)$ and $\mu_t(x)$ are estimated by the random forest and $\Delta(x)$ are modeled by $\Delta(x) \approx \alpha + x^T \beta$. The reported coefficients are $\beta$, which is the best linear approximation of $\Delta(x)$ in the sense of (8). Since there are 27 regressors in total and many of them are strongly correlated, it is difficult to interpret these coefficients.

covariates. Our method can be used in observational and high-dimensional setting, though in the $p \gg n$ case, it seems inevitable that strong sparsity assumptions about the true causal model are needed (in which case the debiased lasso would be more appealing). Another interesting approach to high-dimensional regression is the knockoff filter that aims at controlling the false discovery rate (Barber and Candès, 2015).

There are two situations where selective inference should not be used to model effect modification. The first is when prediction accuracy is the only goal. This can happen if we want to learn the optimal treatment regime and are not concerned about interpretability at all. In this case, machine learning methods such as outcome-weighted learning (Zhao et al., 2012) should be used, though this black box approach also raises many policy concerns and challenges (Price, 2014). Although selective inference can be used to generate interpretable decision rules, a generally more efficient low-complexity policy can be learned by directly maximizing the utility (Athey and Wager, 2017).
|                         | Estimate | p-value | CI low  | CI up  |
|-------------------------|----------|---------|---------|--------|
| Gender (Female)         | 0.494    | 0.000   | 0.350   | 0.639  |
| Age                    | -0.021   | 0.000   | -0.025  | -0.017 |
| Income                 | -0.013   | 0.582   | -0.057  | 0.032  |
| Race (Hispanic)        | 0.108    | 0.399   | -0.143  | 0.359  |
| Race (White)           | -0.060   | 0.416   | -0.204  | 0.084  |
| Race (Black)           | 0.175    | 0.076   | -0.018  | 0.368  |
| Race (Other)           | -0.069   | 0.683   | -0.399  | 0.261  |
| Marital (Widowed)      | -0.529   | 0.000   | -0.790  | -0.268 |
| Marital (Divorced)     | 0.088    | 0.455   | -0.143  | 0.320  |
| Marital (Separated)    | -0.135   | 0.554   | -0.583  | 0.313  |
| Marital (Never married)| 0.454    | 0.000   | 0.257   | 0.651  |
| Marital (Living with partner) | 0.073 | 0.609   | -0.206  | 0.351  |
| Education (9–11th grade) | -0.005  | 0.964   | -0.200  | 0.191  |
| Education (High school)| 0.068    | 0.433   | -0.102  | 0.238  |
| Education (Some college)| 0.090  | 0.278   | -0.073  | 0.254  |
| Education (College graduates) | 0.005 | 0.953   | -0.165  | 0.175  |
| Vigorous work          | 0.043    | 0.654   | -0.145  | 0.230  |
| Vigorous recreation    | -0.048   | 0.602   | -0.229  | 0.133  |
| Ever smokes            | -0.138   | 0.062   | -0.282  | 0.007  |
| # Cigarettes last month| 0.000    | 0.651   | -0.000  | 0.000  |
| Estrogen               | 0.070    | 0.746   | -0.352  | 0.491  |
| Bronchitis             | -0.194   | 0.457   | -0.704  | 0.317  |
| Asthma                 | 0.229    | 0.155   | -0.086  | 0.544  |
| Emphysema              | -0.453   | 0.067   | -0.937  | 0.032  |
| Thyroid                | -0.007   | 0.962   | -0.296  | 0.282  |
| Arthritis              | -0.410   | 0.000   | -0.576  | -0.244 |
| Heart attack           | -0.730   | 0.000   | -1.137  | -0.324 |
| Stroke                 | -0.919   | 0.000   | -1.332  | -0.506 |
| Liver condition        | -0.526   | 0.149   | -1.240  | 0.189  |
| Gout                   | -0.987   | 0.000   | -1.428  | -0.546 |

Table 6. Results of the univariate screening (method 3) where $\mu_y(x)$ and $\mu_t(x)$ are estimated by the random forest and $\Delta(x)$ are then modeled by $\Delta(x) \approx \alpha + x^T \beta_j$ for each $j = 1, \ldots, p$. This simple method can be used to detect potential effect modifiers. However, all the other significant regressors are strongly correlated with gender or Age, so it is very likely that they are not the actual effect modifiers.

