High-dimensional doubly robust tests for regression parameters

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Abstract

After variable selection, standard inferential procedures for regression parameters may not be uniformly valid; there is no finite sample size at which a standard test is guaranteed to attain its nominal size (within pre-specified error margins). This problem is exacerbated in high-dimensional settings, where variable selection becomes unavoidable. This has prompted a flurry of activity in developing uniformly valid hypothesis tests for a low-dimensional regression parameter (e.g. the causal effect of an exposure $A$ on an outcome $Y$) in high-dimensional models. So far there has been limited focus on model misspecification, although this is inevitable in high-dimensional settings. We propose tests of the null that are uniformly valid under sparsity conditions weaker than those typically invoked in the literature, assuming working models for the exposure and outcome are both correctly specified. When one of the models is misspecified, by amending the procedure for estimating the nuisance parameters, our tests continue to be valid; hence they are then doubly robust. Our proposals are straightforward to implement using existing software for penalized maximum likelihood estimation and do not require sample-splitting. We illustrate them in simulations and an analysis of data obtained from the Ghent University Intensive Care Unit.

Key words: Causal inference; doubly-robust estimation; high-dimensional inference; post-selection inference.
1 Introduction

We will consider a study design which collects i.i.d. data on an outcome $Y$, an exposure of interest $A$ and a vector of covariates $L$, some of which may confound the relationship between $A$ and $Y$. A common means of assessing the effect of $A$ on $Y$ is to fit a regression model, adjusted for $A$ and the covariates; the estimate of the coefficient for $A$ is then used to obtain inference on the exposure effect. In practice, there is often little prior knowledge on which variables in a given data set are confounders, and furthermore how one should model the association between these confounders and outcome. Hence, data-adaptive procedures are typically employed in order to select the variables to adjust for and/or choose a model for their dependence on $Y$. In particular, data-adaptive model selection becomes increasingly necessary when the dimension of $L$ is close to or greater than the number of observations.

However, obtaining hypothesis tests and confidence intervals that enjoy their nominal size/coverage (within pre-specified error margins) after model selection is challenging. The estimate of the effect of $A$ obtained directly via regularization techniques - e.g. using a penalized maximum likelihood estimator (PMLE) - will inherit a so-called regularization bias. Furthermore, the moderate-sample distribution of this estimator will typically be non-normal \citep{LeebPotscher2005}. This is because convergence to the asymptotic distribution is not uniform with respect to the parameters indexing the true model for $Y$. Therefore, there exists no finite $n$ such that normal-based tests and intervals are guaranteed to perform well. This issue applies more generally to post-regularization estimators (where the model selected via regularization is refitted using the chosen covariates) and routinely-used stepwise variable selection strategies. Standard inferential procedures also ignore the additional uncertainty created during the model-selection process.
This has prompted the development recently of methods to obtain uniformly valid inference for a low-dimensional regression parameter in a high-dimensional model. Initial focus was given to tests and confidence intervals for a coefficient in a regression model fit using the Lasso (Zhang and Zhang, 2014; van de Geer et al., 2014); after which attention has turned to more general data-adaptive methods (Ning and Liu, 2017; Chernozhukov et al., 2017), and model selection techniques e.g. standard t-tests (Belloni et al., 2014). The key insight has been that one should perform selection based on an additional working model for the association between A and L (in addition to Y and L). The majority of the recent proposals rely on strong assumptions on sparsity e.g. the number of relevant covariates in L, which needs to be much smaller than the square root of the sample size n.

In this work, we describe how to obtain uniformly valid tests of the causal null hypothesis for a regression parameter in a high-dimensional Generalized Linear Model (GLM). Our test requires postulation of working models for the conditional mean of the exposure and the outcome given covariates. We will work under parametric models, as this is what is typically done in practice. First, we describe a procedure for estimating the nuisance parameters which yields a valid test so long as all working models are correct. However, given that regularization/model selection is required because we do not know the true models to start with, some degree of misspecification is likely. This is felt most acutely when the number of covariates in the data set is very large relative to the number of observations. We then show how to amend the earlier procedure for nuisance parameter estimation, so that the test statistic will converge uniformly to a limiting normal distribution if either working model is correct. Hence the test can be made uniformly doubly robust. This is in contrast to several existing proposals, which give doubly robust estimators but not inference. Furthermore, we will show that when both working models are correct, then in certain cases the test will continue to attain its nominal size
under sparsity conditions weaker than those invoked in the literature. Our test statistic is straightforward to construct, and all procedures for estimating the nuisance parameters can be performed using existing penalized regression software.

The paper is organized as follows: in Section 2 we state the null hypothesis we are interested in testing and describe issues with obtaining valid inference in the high-dimensional setting. Section 3 presents the score test statistic. In Sections 4 and 5 we describe specific procedures for estimating the nuisance parameters, first when all working models are correct and then under misspecification. We also discuss the asymptotic properties of the various methods. Section 6 positions our work within the recent literature on high-dimensional inference. We illustrate the methods via simulation studies in Section 7 and an analysis of data from the Ghent University Intensive Care Unit in Section 8, where we consider the effect of a change in glycemia level on mortality in critically ill patients.

2 Motivation

We consider a test of the null hypothesis $H_0$ that $Y$ is independent of $A$ within strata defined by $L$, or

\[ H_0 : \ Y \perp\!
\perp A | L. \]  

We will let the exposure $A$ be binary e.g. it is coded as 1 if an individual undergoes a particular medical treatment and 0 otherwise; extensions to more general exposures will be discussed later in the paper. Then given the standard structural conditions in the causal inference literature, in particular that $L$ is sufficient to adjust for confounding, the null hypothesis also expresses the absence of a casual effect of $A$ on $Y$, conditional on $L$.

Standard score tests of $H_0$ require estimation of $E(Y|L)$, since under the null $E(Y|A =$
\(a, L) = E(Y|L)\); in realistic settings where \(L\) has multiple continuous components, non-parametric estimation of this functional is not feasible. A common strategy is to instead postulate a regression model \(B\) for the association between the outcome and covariates. One might postulate the conditional mean model \(E(Y|L) = m(L; \beta)\), where \(m(L; \beta)\) is a known function smooth in an unknown parameter \(\beta\). Then, via maximum likelihood estimation of GLMs, under the pre-specified model \(B\) one can obtain a consistent and uniformly asymptotically normal (UAN) score statistic for testing \(H_0\) (where uniformity is with respect to \(\beta\)).

Unfortunately, this standard methodology does not straightforwardly extend to high-dimensional settings. Let \(\eta\) denote all nuisance parameters required in constructing a test, such that here \(\eta = \beta\). Also, let \(U(W; \eta)\) be an unbiased (unscaled) score test statistic. In low-dimensional settings, one can perform a score test of the causal null \(H_0\) based on the asymptotic distribution of \(U(W; \eta)\); for likelihood estimation of canonical GLMs, \(U(W; \eta) = A\{Y - m(L; \beta)\}\). Then let \(\tilde{\eta}\) denote an estimate of \(\eta\) obtained either directly via some regularization method or after model selection. Following a Taylor expansion,

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} U(W_i; \tilde{\eta}) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} U(W_i; \eta) + \frac{1}{n} \sum_{i=1}^{n} \frac{\partial U(W_i; \tilde{\eta})}{\partial \eta} \sqrt{n}(\tilde{\eta} - \eta) + O_P(||\tilde{\eta} - \eta||_2^2) \tag{2}
\]

where \(||.||_2\) denotes the Euclidean norm. For fixed \(\eta\), by appealing to the oracle properties of \(\tilde{\eta}\) it may be argued that the right hand side of (2) is asymptotically normal. Indeed, assuming that \(\tilde{\eta}\) converges sufficiently quickly, the remainder term \(O_P(\sqrt{n}||\tilde{\eta} - \eta||_2^2)\) converges to zero. But in general this does not prevent the existence of converging sequences \(\eta_n\) for which \(\sqrt{n}(\tilde{\eta} - \eta_n)\) (and thus the test statistic) has a complex, non-normal distribution. One root cause of this is the discrete nature of many data-adaptive methods (e.g. stepwise selection); in some samples \(\tilde{\eta}\) will be forced to zero whereas in others it will be allowed to take on its estimated value. This discrete behavior persists with increas-
ing sample size under certain sequences \( \eta_n \). The convergence of the resulting score test statistic to the limiting standard normal is hence not uniform over the parameter space (Leeb and Pötscher, 2005). This is troubling, as one wishes there to be a finite \( n \) where the normal approximation is guaranteed to hold well, regardless of the (unknown) true values of the nuisance parameters, in order to guarantee that the procedure will work well in finite samples.