The second situation is when we are interested in the causal effect of both the treatment and the discovered effect modifiers. Since we do not control for confounding between the effect modifiers and the outcome, selective inference nor any other method that does not control for such confounding can be used to estimate the causal effect of the effect modifiers. In other words, effect modifiers explain variation of the causal effect and may themselves be non-causal. Nonetheless, the advocated selective inference approach is useful for post-hoc discovery of important effect modifiers which are usually informative proxies to the underlying causes (VanderWeele and Robins, 2007). See VanderWeele (2015, Section 9.6) and the references therein for more discussion.

7.2. Assumptions in the paper. Our main theoretical result (Theorem 2) hinges on a number of assumptions. Here we explain when they are reasonable and discuss their implications in more detail.

Assumption 1A is fundamental to causal inference. It transforms the estimation of causal effect into a regression problem. Unconfoundedness (Assumption 1A) is crucial to identify the causal effect for
Table 7. Results of the selective inference (method 4) where $\mu_y(x)$ and $\mu_t(x)$ are estimated by the random forest and $\Delta(x)$ are modeled by $\Delta(x) = \alpha + x^T \hat{\beta}_M$ where $\hat{M}$ is selected after fitting a lasso with the main effects (Table 7a) or the main effects and first-order interactions (Table 7b). The selective $p$-values and confidence intervals are obtained using the pivotal statistic (15), which are asymptotically valid given the assumptions in this paper.

Table 8. Results of data snooping (method 5). Everything is the same as the selective inference (method 4) except that $\hat{M}$ is treated as given. The $p$-values and confidence intervals are not valid because the bias due to model selection was not taken into account.

observational studies, but it is unverifiable using observational data. It would be an interesting further investigation to study the sensitivity of the proposed method to the unconfoundedness assumption.
prediction accuracy than conventional parametric models. This practical advice is inspired by van der Laan and Rose (2011) and Chernozhukov et al. (2018a). Recently van der Laan (2017) proposed a nonparametric regression estimator called the highly adaptive lasso (HAL) which converges faster than $n^{-1/4}$ for functions with bounded variation norm.

Assumption 5 strongly restricts the size of the effect modification model. We believe it is indispensable in our approach and other semiparametric regressions to control the complexity of the parametric part. Assumption 5 is also used by Tian and Taylor (2017) to relax the Gaussianity assumption of the noise. Assumption 6 assumes the selected design matrix is not collinear and is a sparse eigenvalue assumption in high-dimensional regression (Bühlmann and van de Geer, 2011). It is needed to define the partial regression coefficient $\beta_{i,4}$ in (8). The boundedness assumptions in Assumptions 3, 7 and 8 are technical assumptions for the asymptotic analysis. Similar assumptions can be found in Tian and Taylor (2017) that are used to prove the asymptotics under non-Gaussian error. In our experience, the inversion of the pivot (to obtain selective confidence interval) is often unstable when Assumption 7 is not satisfied. In this case, Tian and Taylor (2018) proposed to smooth out the selection event by injecting noise to the outcome. Assumption 8 is used to ensure that the selection event using the estimated $\mu_y$ and $\mu_t$ is with high probability the same as the selection event using the true $\mu_y$ and $\mu_t$. We expect that Assumptions 7 and 8 can be greatly weakened using the randomized response approach to selective inference of Tian and Taylor (2018).

In our main Theorem we also assumed the noise is homoskedastic and Gaussian. This simplifies the proof as we can directly use the exact selective inference Lemma 1 derived by Lee et al. (2016a). We expect that this assumption can be weakened (see e.g. Tian and Taylor, 2018) as we only need asymptotic validity of the pivot when $\mu_y(x)$ is known (see the proof of Theorem 2 in the Appendix A.4).

7.3. Future directions. We have focused on semiparametric regression with additive noise in this paper so Robinson (1988)'s transformation can be applied. In general, many interesting estimands in causal inference and other statistical problems can be defined by estimating equations. While the present paper was being drafted and reviewed, a parallel literature has used the idea of Neyman orthogonalization (a generalization of Robinson's transformation) in a number of related problems, including inference about low-dimensional projections of causal functions (Semenova and Chernozhukov, 2017, Chernozhukov et al., 2018b), debiased-lasso inference for coefficients of the CATE $\Delta(X)$ assuming a sparse and linear model for $\Delta(X)$ (Semenova et al., 2017), nonparametric estimation of the CATE $\Delta(X)$ (Nie and Wager, 2017), regularized estimation of high-dimensional semiparametric nonlinear models (Chernozhukov et al., 2018b), and statistical learning with nuisance parameters (Foster and Syrgkanis, 2019). Our work is the first to consider post-selection inference for this type of problems. For future research it would be very interesting to develop selective inference in more general semiparametric problems, beyond the effect modification problem considered here. Other possible future directions include selective inference for non-linear models (e.g. trees) of $\Delta(x)$ and extending the method in this paper to longitudinal problems.
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A.1. Proof of Lemma 2. We first prove a Lemma that shows $\beta_\mathcal{M}^*$ is bounded.

**Lemma 4.** Under Assumptions 1 and 2 and $E[\mathbf{X}_{i,\mathcal{M}}\mathbf{X}_{i,\mathcal{M}}^T] \succeq (1/C)I_{|\mathcal{M}|}$, $\|\beta_\mathcal{M}^*\|_{\infty} = O_p(1)$.

**Proof.** See Appendix A.3 below. □

Next we prove Lemma 2. For simplicity we suppress the subscript $\mathcal{M}$ since it is a fixed set in Section 3. Let

$$
\psi(\beta, \mu_t) = \frac{1}{n} \sum_{i=1}^{n} (T_i - \mu_t(X_i))^2(\Delta(X_i) - X_i^T \beta)X_i.
$$

The first-order conditions for $\beta^*$ and $\tilde{\beta}$ are $\psi(\beta^*, \mu_t) = 0$ and $\psi(\tilde{\beta}, \tilde{\mu}_t) = 0$. Notice that $\psi$ is a linear function of $\beta$, so

$$
0 = \sqrt{n}\psi(\tilde{\beta}, \tilde{\mu}_t)
$$

$$
= \sqrt{n}\psi(\beta^*, \tilde{\mu}_t) + \left[\frac{1}{n} \sum_{i=1}^{n} (T_i - \tilde{\mu}_t(X_i))^2 X_i X_i^T\right] \sqrt{n}(\tilde{\beta} - \beta^*).
$$

Similar to the proof of Lemma 4, the term in the squared bracket converges to $E[\text{Var}(T_i|X_i) \cdot X_i X_i^T]$ which is positive definite by assumption. Thus it suffices to show $\sqrt{n}\psi(\beta^*, \tilde{\mu}_t) \xrightarrow{p} 0$. This is true because

$$
\sqrt{n}\psi(\beta^*, \tilde{\mu}_t)
$$

$$
= \frac{1}{\sqrt{n}} \sum_{i=1}^{n} [(T_i - \mu_t(X_i) + \mu_t(X_i) - \tilde{\mu}_t(X_i))^2(\Delta(X_i) - X_i^T \beta^*)X_i]
$$

$$
= \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (T_i - \mu_t(X_i))^2 \cdot (\Delta(X_i) - X_i^T \beta^*)X_i
$$

$$
+ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} 2(\mu_t(X_i) - \tilde{\mu}_t(X_i))(T_i - \mu_t(X_i))(\Delta(X_i) - X_i^T \beta^*)X_i
$$

$$
+ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} (\mu_t(X_i) - \tilde{\mu}_t(X_i))^2 \cdot (\Delta(X_i) - X_i^T \beta^*)X_i.
$$

(18)

The first term is 0 because $\psi(\beta^*, \mu_t) = 0$. The second term is $o_p(n^{-1/4})$ because $\|\mu_t - \tilde{\mu}_t\|_2 = o_p(n^{-1/4})$ and the rest is an i.i.d. sum with mean $E[(T_i - \mu_t(X_i))(\Delta(X_i) - X_i^T \beta^*)X_i] = 0$. The third
term is $o_p(1)$ because of the rate assumption $\|\mu_t - \hat{\mu}_t\|_2 = o_p(n^{-1/4})$ and boundedness of $\Delta(X)$, $X$, and $\beta^*$.