3 A uniformly valid test of the causal null hypothesis

We introduce in this section the statistic we will use for testing \( H_0 \) in a high-dimensional setting. Let us now formally define \( \gamma \) to be the nuisance parameter indexing the working model \( \mathcal{A} \) for the conditional mean \( E(A|L) = \pi(L; \gamma) \) where \( \pi(L; \gamma) \) is a known function smooth in an unknown parameter \( \gamma \); the conditional mean \( E(A|L) \) is known as the propensity score for binary \( A \). Our analysis is based on the score function

\[
\psi(W; \eta) \equiv \{A - \pi(L; \gamma)}\{Y - m(L; \beta)\}.
\]

This will require initial estimates of \( \gamma \) and \( \beta \) under working models \( \mathcal{A} \) and \( \mathcal{B} \) respectively. Hence in our setting \( \eta = (\gamma^T, \beta^T)^T \). It is natural to model the dependence of \( A \) on \( L \) using a logistic regression e.g. \( \pi(L; \gamma) = \expit(\gamma^T L) \) (if \( A \) were continuous, one might postulate a linear or log-linear model instead and the proposal can then be easily adapted). The form that model \( \mathcal{B} \) takes will depend on the nature of the outcome. If \( Y \) is continuous and unconstrained, one might postulate a linear model e.g. \( m(L; \beta) = \beta^T L \).

One can then construct a test statistic

\[
T_n = \frac{1}{\sqrt{n}} \frac{\sum_{i=1}^{n} \psi(W_i; \hat{\eta})}{\sqrt{\frac{1}{n} \sum_{i=1}^{n} \left[ \psi(W_i; \hat{\eta}) - \psi(W; \hat{\eta}) \right]^2}}
\]

that we will compare to the standard normal distribution. Here, \( \hat{\psi}(W; \hat{\eta}) = n^{-1} \sum_{i=1}^{n} \psi(W_i; \hat{\eta}) \) and \( \hat{\eta} \) are estimates of \( \eta \); in what follows, we will focus on regularized estimation of this
parameter. Note that in evaluating the functions \( \pi(L; \gamma) \) and \( m(L; \beta) \) at their limiting values, it follows that the mean of \( \psi(W; \eta) \) under the null is equal to

\[
E[\{E(A|L) - \pi(L; \gamma)\}\{E(Y|A, L) - m(L; \beta)\}]
\]

which equals zero if either model \( \mathcal{A} \) or \( \mathcal{B} \) is correct a.k.a under the union model \( \mathcal{A} \cup \mathcal{B} \). Hence we refer to the score \( \psi(W; \eta) \) as doubly robust.

4 Estimation of \( \eta \) when all models are correct

4.1 Proposal

We will first consider data generating processes where both models \( \mathcal{A} \) or model \( \mathcal{B} \) are correctly specified e.g. we will work under the intersection submodel \( \mathcal{A} \cap \mathcal{B} \). In high-dimensional settings, under model \( \mathcal{A} \cap \mathcal{B} \) one can estimate \( \gamma \) and \( \beta \) using any sufficiently fast-converging sparse estimator. Specifically, assuming that the estimators meet rate conditions \((A.4)\) and \((A.5)\) given in Appendix A, then plugging the resulting estimates into \( T_n \) will yield a test statistic that (under the null) follows a standard normal distribution. These conditions are met (for example) by standard PMLE with a Lasso penalty but we conjecture that they hold much more generally. In what follows, we focus on Lasso-based estimation since this is popular with applied researchers, can be easily implemented using standard statistical software and is well understood in terms of its theoretical properties; let \( \hat{\gamma} \) and \( \hat{\beta} \) now refer to the resulting estimators of \( \gamma \) and \( \beta \) respectively.

To give some intuition about why one can plug Lasso estimates into \( T_n \) and yet obtain a UAN test statistic, then repeating the expansion in \((2)\) for the score \( \psi(W; \hat{\eta}) \), we observe the first-order term

\[
\frac{1}{n} \sum_{i=1}^{n} \left. \frac{\partial \psi(W_i; \hat{\eta})}{\partial \eta} \right| \sqrt{n}(\hat{\eta} - \eta).
\]
We can control this term under the model $A \cap B$, since $\partial \psi(W; \eta)/\partial \eta$ will then have expectation zero at the limiting value of $\eta$. For example, when $\pi(L; \gamma) = \expit(\gamma^T L)$ and $m(L; \beta) = \beta^T L$, then using the law of iterated expectation

$$E[\partial \psi(W; \eta)/\partial \beta] = E[E[A - \pi(L; \gamma)]|L] = 0 \quad \text{and}$$

$$E[\partial \psi(W; \eta)/\partial \gamma] = E[\pi(L; \gamma)\{1 - \pi(L; \gamma)\}E[Y - m(L; \beta)]|L] = 0.$$ 

This property helps to ensure that term (3) is asymptotically negligible, regardless of the complex behavior of $\hat{\eta}$. Such phenomena (in the context of doubly robust estimators) is well-understood when $L$ is low-dimensional. What is surprising is that it continues to hold in high-dimensional settings, even when non-regular estimators are used for $\eta$ (Belloni et al., 2016).

We recommend selecting the penalty parameters in practice via standard cross validation, although there are limited theoretical results available on its validity in this context, since our inferences assume that these parameters are fixed. In practice, we also recommend refitting both working models; model refitting is typically done in the literature in order to improve finite sample performance (Belloni et al., 2016; Ning and Liu, 2017). Our theory can allow for this by appealing to results on Post-Lasso estimators (Belloni and Chernozhukov, 2013; Belloni et al., 2014, 2016). For any vector $a \in \mathbb{R}^p$, let us define its support as support($a$) = \{ $j \in \{1, \ldots, p\} : a_j \neq 0$\}; then we refit each model $A$ and $B$ using support($\gamma$) $\subseteq$ support($\hat{\gamma}$) and support($\beta$) $\subseteq$ support($\hat{\beta}$) respectively. One can also refit the working models using the union of the selected covariates support($\hat{\beta}$) $\cup$ support($\hat{\gamma}$), similar to what is done in the ‘post-double selection’ procedure of Belloni et al. (2014). As we will discuss further in Section 6, however, refitting using the covariate union may hold implications in terms of the corresponding conditions on model sparsity.
4.2 Asymptotic properties

Let \( P \) be the class of laws that obey the intersection submodel \( \mathcal{A} \cap \mathcal{B} \); then we are interested in convergence under a sequence of laws \( P_n \in P \). We will allow for \( p \) to increase with \( n \), and for the values of the parameters \( \gamma \) and \( \beta \) to depend on \( n \), and hence also models \( \mathcal{A} \) and \( \mathcal{B} \) (although the notation with respect to the models will be suppressed). This is done in order to better gain insight into the finite-sample behavior of the test statistic when \( L \) is high-dimensional. Let \( \gamma_n \) and \( \beta_n \) be the population values of the parameters indexing models \( \mathcal{A} \) and \( \mathcal{B} \) respectively. Finally, let \( \mathbb{P}_{P_n}[] \) denote a probability taken with respect to the local data generating process \( P_n \).

**Theorem 1.** Let us define the active set of variables as \( S_\gamma = \text{support}(\gamma_n) \) and \( S_\beta = \text{support}(\beta_n) \). Furthermore, let \( s_\gamma \) denote the cardinality \( |S_\gamma| \) and likewise \( s_\beta = |S_\beta| \). Suppose, in addition to Assumptions 1 and 2 in Appendix A, the following sparsity conditions hold:

(i) \((s_\gamma + s_\beta) \log(p \vee n) = o(n)\)

(ii) \(s_\gamma s_\beta \log^2(p \vee n) = o(n)\)

Then under the intersection submodel, for all estimators satisfying conditions (A.4) and (A.5) in Appendix A, we have for any \( t \in \mathbb{R} \):

\[
\lim_{n \rightarrow \infty} \sup_{P_n \in P} \mathbb{P}_{P_n}(T_n \leq t) - \Phi(t) = 0
\]  

(4)

**Remark.** Condition [i] requires that both \( s_\gamma << n \) and \( s_\beta << n \); such conditions are quite standard in order to guarantee consistency of the Lasso-based estimators. Condition [ii] implies that we can allow for \( s_\gamma \) to be large if \( s_\beta \) is small, and vice versa. We view this as useful given that in many medical settings, doctors may rely on a limited number of
factors when deciding on a patient’s treatment. Hence it may even be plausible that the exposure model is ‘ultra-sparse’ e.g. $s_\gamma << \sqrt{n}$. In contrast, it appears less likely that a model for a clinical outcome (e.g. disease occurrence) can be well approximated by a small number of covariates. Similarly, in genetic association studies, one may appeal to gene-environment independence (Chatterjee et al., 2005), to justify that the model for a genetic exposure is sparse in the confounders. Our procedure can extend to non-binary exposures, but it is currently unclear whether uniformly valid inference for $\theta$ is more widely obtainable without imposing additional ultra-sparsity conditions or using sample splitting.