A.2. Proof of Theorem 1

Lemma 5. Under Assumptions 1 to 4 we have

$$\left( \sum_{i=1}^{n} (T_i - \hat{\mu}_i(X_i))^2 X_{i,M} X_{i,M}^T \right)^{-1/2} (\hat{\beta}_M - \beta_M) \xrightarrow{d} N(0, \sigma^2 I_{|M|}).$$

Combining Lemma 2 and Lemma 5 we obtain the asymptotic inference of $\beta^*_M$ in Theorem 1. Next we prove Lemma 5.

Like in Appendix A.1 we suppress the subscript $M$ for simplicity of notation. Denote $\mu_{yi} = \mu_y(X_i)$, $\mu_{ti} = \mu_t(X_i)$ and similarly for $\hat{\mu}_{yi}$ and $\hat{\mu}_{ti}$. Since $\hat{\beta}$ is the least squares solution, we have

$$\hat{\beta} = \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i)^2 X_i X_i^T \right]^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i) X_i (y_i - \hat{\mu}_{yi}) \right]$$

$$= \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i)^2 X_i X_i^T \right]^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i) X_i [\mu_{yi} - \hat{\mu}_{yi} + (T_i - \mu_{ti}) \Delta(X_i) + \epsilon_i] \right]$$

$$= \hat{\beta} + \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i)^2 X_i X_i^T \right]^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i) \epsilon_i X_i \right]$$

$$+ \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \hat{\mu}_i)^2 X_i X_i^T \right]^{-1} \left[ \frac{1}{n} \sum_{i=1}^{n} (T_i - \mu_{ti} + \mu_{ti} - \hat{\mu}_{ti}) X_i [\mu_{yi} - \hat{\mu}_{yi} + (\hat{\mu}_{ti} - \hat{\mu}_{ti}) \Delta(X_i)] \right]$$

In the last equation, the residual terms are smaller than $n^{-1/2}$ because of the rate assumptions in the Lemma (each term can be analyzed as in the proof of Lemma 2).

A.3. Proof of Lemma 3. We first prove a Lemma. Denote $\kappa(Z)$ be the all the eigen-values of a square matrix $Z$.

Lemma 6. Under Assumptions 1, 2, 5, and 6 with probability going to 1, for any $k$,

$$1/(2C^2) \leq \kappa((1/n)\hat{X}_{M}^T \hat{X}_{M}) \leq 2mC^3.$$

Therefore $\tilde{\eta}^T \tilde{\eta} = \Theta_p(1/n)$, meaning that for any $\epsilon > 0$, there exists a constant $C > 1$ such that $P(1/(Cn) \leq \tilde{\eta}^T \tilde{\eta} \leq C/n) \geq 1 - \epsilon$ for sufficiently large $n$.

Proof. For the first result, by Assumption 5 we only need to bound, for every $|M| \leq m$, the eigenvalues of $((1/n)\hat{X}_{M}^T \hat{X}_{M})$. This matrix converges to $E[\text{Var}(T_i | X_i) \cdot X_{i,M} X_{i,M}^T]$, whose eigenvalues are bounded by

$$\kappa\left(E[\text{Var}(T_i | X_i) \cdot X_{i,M} X_{i,M}^T]\right) \in \left[ \frac{1}{C} \cdot \kappa_{\min}\left(E[X_{i,M} X_{i,M}^T]\right), C \cdot \kappa_{\max}\left(E[X_{i,M} X_{i,M}^T]\right) \right] \in [1/C^2, mC^3].$$

Here we use the fact that the largest eigenvalue of a symmetric matrix is upper-bounded by the largest row sum of the matrix. Using the matrix Chernoff bound (Tropp, 2012), the eigenvalues of $((1/n)\hat{X}_{M}^T \hat{X}_{M})$ are bounded by $1/(2C^2)$ and $2mC^3$ with probability going to 1.