Remark. In Farrell (2015), uniformly valid inference for the marginal treatment effect is obtained under conditions equivalent to (i) and (ii). However, in a corrigendum to that work, it was noted that stronger assumptions are in fact required on the outcome regression model. To obtain uniformly valid estimators and tests based on trading-off assumptions on $s_\gamma$ and $s_\beta$, it turns out to be crucial that first order terms like (3) have expectation zero, conditional only on $\{L_i\}_{i=1}^n$; in many estimation problems this is not possible, because fitting a model for $Y$ requires adjusting for/conditioning on the exposure, so the estimated coefficients depend on $\{A_i\}_{i=1}^n$. One way to get round this could be to use sample splitting (Chernozhukov et al., 2017); however, for a score test under the null, one can estimate $m(L; \beta)$ without using data on the exposure.

5 Estimation of $\eta$ under model misspecification

5.1 Proposal

Under the union model $\mathcal{A} \cup \mathcal{B}$, plugging in any Lasso-based estimator $\hat{\eta}$ of $\eta$ into $T_n$ will not generally lead to the test statistic converging uniformly to the standard normal. Hence although the score is doubly robust, plugging in $\hat{\eta}$ will not yield uniformly valid,
doubly robust inference. This can be seen by replicating the Taylor expansion in (2) for the score \( \psi(W; \hat{\eta}) \); the gradient \( \partial \psi(W; \eta) / \partial \eta \) is no longer guaranteed to be mean zero and one would generally need to approximate \( \sqrt{n}(\hat{\eta} - \eta_n) \) to assess the variability in the score function under the union model. However, as previously discussed, approximating this term well is generally not possible in the high-dimensional setting.

We will handle the problematic term (3) by using the gradient \( \partial \psi(W; \eta) / \partial \eta \) in order to estimate \( \eta \), so as to ensure that \( 0 = \sum_{i=1}^{n} \partial \psi(W_i; \eta) / \partial \eta \) at the estimator of the nuisance parameter. This leaves (aside from the remainder) only the score function \( \psi(W; \eta) \), which we will show is UAN. Specifically, one can estimate \( \eta \) by solving the following penalized estimating equations with a bridge penalty (Fu, 2003):

\[
0 = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial}{\partial \beta} \psi(W_i; \hat{\eta}_{BR}) + \lambda_\gamma \delta |\hat{\gamma}_{BR}|^{\delta-1} \circ \text{sign}(\hat{\gamma}_{BR}) \\
0 = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial}{\partial \gamma} \psi(W_i; \hat{\eta}_{BR}) + \lambda_\beta \delta |\hat{\beta}_{BR}|^{\delta-1} \circ \text{sign}(\hat{\beta}_{BR})
\]

Here, \( \lambda_\gamma > 0 \) and \( \lambda_\beta > 0 \) are penalty parameters, \( \delta \geq 1 \) and \( \circ \) is the Hadamard product operator. Also, for a vector \( a \in \mathbb{R}^p \), \( \text{sign}(a) \) denotes a vector of elements \( \text{sign}(a_j) \), for \( j = 1, ..., p \) and \( \delta |\hat{\gamma}|^{\delta-1} \circ \text{sign}(\gamma) \) and \( \delta |\hat{\beta}|^{\delta-1} \circ \text{sign}(\beta) \) refer to the partial derivatives of \( ||\gamma||_\delta \) and \( ||\beta||_\delta \) with respect to \( \gamma \) and \( \beta \); we define the \( \ell_\delta \) norm as \( ||a||_\delta \equiv \left( \sum_{i=1}^{p} |a_i|^{\delta} \right)^{1/\delta} \). Similar to Avagyan and Vansteelandt (2017), the above procedure extends the bias-reduced doubly robust estimation methodology of Vermeulen and Vansteelandt (2015) to incorporate penalization; we thus use \( \hat{\gamma}_{BR} \) and \( \hat{\beta}_{BR} \) to refer to the resulting estimators of \( \gamma \) and \( \beta \) respectively. Note that by letting \( \delta \to 1+ \), the penalty terms correspond to the sub-gradient of the \( \ell_1 \) or Lasso norm penalty \( ||\eta||_1 \) with respect to \( \eta \) (Tibshirani, 1996).

Whilst our procedure requires that the initial working models \( \mathcal{A} \) and \( \mathcal{B} \) are of the same dimension, using a Lasso penalty will tend to return nuisance parameter estimates with different numbers of non-zero components. We again recommend refitting each working
model using the covariates selected via penalization.

5.1.1 Example 1: continuous outcome

Returning to the example of Section 3, we might postulate a linear model for the outcome and a logistic model for the exposure. Then $\gamma$ and $\beta$ can be estimated as the solution to the equations

$$
0 = \frac{1}{n} \sum_{i=1}^{n} \{ A_i - \expit(\hat{\gamma}_{BR}^T L_i)\} L_i + \lambda_\gamma |\hat{\gamma}_{BR}|^{\delta-1} \circ \text{sign}(\hat{\gamma}_{BR})
$$

$$
0 = \frac{1}{n} \sum_{i=1}^{n} \expit(\hat{\gamma}_{BR}^T L_i) \{ 1 - \expit(\hat{\gamma}_{BR}^T L_i)\} \{ Y_i - \hat{\beta}_{BR}^T L_i\} L_i + \lambda_\delta |\hat{\beta}_{BR}|^{\delta-1} \circ \text{sign}(\hat{\beta}_{BR})
$$

Then letting $\delta \to 1+$, one can rephrase the above as the following minimization problems:

$$
\hat{\gamma}_{BR} = \arg\min_\gamma \frac{1}{n} \sum_{i=1}^{n} \log \{ 1 + \exp(\gamma^T L_i)\} - A_i (\gamma^T L_i) + \lambda_\gamma ||\gamma||_1
$$

$$
\hat{\beta}_{BR} = \arg\min_\beta \frac{1}{2n} \sum_{i=1}^{n} \{ \expit(\hat{\gamma}_{BR}^T L_i) \{ 1 - \expit(\hat{\gamma}_{BR}^T L_i)\} \{ Y_i - \beta^T L_i\}^2 \} + \lambda_\beta ||\beta||_1
$$

Hence one can estimate $\gamma$ by fitting a logistic regression model with a Lasso penalty, and then estimate $\beta$ by fitting a linear regression model again with a Lasso penalty and weights constructed using the estimates $\hat{\gamma}_{BR}$. Then the (unscaled) test statistic equals:

$$
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ A_i - \expit(\hat{\gamma}_{BR}^T L_i)\} \{ Y_i - \hat{\beta}_{BR}^T L_i\}
$$

5.1.2 Example 2: binary outcome

A more appropriate working model for the conditional mean of binary $Y$ might be $E(Y|A = 0, L) = \expit(\beta^T L)$. Hence we must now solve the equations

$$
0 = \frac{1}{n} \sum_{i=1}^{n} \expit(\hat{\beta}_{BR}^T L_i) \{ 1 - \expit(\hat{\beta}_{BR}^T L_i)\} \{ A_i - \expit(\hat{\gamma}_{BR}^T L_i)\} L_i + \lambda_\gamma |\hat{\gamma}_{BR}|^{\delta-1} \circ \text{sign}(\hat{\gamma}_{BR})
$$

$$
0 = \frac{1}{n} \sum_{i=1}^{n} \expit(\hat{\gamma}_{BR}^T L_i) \{ 1 - \expit(\hat{\gamma}_{BR}^T L_i)\} \{ Y_i - \expit(\hat{\beta}_{BR}^T L_i)\} L_i + \lambda_\delta |\hat{\beta}_{BR}|^{\delta-1} \circ \text{sign}(\hat{\beta}_{BR})
$$
An additional complication is then that solving each set of equations requires initial estimates of the other nuisance parameter. There are then two possible approaches one might take; one is to estimate $\gamma$ and $\beta$ together by maximizing a joint penalized likelihood. Alternatively, one could use the iterative procedure described in Algorithm 1, which could be easily adapted for other types of outcome. In practice, one can take the penalty terms obtained via cross validation during the first iteration of the algorithm $(j = 1)$ and use the same terms in subsequent iterations.

5.2 Asymptotic properties

We will now study convergence of $T_n$ under a sequence of laws $P_n \in \mathcal{P}^*$, where $\mathcal{P}^*$ represents a class of laws that obey the union model $\mathcal{A} \cup \mathcal{B}$; hence this class is much larger than that considered in Section 4.2.

Theorem 2. Suppose, in addition to Assumptions A and B in Appendix A, the following sparsity condition holds:

(iii) $(s^2_\gamma + s^2_\beta) \log^2(p \vee n) = o(n)$

Then under the union model $\mathcal{A} \cup \mathcal{B}$, using estimators $\hat{\gamma}_{BR}$ and $\hat{\beta}_{BR}$ that satisfy (A.10)-(A.15) in Appendix A, we have for any $t \in \mathbb{R},$

$$\lim_{n \to \infty} \sup_{P_n \in \mathcal{P}^*} |P_{P_n}(T_n \leq t) - \Phi(t)| = 0$$

Remark. This theorem states that under the key ultra-sparsity condition (iii) our proposed test is uniformly doubly robust over the parameter space. This condition entails that the number of non-zero coefficients in models $\mathcal{A}$ and $\mathcal{B}$ are small relative to the square root of the overall sample size; this is much stronger than conditions (i) and (ii).

Remark. Our proposal assumes that the misspecified models are sparse in their parameters. To give some motivation for the plausibility of this assumption, let us partition $L$
Algorithm 1 An algorithm for estimating $\eta$ when $Y$ is binary

1. Estimate $\gamma$ and $\beta$ as $\hat{\gamma}^{(0)}$ and $\hat{\beta}^{(0)}$ using (unweighted) $\ell_1$-penalized logistic regression. Let $\hat{\gamma}^{(0)}$ and $\hat{\beta}^{(0)}$ denote the refitted estimates.

2. Calculate the weights $w(L_i; \hat{\gamma}^{(0)}) = \expit(\hat{\gamma}^{(0)} L_i) \{1 - \expit(\hat{\gamma}^{(0)} L_i)\}$, $w(L_i; \hat{\beta}^{(0)}) = \expit(\hat{\beta}^{(0)} L_i) \{1 - \expit(\hat{\beta}^{(0)} L_i)\}$, $w(L_i; \hat{\gamma}^{(0)})$ and $w(L_i; \hat{\beta}^{(0)})$. Calculate the objective function

$$\check{\nu}^{(0)} = \frac{1}{n} \sum_{i=1}^{n} \left[ \log \{1 + \exp(\hat{\gamma}^{(0)} L_i)\} - A_i (\hat{\gamma}^{(0)} L_i) + \log \{1 + \exp(\hat{\beta}^{(0)} L_i)\} - Y_i (\hat{\beta}^{(0)} L_i) \right]$$

3. Set $j = 0$ and carry out the following recursive algorithm:

(a) Set $j = j + 1$.

(b) Using the initial estimates, re-estimate $\gamma$ and $\beta$ as the solutions $\hat{\gamma}^{(j)}$ and $\hat{\beta}^{(j)}$ to

$$0 = \sum_{i=1}^{n} w(L_i; \hat{\beta}^{(j-1)}) \{ A_i - \expit(\gamma^{(j)} L_i) \} L_i + \lambda_\gamma |\gamma|^{\delta-1} \circ \text{sign}(\gamma)$$

$$0 = \sum_{i=1}^{n} w(L_i; \hat{\gamma}^{(j-1)}) \{ Y_i - \expit(\beta^{(j)} L_i) \} L_i + \lambda_\beta |\beta|^{\delta-1} \circ \text{sign}(\beta)$$

Similarly, using $w(L_i; \hat{\gamma}^{(j-1)})$ and $w(L_i; \hat{\beta}^{(j-1)})$, obtain the refitted $\hat{\gamma}^{(j)}$ and $\hat{\beta}^{(j)}$.

(c) Re-evaluate the objective function as:

$$\check{\nu}^{(j)} = \frac{1}{n} \sum_{i=1}^{n} \left[ \log \{1 + \exp(\hat{\gamma}^{(j)} L_i)\} - A_i (\hat{\gamma}^{(j)} L_i) \right] w(L_i; \hat{\beta}^{(j-1)})$$

$$+ \left[ \log \{1 + \exp(\hat{\beta}^{(j)} L_i)\} - Y_i (\hat{\beta}^{(j)} L_i) \right] w(L_i; \hat{\gamma}^{(j-1)})$$

(d) If $|\check{\nu}^{(j)} - \check{\nu}^{(j-1)}| < 0.0001$, stop the algorithm, and set $\hat{\gamma}_{BR} = \hat{\gamma}^{(j)}$ and $\hat{\beta}_{BR} = \hat{\beta}^{(j)}$. 

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as \( L = (L^*, Z^T)^T \), where \( L^* \) includes the true confounders of the \( A - Y \) association and \( Z \) is independent of \( Y \) and \( A \), conditionally on \( L^* \) a.k.a. \((Y, A) \perp\!
abla\! Z|L^*\). Hence the true regression functions \( E(A|L) \) and \( E(Y|L) \) depend only on \( L^* \) but not \( Z \); we will assume that the dimension of \( L^* \) is sufficiently small such that sparsity holds in both models (a.k.a. conditions (i) and (ii) in Theorem 1). In Appendix B we show that if \( E(Z|L^*) \) is linear in \( L^* \), then when either models \( A \) or \( B \) are misspecified one can still expect the incorrect model to depend on \( L^* \) but not \( Z \). More generally, if one objects to our conceptualization of sparse misspecified models - possibly arguing that a model will be approximately correct given that enough higher order terms and interactions are added - then our procedure still applies under the intersection submodel \( A \cap B \). Since in practice, all models are likely to be at least misspecified to a degree, then if a misspecified model cannot be sparse, this also calls into question the utility of sparsity assumptions in general.

An advantage of our proposal is that any \textit{a priori} knowledge on the distribution of the exposure can be easily incorporated into the test statistic. Indeed, note that when \( E(A|L) \) is known, then following our proposal, one can estimate \( \beta \) using standard \( \ell_1 \)-penalized regression without weights; hence the proposal reduces to the one described in Section 4. This is because there is no gradient with respect to the parameters in model \( A \) and the exposure model is guaranteed to be correct.

\textbf{Corollary 1.} Suppose that \( A \) is randomized, with randomization probability \( E(A|L) = \pi(L; \gamma^*) \) for known \( \gamma^* \). If \( \gamma^* \) is plugged into \( T_n \), one can obtain a uniformly valid test using the weaker sparsity condition \( s \beta \log(p \vee n) = o(n) \) regardless of whether model \( B \) is correctly specified.

\textbf{Remark.} This corollary of Theorems 1 and 2 states that when we know the randomization probabilities, one can rely merely on this weaker sparsity condition in order to get a valid
test, even if model $B$ is misspecified. Our asymptotic results here complement sharper finite-sample results in Wager et al. (2016), by being applicable to non-linear models without the need for sample splitting.

When both working models are correctly specified and the outcome regression model is linear, then we have some additional robustness to violations of sparsity, as the following theorem illustrates:

**Theorem 3.** When $m(L; \beta)$ is linear in $L$, and we restrict ourselves to the class of laws in $\mathcal{P}^*$ that obey the intersection submodel $A \cap B$, then (using estimators $\hat{\gamma}_{BR}$ and $\hat{\beta}_{BR}$) the score test statistic converges uniformly as in (9) under conditions (i) and (ii), without requiring the ultra-sparsity condition (iii) on $s_{\gamma}$ and $s_{\beta}$.