The second result follows from

$$\tilde{\eta}^T \tilde{\eta} = e_j^T (\hat{X}_{M}^T \hat{X}_{M})^{-1} e_j = \frac{1}{n} \left( \frac{1}{n} \hat{X}_{M}^T \hat{X}_{M} \right)^{-1} e_j e_j^T.$$
The diagonal entries of \((1/n)\\hat{X}^T_{M,\hat{M}} \hat{X}_{M,\hat{M}}\) are bounded by its smallest and largest eigenvalues, i.e. the reciprocal of the largest and smallest eigenvalue of \((1/n)\\hat{X}^T_{M,\hat{M}} \hat{X}_{M,\hat{M}}\).

Now we turn to the proof of Lemma 3. By Assumption 5 \(\|\beta^*_{\hat{M}}\|_\infty \leq \max_{|M| \leq m} \|\beta^*_M\|_\infty\), \(\|\hat{\beta}_M - \beta^*_{\hat{M}}\|_\infty \leq \max_{|M| \leq m} \|\beta^*_M - \beta^*_{\hat{M}}\|_\infty\) with probability tending to 1. By definition,

\[
\hat{\beta}_M = \left[ \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 X_{i,M} X_{i,M}^T \right]^{-1} \left[ \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 \Delta(X_i)X_{i,M} \right].
\]

By the boundedness of \(\text{Var}(T_i|X_i), \Delta(X_i)\) and the uniform boundedness of \(X_i\),

\[
\left\| \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 \Delta(X_i)X_{i,M} \right\|_\infty \leq C^2 \cdot \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 = O_p(1).
\]

Therefore

\[
\left\| \hat{\beta}^*_M \right\|_\infty \leq \left\| \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 X_{i,M} X_{i,M}^T \right\|^{-1}_1 \cdot \left\| \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 \Delta(X_i)X_{i,M} \right\|_\infty \\
\leq \sqrt{m} \left\| \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 X_{i,M} X_{i,M}^T \right\|^{-1}_2 \cdot C^2 \cdot \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 \\
\leq \sqrt{m} C^4 \frac{1}{n} \sum_{i=1}^n (T_i - \mu_{ti})^2 = O_p(1).
\]

The last inequality uses Lemma 6. Notice that the upper bound above holds uniformly for all \(|M| \leq m\). Thus \(\|\hat{\beta}^*_{\hat{M}}\|_\infty = O_p(1)\).

For \(\|\hat{\beta}_M - \beta^*_{\hat{M}}\|_\infty\), by Lemma 7 and the boundedness assumptions (including the boundedness of \(\beta^*\)), it is easy to show that \(\max_{|M| \leq m} \sqrt{n} \|\psi(\beta^*_M, \hat{\mu}_i)\|_\infty = o_p(1)\). Therefore by the same argument in the proof of Lemma 3 \(\max_{|M| \leq m} \|\hat{\beta}_M - \beta^*_{\hat{M}}\|_\infty = o_p(n^{-1/2})\).

A.4. Proof of Theorem 2. We prove this Theorem through a series of Lemmas.

Lemma 7. Under the assumptions of Lemma 5 and Assumption 3

\[
\max_{|M| \leq m} \left\| (\hat{X}^T_{M,\hat{M}} \hat{X}_{M,\hat{M}})^{-1} \hat{X}^T_{M,\hat{M}} (\hat{\mu}_y - \mu_y) \right\|_\infty = o_p(n^{-1/2}).
\]

Proof. The proof is similar to the one of Lemma 5. For any \(|M| \leq m\),

\[
\left\| (\hat{X}^T_{M,\hat{M}} \hat{X}_{M,\hat{M}})^{-1} \hat{X}^T_{M,\hat{M}} (\hat{\mu}_y - \mu_y) \right\|_\infty \\
= \left\| \left[ \frac{1}{n} \sum_{i=1}^n (T_i - \hat{\mu}_{ti})^2 X_{i,M} X_{i,M}^T \right]^{-1} \left[ \frac{1}{n} \sum_{i=1}^n (T_i - \hat{\mu}_{ti})X_{i,M}(\hat{\mu}_{yi} - \mu_{yi}) \right] \right\|_\infty \\
\leq \left\| \left[ \frac{1}{n} \sum_{i=1}^n (T_i - \hat{\mu}_{ti})^2 X_{i,M} X_{i,M}^T \right]^{-1} \right\|_1 \cdot \left\| \left[ \frac{1}{n} \sum_{i=1}^n [(T_i - \hat{\mu}_{ti}) + (\mu_{ti} - \hat{\mu}_{ti})]X_{i,M}(\hat{\mu}_{yi} - \mu_{yi}) \right] \right\|_\infty \\
\leq \sqrt{m} C^4 \frac{1}{n} \sum_{i=1}^n [(T_i - \mu_{ti}) + (\mu_{ti} - \hat{\mu}_{ti})](\hat{\mu}_{yi} - \mu_{yi}) \\
= o_p(n^{-1/2}).
\]

The last inequality uses the rate assumptions in Assumption 4. As an example, consider \((1/n) \sum_{i=1}^n (T_i - \mu_{ti})(\hat{\mu}_{yi} - \mu_{yi})\). Because cross-fitting is used to obtain \(\hat{\mu}_{yi}\), the two terms in the summand are independent. Thus \(E(T_i - \mu_{ti})(\hat{\mu}_{yi} - \mu_{yi}) = 0\). Using the consistency of \(\hat{\mu}_y\) and the Chebyshev inequality, it is straightforward to show \((1/\sqrt{n}) \sum_{i=1}^n (T_i - \mu_{ti})(\hat{\mu}_{yi} - \mu_{yi}) = o_p(1)\). Finally, notice that the bound above is universal for all \(|M| \leq m\).
Lemma 8. Under Assumption b₁(\hat{M}, \hat{s}) - A₁(\hat{M}, \hat{s}) \cdot (Y - \hat{\mu}_y) \geq 1/(C\sqrt{n}).

Proof. By the definition of A₁ and b₁,
\[ b₁(\hat{M}, \hat{s}) - A₁(\hat{M}, \hat{s}) \cdot (Y - \hat{\mu}_y) = -\lambda \text{diag}(s)(X^T_{s,M}X_{s,M})^{-1}s + \text{diag}(s)X^T_{s,M}(Y - \hat{\mu}_y). \]
The lasso solution \( \hat{\beta}_{1,...,p}(\lambda) \) satisfies the Karush-Kuhn-Tucker condition which says that
\[ X^T_{s,M}[X_{s,M}(\hat{\beta}_{1,...,p}(\lambda))_{\hat{M}} - (Y - \hat{\mu}_y)] + \lambda \hat{s} = 0. \]
Therefore by Assumption b₁(\hat{M}, \hat{s}) - A₁(\hat{M}, \hat{s}) \cdot (Y - \hat{\mu}_y) = |(\hat{\beta}_{1,...,p}(\lambda))_{\hat{M}}| \geq 1/(C\sqrt{n}).

Lemma 9. Under the assumptions in Theorem \[ \Phi \left( \frac{U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \right) - \Phi \left( \frac{L(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \right) = \Theta_p(1). \]

Proof. By the definition of U and Lemmas \[ U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})_j \]
\[ = \eta^T_M(Y - \hat{\mu}_y) - (\beta^*_{\hat{M}})_j + \min_{k:(A\eta_M)_k > 0} \frac{b_k - (A(Y - \hat{\mu}_y))}{(A\eta_M)_k} \]
\[ = \eta^T_M\epsilon + \eta^T_M(\mu_y - \hat{\mu}_y) + [(\beta^*_{\hat{M}})_j - (\beta^*_{\hat{M}})_j] + \min_{k:(A\eta_M)_k > 0} \frac{b_k - (A(Y - \hat{\mu}_y))}{(A\eta_M)_k} \]
\[ \geq \eta^T_M\epsilon + o_p(1/\sqrt{n}). \]
The last inequality uses the KKT conditions. Therefore
\[ \frac{U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \geq \left( \frac{\eta_M}{\|\hat{M}\|} \right)^T \left( \frac{\epsilon}{\sigma} \right) + o_p(1). \]
Notice that the first term on the right hand side follows the standard normal distribution. Similarly,
\[ \frac{L(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \leq \left( \frac{\eta_M}{\|\hat{M}\|} \right)^T \left( \frac{\epsilon}{\sigma} \right) + o_p(1), \]
This means the two terms in \( \Phi \) in \[ \Phi \left( \frac{U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \right) - \Phi \left( \frac{U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \right) = o_p(1), \]
and the same conclusion holds for the lower truncation threshold L.