In the context of linear models for $Y$, our proposal is ‘sparsity-adaptive’, in the sense that when both models are correct, our proposal obtains the weaker rates given in Theorem 1. As the example in Section 5.1.1 shows, estimated weights (dependent on $\{A_i\}_{i=1}^n$) are only required in this setting when fitting the outcome model; the proof of Theorem 3 hinges on showing that estimating the weights is of lesser impact than estimating $\beta$ at fixed weights. For non-linear outcome models, an equivalent result will be difficult to obtain, in light of the fact that fitting the exposure model also requires weights that are dependent on $\{Y_i\}_{i=1}^n$; however, we conjecture that a general result could be shown using sample splitting (by estimating the weights in a sample separate to the one used in constructing the test statistic). Nonetheless, this illustrates the trade off between modeling and sparsity conditions; if we wish to obtain inference under the union model then we generally need stronger conditions on $s_{\gamma}$ or $s_{\beta}$.
6 Relation to the existing literature

To contextualize our work, an overview is given here of recent developments in high-dimensional inference, first focusing on testing and estimation of regression parameters, and afterwards marginal treatment effects. We will then outline the contribution of our proposal to the literature.

6.1 Literature review

Ning and Liu (2017) propose a score test for a low-dimensional parameter $\theta$ in a (high-dimensional) linear model for the conditional mean $E(Y|A, L) = \theta A + \beta^T L$, where $\theta$ and $\beta$ are estimated via penalized regression. As an additional step, they fit a linear model for the conditional mean $E(A|L) = \gamma^T L$, and propose estimating $\gamma$ either using the Lasso or via a Dantzig selector-type approach. Their test is then based on the score $(A - \gamma^T L)(Y - \beta^T L)$; it is shown that under regularity conditions (including assumptions on the sparsity of the underlying linear models), the resulting test statistic is UAN. They also extend the methodology to estimation of the mean difference parameter $\theta$, giving the closed form expression

$$\frac{\sum_{i=1}^{n} (A_i - \hat{\gamma}^T L_i)(Y_i - \hat{\beta}^T L_i)}{\sum_{i=1}^{n} (A_i - \hat{\gamma}^T L_i)A_i}$$

(10)

When both $\hat{\gamma}$ and $\hat{\beta}$ are estimates obtained using the Lasso, this proposal reduces to the ‘desparsified Lasso’ estimator of Zhang and Zhang (2014) and van de Geer et al. (2014). These authors propose uniformly valid Wald-based tests using the desparsified estimator. Belloni et al. (2014) observe that by refitting both linear models using the union of the covariates selected (via the Lasso), then (10) reduces to the Ordinary Least Squares (OLS) estimator from a regression of $Y$ on $A$ and the covariate union. This motivates their ‘post-double selection’ procedure. Ning and Liu (2017) also provide extensions to non-linear
models based on the score function

\[(A - \gamma^T L)\{Y - m(\theta A + \beta^T L)\}\]  

(11)

see van de Geer et al. (2014) and Belloni et al. (2016) for related proposals.

Little focus has been given to testing and inference for a regression parameter \(\theta\) under misspecification of the outcome model \(\mathcal{B}\). In settings where there are more covariates than observations, specifying a correct parametric model is non-trivial, and some degree of misspecification is inevitable. In particular, misspecification of a model for \(Y\) is highly likely in observational studies, when the distribution of \(L\) is very different in exposed and unexposed individuals, since one then must extrapolate outside of the observed data range.

Several of the papers have described the estimating function of the ‘desparsified Lasso’ estimator (10) as ‘doubly robust’ in the context of linear models (Zhu and Bradic, 2016). In non-linear models, the estimating functions underpinning several of the proposed tests are doubly robust under the null; for example, when \(m()\) is the inverse of the logit link and \(\theta = 0\), (11) will have expectation equal to zero when the mean of \(A\) is linear in \(L\), even if the logistic outcome model is misspecified. However, when \(A\) is binary, a linear exposure model is almost guaranteed to be misspecified. Moreover, many of the testing procedures also implicitly rely on model-based (rather than robust) estimators of the variance (although there are exceptions e.g. Belloni et al. (2014) and Bühlmann and Geer (2015)), such that the any additional robustness of the estimating function will not translate into doubly robust inference.

In parallel to the work on inference for regression parameters, there has developed a literature on uniformly valid inference for marginal treatment effects in high-dimensional settings. Progress has been made by reconsidering augmented inverse probability weighted estimators (Robins et al., 1994). These estimators require postulating a working model for
the conditional mean of the outcome, in addition to the propensity score. Initial proposals were given by Belloni et al. (2014) and Farrell (2015), where both working models are assumed to be correct. Avagyan and Vansteelandt (2017) obtain valid tests and confidence intervals when either the propensity score or outcome model is correct, and as such obtain uniformly valid, doubly robust inference after regularization/model selection; see also Benkeser et al. (2017). Note that the causal null hypotheses tested by our score test and via estimators of marginal treatment effects (e.g. using inverse probability weighting) differ. The latter enable testing whether 
\[ E[E(Y|A = 1, L) - E(Y|A = 0, L)] = 0 \] e.g. no marginal causal effect of \( A \) on \( Y \). This null is implied by (I) but not vice versa.

6.2 Our contribution

If one is willing to assume at all models are correctly specified, in Section 4 we show that one can obtain a uniformly valid test of the causal null by plugging-in Lasso-based estimates of \( \eta \) into \( T_n \). Unlike existing proposals for GLM parameters, this proposal allows for linear or non-linear models for both the exposure and outcome; we can also let \( s_\beta \) be large relative to \( n \) if \( s_\gamma \) is small and vice versa. It is doubtful whether the other tests discussed above can still obtain their nominal size without ultra-sparsity when \( A \) is binary, because they use a misspecified model for \( A \). The proposal here builds on the groundbreaking work of Farrell (2015) and Chernozhukov et al. (2017) in order to obtain tests for regression parameters. Compared to the former work, we obtain inference under weaker assumptions by exploiting the special form of a score test of the null. Unlike in the latter work, sample splitting is not required which is a considerable practical advantage, although our analysis is currently restricted to sparse parametric working models.

In Section 5 we describe an estimation procedure for \( \eta \) that yields a uniformly valid test, even when model \( \mathcal{B} \) is incorrect. When both models \( \mathcal{A} \) and \( \mathcal{B} \) are linear, the score
ψ(W; η) coincides with that of Ning and Liu (2017), and our estimation procedure for η reduces to theirs (although they allow for more general sparse estimators). Our proposal thus extends the robustness of their score function to the construction of a test that is UAN under the model A ∪ B. By allowing for arbitrary exposure and outcome models, our test has greater robustness to misspecification than the proposals of van de Geer et al. (2014), Belloni et al. (2016) and Ning and Liu (2017), under equivalent assumptions on sγ and sβ.

Refitting the working models using the post-double selection procedure of Belloni et al. (2014) is unlikely to enable one to weaken the ultra-sparsity conditions given here, even when both working models implicit in the procedure are correctly specified. By using the union of the selected covariates when refitting, the variables selected in the model for E(Y|L) depend additionally on the data \{Ai\}_{i=1}^n (Farrell, 2015). However, in certain ultra-sparse simulation settings, refitting with the covariate union can lead to improved performance (Belloni et al., 2016); this is possibly due to the condition that the gradient of the estimating function with respect to the nuisance parameters is approximately zero being better satisfied within the sample. Using sample splitting, Belloni et al. (2014) can consistently estimate a regression parameter θ by invoking only sparsity conditions (i) and (ii). However, in order to derive valid inference, they require also that 

\[ n^{2/r} s \log(p \vee n) = o(n) \]

for some \( r > 4 \). By focusing on binary exposures, we do not require such a condition, since sharper bounds on (functions of) A and the propensity score can be obtained.

It may be possible to weaken the sparsity conditions even further, by going outside of the Lasso framework when estimating the nuisance parameters. Zhu and Bradic (2016) propose a score test of the same form as \( T_n \), where both working models are linear in L, and γ and β are estimated via specialized optimization procedures. They allow for
either linear working model to be arbitrarily dense. For example, their estimator of $\gamma$ is designed to behave well in settings where the exposure model is in truth dense in $L$, in the sense that the corresponding remainder terms converge to zero sufficiently quickly; see also Javanmard and Montanari (2014). An extension to more general models for $Y$ is mentioned in Zhu and Bradic (2017). However, it is currently unclear how feasible such an extension is in practice, given that the constraints in the optimization procedure are not linear and iteration may be required.

7 Simulation Study

In this section, we conduct a simulation analysis to compare the performance of the proposed hypothesis test with that of different tests of the causal null hypothesis. In our study, we consider the following tests for the null hypothesis (1).

1. A naïve post-selection approach where a $t$-test is considered for the null using a linear regression after the standard post-selection of $\beta$ based on $\ell_1$-penalized linear regression. We study the performance of this approach both when the exposure is forced (i.e., the treatment effect $\theta$ is not penalised) and not forced to be included in the model.