Lemma 10. Under the assumptions in Theorem \[ \Phi \left( \frac{U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \right) - \Phi \left( \frac{U(Y - \hat{\mu}_y; \hat{M}, \hat{s}) - (\beta^*_{\hat{M}})}{\sigma \|\hat{M}\|} \right) = o_p(1), \]
Proof. First, we prove an elementary inequality. Suppose \( \{b_k\} \) and \( \{\tilde{b}_k\} \) are two finite sequences of numbers, \( b_k \geq 0 \) and \( |\tilde{b}_k - b_k| \leq b_k \). Then
\[ \min_k b_k - \min_k \tilde{b}_k \leq (\min_k b_k) \cdot \max_k (|\tilde{b}_k/b_k| - 1). \]
To prove this, notice that
\[
\hat{b}_k = b_k + b_k((\hat{b}_k/b_k) - 1) \geq b_k - b_k \max_k |(\hat{b}_k/b_k) - 1| \geq (\min_k b_k)(1 - \max_k |(\hat{b}_k/b_k) - 1|).
\]
Therefore \( \min_k \hat{b}_k - \min_k b_k \geq -(\min_k b_k) \cdot \max_k |(\hat{b}_k/b_k) - 1| \). Conversely, \( \min_k \hat{b}_k - \min_k b_k \leq \hat{b}_k - b_k = (\hat{b}_k - b_k) / (b_k - 1) \leq \max_k |\hat{b}_k/b_k - 1| \) where \( k^* = \arg \min b_k \).

Next, we bound the difference between \( U(Y - \mu_y) \) and \( U(Y - \mu_y) \). For notational simplicity, we suppress the parameters of the selected model \((\mathcal{M}, \mathcal{S})\) in \( U \) and \( \eta \).

\[
\frac{|U(Y - \mu_y) - U(Y - \mu_y)|}{\sigma ||\eta||} = \frac{1}{\sigma ||\eta||} \min_{k: (A\eta) \neq 0} b_k - (A(Y - \mu_y))_k - \min_{k: (A\eta) \neq 0} b_k - (A(Y - \mu_y))_k + \eta_T (\mu_y - \mu_y)_k + o_p(1)
\]

\[
\leq \frac{1}{\sigma ||\eta||} \min_{k: (A\eta) \neq 0} b_k - (A(Y - \mu_y))_k - \min_{k: (A\eta) \neq 0} b_k - (A(Y - \mu_y))_k + o_p(1)
\]

\[
= \frac{U(Y - \mu_y) - \eta^T (Y - \mu_y)}{\sigma ||\eta||} \cdot \max_{k: (A\eta) \neq 0} \left| b_k - \frac{(A(Y - \mu_y))_k}{b_k - (A(Y - \mu_y))_k} - 1 \right| + o_p(1)
\]

The first inequality uses Lemma 7 and the second inequality uses 20.