2. The procedure described in Section 4 valid under model $\mathcal{A} \cap \mathcal{B}$, where a score test is considered using standard logistic regression and linear regression after the post-selection of parameters $\gamma$ and $\beta$ based on $\ell_1$-penalized logistic regression and $\ell_1$-penalized linear regression, respectively (hereafter, PMLE-DR).

3. The procedure described in Section 5 valid under model misspecification, where a score test is considered for the null using standard logistic regression and weighted linear regression after the post-selection of parameters $\gamma$ and $\beta$ based on $\ell_1$-penalized
logistic regression (7) and $\ell_1$-penalized weighted linear regression (8), respectively (hereafter, BR-DR).

Note that all the considered approaches require the selection of penalty parameters. In our simulation study, we use 10-fold Cross-Validation technique. We obtain $\lambda_\gamma$ and $\lambda_\beta$ using R package glmnet through the argument min. In our study, we also include the post-double selection (PDS) and ‘partialling out’ (PO) approaches proposed by Belloni et al. (2016), which are implemented in R package hdm and rely on pre-specified values for the penalty parameters (Chernozhukov et al., 2016). In order to study the impact of using different penalties, we also performed PDS as described in Belloni et al. (2014) using cross-validation instead of the pre-specified values.

In the simulation analysis, we generate $n$ mutually independent vectors $(L_i, A_i, Y_i), i = 1, ..., n$. Here, $L_i = (L_{i,1}, ..., L_{i,p})$ is a mean zero multivariate normal covariate with covariance matrix $I_{p \times p}$. For simplicity we consider a binary exposure model and linear outcome model. We let for each $i = 1, ..., n$, the dichotomous exposure $A_i$ take on values 0 or 1 with $P(A_i = 1|L_i) \equiv \pi(L_i)$, the outcome $Y_i$ be normally distributed with mean $m(L_i)$ and unit variance, conditional on $L_i$ and $A_i$. Further, the simulated data are analysed using the following parametric working models: $\pi(L, \gamma) = \expit(\gamma_0 + \sum_{i=1}^p \gamma_i L_i)$ and $m(L, \beta) = \beta_0 + \sum_{i=1}^p \beta_i L_i$, where $\beta_0 = 1$, $\gamma_0 = 2$. The nuisance parameters $\beta =
$(\beta_1, \ldots, \beta_p) \in \mathbb{R}^p$ and $\gamma = (\gamma_1, \ldots, \gamma_p) \in \mathbb{R}^p$ are defined as

$$b = \left(\frac{2 \log(20)}{n_1^{1/2}}, \frac{2 \log(19)}{n_1^{1/2}}, \ldots, \frac{2 \log(2)}{n_1^{1/2}}, 0_{20}, \ldots, 0_{81}, 10 \frac{\log(2)}{n_1^{1/2}}, \ldots, 10 \frac{\log(20)}{n_1^{1/2}}, 0_{101}, \ldots, 0_p\right)$$

$$\beta = 2 \cdot b \cdot \left(\sum_{i=1}^{p} b_i^2\right)^{-1/2}$$

$$g = \left(\frac{40 \log(20)}{n_1^{1/2}}, \frac{40 \log(19)}{n_1^{1/2}}, \ldots, \frac{40 \log(2)}{n_1^{1/2}}, 0_{20}, \ldots, 0_p\right)$$

$$\gamma = 3 \cdot g \cdot \left(\sum_{i=1}^{p} g_i^2\right)^{-1/2}$$

where the subscripts indicate the index (i.e., position) of 0 in the vector. The considered settings for nuisance parameters are attractive in the sense that there are confounders that are strongly predictive of the exposure and weakly predictive of the outcome. Moreover, there are covariates which are moderately predictive of the outcome but are not associated with the exposure. In order to evaluate the impact of model misspecification, we next generate data with the following outcome model: $m(L, \beta) = 1 + \beta^T \left(\sum_{t=1}^{3} |L_{t,[1:3]}| + L_{t,[4:p]}\right)$. Finally, for the data generating mechanism described above, we perform 1,000 Monte Carlo runs for $n = 200$, $p = 200$ and for $n = 500$, $p = 500$.

Table 1 shows the Type I errors based on 1,000 replications. The simulation results show that under both settings PMLE-DR and BR-DR approaches have rejection rates close to the nominal level of 5%, even when the outcome model is misspecified. The comparable performance under misspecification is somewhat surprising; however we note that any additional robustness from BR-DR may be offset by the true outcome model being fairly dense. On the other hand, we observe that even when both models are correctly specified, the naïve approaches provide high rejection rates. Moreover, these rates do not diminish with larger sample size. This poor performance is well aligned with the theory of Leeb and Pötscher (2005). Finally, we observe that the rejection rates of PDS and PO are relatively high. Note that they increase drastically if pre-specified values
of penalty parameters are used.

Table 1: Type I errors based on 1,000 replications.

| Methods                              | n = 200 | n = 500 |
|--------------------------------------|---------|---------|
|                                      | p = 200 | p = 500 |
| Standard naïve (forced)              | 0.548   | 0.809   |
| Standard naïve (not forced)          | 0.275   | 0.555   |
| PDS (pre-specified)                  | 0.517   | 0.761   |
| PO (pre-specified)                   | 0.508   | 0.748   |
| PDS (CV)                             | 0.183   | 0.118   |
| PMLE-DR                              | 0.049   | 0.067   |
| BR-DR                                | 0.051   | 0.061   |

| Methods                              | n = 200 | n = 500 |
|--------------------------------------|---------|---------|
|                                      | p = 200 | p = 500 |
| Standard naïve (forced)              | 0.368   | 0.586   |
| Standard naïve (not forced)          | 0.175   | 0.313   |
| PDS (pre-specified)                  | 0.319   | 0.634   |
| PO (pre-specified)                   | 0.317   | 0.615   |
| PDS (CV)                             | 0.176   | 0.113   |
| PMLE-DR                              | 0.045   | 0.060   |
| BR-DR                                | 0.036   | 0.067   |

8 Data analysis

Glycemic control in critically ill patients is still the subject of controversy, in terms of the optimal limits in which glucose levels are best kept. In the Leuven II randomised trial (Van den Berghe et al., 2001), strict glycemic control (with the maintenance of glycemia between 80 and 110 milligram per deciliter (mg/dl)) resulted in reduced mortality. Later multi-center studies could not replicate these findings, including the NICE-SUGAR trial (Finfer et al., 2009). Current guidelines usually recommend glycemic control between 140
and 180mg/dl. In the Ghent University Intensive Care Unit (UZ Ghent ICU) a glycemic protocol is used, targeting values between 80 and 150 mg/dl. In practice, glycemia in patients often falls outside of this range, partly due to a lack of compliance in following the protocol. We sought to investigate the relationship between glycemic control and 30-day mortality, using routinely collected data from the UZ Ghent ICU on a large representative cohort of intensive care patients. Specifically, we aimed to test for a causal effect of a change in glycemia level (from <110 to ≥110 mg/dl, and then from ≤150 to >150 mg/dl) on death within 30 days. We also tested for the effect of a change in glycemia level at day 10.

Data was obtained from the electronic patient data management system (PDMS) of the UZ Ghent ICU. The potential confounders were split up into variables assessed at admission into the intensive care unit and variables where data was collected over time. For covariates that were measured repeatedly, we took the mean of the measurements taken within the first 48 hours in the ICU for continuous covariates, and the maximum value for categorical covariates. We also created covariates for the mean value of glycemia and the number of glycemia measurements within the first 48 hours, since we thought these may also confound the exposure-outcome association. Any patients with missing data on the exposure, outcome or confounders were removed from the dataset. We also created a similar dataset now restricted to patients still alive at day 10 (for covariates that changed over time, we now took the mean/max of measurements in days 8 and 9). In order to perform our test, we assumed a logistic regression model for the probability of glycemia level ≥110 mg/dl (or >150 mg/dl) as well as a logistic model for death within 30 days of entering hospital. We then used the test for binary outcomes described in Section 5.1.2 (implemented using Algorithm 1), allowing for potential misspecification in either the exposure or outcome model. In our modeling, we included all confounders selected
by clinical experts, as well as quadratic terms of continuous variables and all two and three-way interactions between main effects.

We obtained data on 12,105 patients entering the intensive care unit; after restricting to patients still alive at day 3, 10,885 individuals remained. Further removing patients entering prior to 2013 left 4,682 individuals, with a final dataset of 4,082 after removing those with missing data. In this final cohort, 752 (18.4%) of individuals died in hospital within 30 days of entering the ICU. Considering the mean glycemia values for each patient within the first 6 hours of day 3, the average of these values among all patients was 131.5 (minimum: 45, maximum: 492). 955 (23.4%) patients had mean glycemia at day 3 <110 mg/dl, 2,269 (55.6%) had a level ≥110mg/dl and ≤150mg/dl and 858 (21.1%) had a level >150 mg/dl. There were 968 patients who remained in the dataset at day 10; 224 (23.1%) died in hospital within 30 days of entering the ICU. 144 (14.9%) patients had mean glycemia at day 10 <110 mg/dl, 577 (59.6%) had a level ≥110 mg/dl and ≤150 mg/dl, and 247 (25.5%) had a level >150 mg/dl.

After generating interactions, there were 265 covariates to adjust for in the analysis, which was large given the low ratio of non-events (alive after 30 days) to events. At day 3, looking at a change from <110 to ≥110 mg/dl, the test statistic $T_n$ was 0.57 with a $p$-value of 0.57 whereas changing from ≤150 to >150 mg/dl gave a test statistic of 4.04 ($p<0.001$). At day 10, comparing <110 vs. ≥110 mg/dl gave $T_n=0.40$ ($p=0.68$), whilst comparing ≤150 vs. >150 mg/dl yielded $T_n=0.76$ ($p=0.44$). Hence, at the 5% level, at day 3 we saw evidence of a difference in 30 day mortality between those with moderate (≤150mg/dl) and high (>150 mg/dl) glycemia levels; however, at day 10 there was no longer a significant difference (although there was a loss in power due to the reduced sample size). On the other hand, in comparing those with low (<110mg/dl) vs. higher (≥110 mg/dl) glycemia levels, we did not observe a statistically significant difference at
the 5% level either at day 5 or 10.

9 Discussion

We have proposed a general framework for constructing uniformly valid tests of GLM parameters in high-dimensional settings. We hope to have clarified why locally doubly robust methods (in this case, doubly robust under the null) have a privileged position in the literature (Farrell, 2015); if all working models are correct, one can obtain a uniformly valid test by plugging in any fast-converging sparse estimator of the nuisance parameters. If one of the working models is misspecified, then one can still obtain uniformly valid inference, so long as a specific estimation procedure for the nuisance parameters is used. We have also indicated why score tests might be preferable in high-dimensional settings, since then the outcome model can be fit under the null hypothesis, enabling one to weaken conditions on sparsity. When choosing a working outcome model, we have focused on the identity and logit link functions. In theory one could choose other links, so long as the corresponding penalized estimators of the nuisance parameters can be shown to converge sufficiently quickly.

In future work, we will extend our procedures to the estimation of regression parameters and the construction of confidence intervals. Consider the model \( \mathcal{M} \) defined by the restriction

\[
g\{E(Y|A = a, L = l)\} - g\{E(Y|A = 0, L = l)\} = \theta a
\]

The score \( \psi(W; \eta) \) implies an estimator of \( \theta \), the conditional causal effect of \( A \) on \( Y \). Let \( H(\theta) = Y - \theta A \) when \( g() \) is the identity link and \( H(\theta) = Y \exp(-\theta A) \) when \( g() \) is the log link; then estimation of \( \theta \) can be based on the function

\[
\psi(W; \theta, \eta) = \{A - \pi(L; \gamma)\}\{H(\theta) - m(L; \beta)\}
\]  

(12)
Then an estimator of $\theta$ based on (12) is consistent under model $\mathcal{M} \cap (A \cup B)$. The goal of constructing uniformly valid confidence intervals could require a revision of the conditions given in Sections 4.2 and 5.2 since we are no longer working under the null. It also remains an open question for which settings doubly robust estimators can be constructed. For example, there currently exists no doubly robust estimator for the Cox proportional hazards model or probit models. In practice it may be more feasible to construct estimators (and confidence intervals) that are locally robust e.g. under the null, and hence in this context enjoy the properties of the tests described in this paper.

When $\theta$ is multivariate, equations (5) and (6) deliver more estimating equations than there are unknown nuisance parameters. To ensure that standard errors are valid, one would also need to ensure that the estimating functions of each component of $\theta$ are orthogonal to those of the remaining components. Such a development would not only be advantageous in terms of testing for and estimating interaction terms, but also for obtaining uniformly valid inference in high-dimensional data with mediators and/or time dependent confounders. Indeed, the estimators of the conditional exposure effects described above are special cases of $G$-estimation (Robins et al., 1992), developed for fitting structural nested models in complex longitudinal studies. Because it turns out to be essentially impossible to correctly specify sequential regression models for an outcome, it is unlikely that existing proposals for high-dimensional inference can be adapted to test the hypothesis of no causal effect of any treatment regime on $Y$ a.k.a the g-null hypothesis (Robins, 1994). In contrast, although we perform selection on both the outcome and exposure models (in order for the relevant gradients to be set to zero), in the proposal of Section 5 only the latter needs to be correctly specified in order to obtain a valid test of the g-null.
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A Appendix A

A.1 Assumptions

Define $N_p = \{1, 2, ..., p\}$. We use $E_{P_n}[]$ for taking expectation w.r.t. the local data generating process (DGP), whereas $E_n[]$ refers to sample expectations. Similarly, $P_{P_n}[]$ and $\text{var}_{P_n}[]$ denote probabilities and variances taken w.r.t. the local DGP respectively.

For a vector $a$ and index set $S \subseteq \{1, ..., p\}$, the $S$ sub-vector is denoted as $a_S \in \mathbb{R}^{|S|}$ and consists of the entries $a_i$, such that $i \in S$. For any matrix $A \in \mathbb{R}^{p \times p}$ and index sets $S_1$ and $S_2$, the $(S_1, S_2)$ block-matrix is denoted as $A_{S_1,S_2} \in \mathbb{R}^{|S_1| \times |S_2|}$ and consists of entries $A_{ij}$, such that $i \in S_1$ and $j \in S_2$. For any set $S$, we denote $\overline{S}$ and $|S|$ as complement and cardinality of the set $S$, respectively. For any symmetric matrix $A$, we denote its maximum and minimum eigenvalues as $\Psi_{\text{max}}(A)$ and $\Psi_{\text{min}}(A)$, respectively. We define the $\ell_\infty$ norm of any matrix $A$ as $||A||_\infty = \max_{i,j} |A_{ij}|$ and use $a \lor b = \max\{a, b\}$. We denote $A \succ 0$ if matrix $A$ is positive definite.

Finally, since $F(\eta)$ is the objective function corresponding to the penalized estimating equations

$$0 = \frac{1}{n} \sum_{i=1}^{n} \frac{\partial}{\partial \eta} \psi(W_i; \eta) + \lambda_\eta |\eta|^{\delta-1} \circ \text{sign}(\eta)$$

such that $\hat{\eta} = \arg\min_\eta F(\eta)$, we use the decomposition $F(\eta) = f(\eta) + \lambda_\eta g(\eta)$. 

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**Assumption 1.** *(Data generating process)* There exist constants \( C_1, C_2, C_3 < \infty \), \( c_4, c_5 > 0 \) and \( 4 < r < \infty \) such that:

(i) \( \mathbb{E}_{P_n}[|Y - m(L; \beta_n)|^4|L|] \leq C_1 \) w.p. 1.

(ii) \( \mathbb{E}_{P_n}[|Y - m(L; \beta_n)|^r] \leq C_2 \).

(iii) \( \max_{j \in \mathbb{N}_p} |L_j| \leq C_3 \) w.p. 1.

(iv) \( c_4 \leq \mathbb{E}_{P_n}[\{A - \pi(L; \gamma_n)\}^2|L|] \) and \( c_5 \leq \mathbb{E}_{P_n}[\{Y - m(L; \beta_n)\}^2|L|] \) w.p. 1.