Using Lemmas 7 and 5 it is easy to show that

\[
\max_{k: (A\eta) \neq 0} \left| b_k - \frac{(A(Y - \mu_y))_k}{b_k - (A(Y - \mu_y))_k} - 1 \right| = o_p(1).
\]

Therefore, using Lemma 3

\[
(21) \quad \frac{|U(Y - \mu_y) - (\beta_\mathcal{M})_j|}{\sigma ||\eta||} - \frac{|U(Y - \mu_y) - (\beta_\mathcal{M})_j|}{\sigma ||\eta||} \leq \frac{|U(Y - \mu_y) - (\beta_\mathcal{M})_j|}{\sigma ||\eta||} \cdot o_p(1) + o_p(1).
\]

Finally, we prove a probability lemma. Let \( \{A_n\}, \{B_n\}, \{C_n\}, \{D_n\}\) be sequences of random variables such that \( |A_n - B_n| \leq |A_n|C_n + D_n, C_n \xrightarrow{p} 0, D_n \xrightarrow{p} 0 \). Then \( |\Phi(A_n) - \Phi(B_n)| \xrightarrow{p} 0 \). We prove this result for deterministic sequences (in probability convergence is changed to deterministic limit). We only need to prove the result for two infinite subsequences of \( \{A_n\} \), \( \{A_n : A_n \leq 1\} \) and \( \{A_n : A_n > 1\} \) (if any subsequent is finite then we can ignore it). Within the first subsequence, we have \( |A_n - B_n| \to 0 \) and hence \( \Phi(A_n) - \Phi(B_n) \to 0 \). Within the second subsequence, for large enough \( n \) we have \( |A_n - B_n| \leq A_n/2 \), so \( |\Phi(A_n) - \Phi(B_n)| \leq \max(\phi(A_n), \phi(B_n))|A_n - B_n| \leq \phi(A_n/2)(|A_n|C_n + D_n) \to 0 \), where we have used the fact that \( \phi(ca) \) is a bounded function of \( a \in [1, \infty] \) for any constant \( c > 0 \).

Using 21 and the result above, we have

\[
\Phi \left( \frac{U(Y - \mu_y) - (\beta_\mathcal{M})_j}{\sigma ||\eta||} \right) - \Phi \left( \frac{U(Y - \mu_y) - (\beta_\mathcal{M})_j}{\sigma ||\eta||} \right) \xrightarrow{p} 0
\]
as desired. \( \square \)
Finally we turn to the proof of Theorem 2. By Lemma 1 we have, conditioning on the event \( \{ \tilde{M}_\lambda(Y - \mu_y) = M, \hat{s}_\lambda(Y - \mu_y) = s \} \),

\[
F\left( (\hat{\beta}_M(Y - \mu_y))_j; (\hat{\beta}_M^*_j)_j, \sigma^2 \tilde{\eta}^T_M \tilde{\eta}_M, L(Y - \mu_y; M, s), U(Y - \mu_y; M, s) \right) \sim \text{Unif}(0, 1),
\]

To prove Theorem 2 we just need to replace \( \mu \) conditions are satisfied with a margin at least 1

By Lemma 9, the denominator of the right hand side is \( \Theta_p \). Therefore we have proved that \( \Phi(L(Y - \mu_y; \hat{M}, \hat{s}) - (\hat{\beta}_M^*)_j; \sigma \| \eta \|) \). By Lemma 8 the denominator of the right hand side is \( \Theta_p(1) \). Therefore using Lemmas 3, 7 and 10 we can replace \( \mu_y \) by \( \hat{\mu}_y \) and \( \hat{\beta} \) by \( \hat{\beta}^* \) in the numerator of the right hand side and show the difference is \( o_p(1) \). Now using Lemma 10 we can replace \( \mu_y \) by \( \hat{\mu}_y \) and \( \hat{\beta} \) by \( \hat{\beta}^* \) in the numerator and show the difference again is \( o_p(1) \). Therefore we have proved that

\[
F\left( (\hat{\beta}_M)_j; (\hat{\beta}_M^*)_j, \sigma^2 \tilde{\eta}^T_M \tilde{\eta}_M, L(Y - \mu_y; \hat{M}, \hat{s}), U(Y - \mu_y; \hat{M}, \hat{s}) \right)
- F\left( (\hat{\beta}_M)_j; (\hat{\beta}_M^*_j)_j, \sigma^2 \tilde{\eta}^T_M \tilde{\eta}_M, L(Y - \mu_y; \hat{M}, \hat{s}), U(Y - \mu_y; \hat{M}, \hat{s}) \right) = o_p(1).
\]

Combining this with (22), we have thus proved the main Theorem.