**Remark.** Assumption 1(i) allows one to bound the conditional variance of \( Y - m(L; \beta_n) \) given \( L \) and also implies a bound on the variance given \( A \) and \( L \). Assumption 1(ii) places a bound on the higher order moments of \( Y - m(L; \beta_n) \), and is required to show uniform consistency of the variance estimator of \( \psi(W; \hat{\eta}) \) and uniform asymptotic normality of the test statistic. We note that Assumptions 1(i)-(ii) allow for non-Gaussianity and heteroscedasticity with respect to the error term \( Y - m(L; \beta_n) \). Assumption 1(iii) requires \( L \) to be restricted to a bounded set, which is an assumption typically made in the literature (Farrell, 2015; Ning and Liu, 2017). It follows from Belloni et al. (2014) that one may be able to prove the main result under weaker conditions on \( L \), but we use 1(iii) as it is easy to understand and because in most applications the covariates will naturally be bounded anyhow. Assumption 1(iv) places additional bounds on the conditional variance, and implies a type of ‘positivity’ condition such that there must be some variation in \( A \) at different levels of \( L \).

**Assumption 2.** *(Order of the penalty term).* \( \lambda_\gamma = O\left(\sqrt{\frac{\log p}{n}}\right) \)

**Remark.** This is a standard assumption on the order of the penalty level \( \lambda \) in the literature, when working either under the intersection submodel (Farrell, 2015; Belloni et al., 2016), or the union model (Avagyan and Vansteelandt, 2017).
Additional regularity assumptions (such as a condition on sparse eigenvalues) are required to guarantee the uniform consistency of the $\ell_1$-penalized estimators and the predictions (see below). We refer the reader to comprehensive conditions for $\ell_1$-penalized linear regression estimators given in Belloni et al. (2012), and for non-linear and weighted estimators in Belloni et al. (2016).

A.2 Proofs of main results

A.2.1 Proof of Theorem 1

Proof. The proof will proceed in four steps. In the first step, we show that

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \psi(W_i; \hat{\eta}) = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \psi(W_i; \eta_n) + o_{P_n}(1) \quad (A.1)$$

in the second, that

$$\frac{\mathbb{E}_n[\psi(W_i; \eta_n)]}{\sqrt{\frac{1}{n} \mathbb{E}_n[\psi(W_i; \eta_n)^2]}} \xrightarrow{d} \mathcal{N}(0, 1) \quad (A.2)$$

in the third, that

$$\mathbb{E}_n[\psi(W_i; \hat{\eta})^2 - \mathbb{E}_n\{\psi(W_i; \hat{\eta})\}^2] - \mathbb{E}_n\{\psi(W_i; \eta_n)\}^2 = \mathbb{E}_n[\psi(W_i; \eta_n)^2]^{-1} + o_{P_n}(1) \quad (A.3)$$

Finally, we will use these results to show result (4) in the main paper.

In what follows, we will rely on the rates below:

$$\mathbb{E}_n[\{\pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma})\}^2] = O_{P_n}\left(\frac{s_\gamma \log(p \vee n)}{n}\right) \quad (A.4)$$

$$\mathbb{E}_n[\{m(L_i; \beta_n) - m(L_i; \hat{\beta})\}^2] = O_{P_n}\left(\frac{s_\beta \log(p \vee n)}{n}\right) \quad (A.5)$$

Results (A.4)-(A.5) follow from the results of Belloni and Chernozhukov (2013), Belloni et al. (2014), Farrell (2015) and Belloni et al. (2016) on Lasso and Post-Lasso-based estimators.
Step 1

Consider the sample mean of $\psi(W_i; \hat{\eta})$:

$$E_n[\psi(W_i; \hat{\eta})] = E_n[\psi(W_i; \eta_n) + \psi(W_i; \hat{\eta}) - \psi(W_i; \eta_n)]$$

After some algebra, we have

$$\sqrt{n}E_n[\psi(W_i; \hat{\eta})] = \sqrt{n}E_n[\psi(W_i; \eta_n)] + R_1 + R_2 + R_3$$

where

$$R_1 = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ A_i - \pi(L_i; \gamma_n) \} \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}) \}$$

$$R_2 = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ Y_i - m(L_i; \beta_n) \} \{ \pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma}) \}$$

$$R_3 = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ m(L_i; \hat{\beta}) - m(L_i; \beta_n) \} \{ \pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n) \}$$

We aim to show that $R_1$, $R_2$ and $R_3$ are all $o_p(n)$ under model $A \cap B$.

For $R_1$, under the null as defined in $[\Pi]$,

$$E_{P_n}[R_1|\{Y_i, L_i\}_{i=1}^n] = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ E_{P_n}[A_i|\{Y_i, L_i\}_{i=1}^n] - \pi(L_i; \gamma_n) \} \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}) \}$$

$$= 0$$

and

$$E_{P_n}[R_1^2|\{Y_i, L_i\}_{i=1}^n] = E_n \left[ \{ E_{P_n}[\{ A_i - \pi(L_i; \gamma_n) \}^2|\{L_i\}_{i=1}^n]\} \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}) \}^2 \right]$$

$$\leq C E_n[\{ m(L_i; \beta_n) - m(L_i; \hat{\beta}) \}^2]$$

where $C$ is a constant. Furthermore, invoking $[A.5]$ and sparsity condition $[i]$ we have

$$C E_n[\{ m(L_i; \beta_n) - m(L_i; \hat{\beta}) \}^2] = o_{P_n}(1)$$

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and \( \mathbb{E}_P \Pi R_1^2 = o(1) \). Hence one can then apply Markov’s Inequality to show that \( |R_1| = o_{P_n}(1) \).

Similarly, for \( R_2 \),

\[
\mathbb{E}_P \Pi R_2^2 \{ A, L \}_{i=1}^n = \mathbb{E}_P \Pi \{ Y_i - \beta' L_i \}^2 \{ A, L \}_{i=1}^n \{ \pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma}) \}^2 \\
\leq C \mathbb{E}_P \Pi \{ \pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma}) \}^2,
\]

where \( C \) is a constant. This inequality follows from Assumption [i]. Invoking (A.4) and sparsity condition (i), we have

\[
C \mathbb{E}_P \Pi \{ \pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma}) \}^2 = o_{P_n}(1)
\]

so \( \mathbb{E}_P \Pi R_2^2 = o(1) \) and using Markov’s inequality, \( |R_2| = o_{P_n}(1) \).

Finally, considering \( R_3 \), by Hölder’s inequality

\[
\left| \frac{1}{\sqrt{n}} \sum_{i=1}^n \{ m(L_i; \hat{\beta}) - m(L_i; \beta_n) \} \{ \pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n) \} \right| \\
\leq \sqrt{n} \mathbb{E}_P \Pi \{ m(L_i; \hat{\beta}) - m(L_i; \beta_n) \}^{2/2} \mathbb{E}_P \Pi \{ \pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n) \}^{2/2}
\]

Then given the joint sparsity condition (ii) on \( s_{\gamma} \) and \( s_{\beta} \), and results (A.4) and (A.5), it follows that

\[
\sqrt{n} \mathbb{E}_P \Pi \{ m(L_i; \hat{\beta}) - m(L_i; \beta_n) \}^{2/2} \mathbb{E}_P \Pi \{ \pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n) \}^{2/2} = o_{P_n}(1)
\]

Therefore \( |R_3| = o_{P_n}(1) \) and we have result (A.1).

**Step 2**

Under the null, we have that \( \text{var}_{P_n}[\psi(W_i; \eta_n)] = \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2] = \mathbb{E}_{P_n}[\{ A_i - \pi(L_i; \gamma_n) \}^2 \{ Y_i - m(L_i; \beta_n) \}^2] \) and by Assumptions [ii] and [iv], \( \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2] \) is bounded away from zero (necessary for the inversion) and above uniformly in \( n \).
For some $\epsilon > 0$, such that $4 + 2\epsilon \leq r$

$$\mathbb{E}_{P_n}[|\psi(W_i; \eta_n)|^{2+\epsilon}] \leq \mathbb{E}_{P_n}||A_i - \pi(L_i; \gamma_n)|^{4+2\epsilon}]^{1/2}\mathbb{E}_{P_n}[|Y_i - m(L_i; \beta_n)|^{4+2\epsilon}]^{1/2}$$

$$\leq C$$

where $C$ is a constant, by Assumption [ii]. This verifies the Lyapunov condition, such that using this result (and the fact that $\mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2]$ is finite) one can then invoke the Lyapunov central limit theorem for triangular arrays to get result (A.2). We rely on array asymptotics here in order to allow for the data-generating process to change with $n$.

**Step 3**

Since $\mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2]$ is bounded away from zero uniformly in $n$ and $\mathbb{E}_{P_n}[\psi(W_i; \eta_n)] = 0$, given the previous steps it suffices to show that $\mathbb{E}_n[\psi(W_i; \tilde{\eta})^2] = \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2] + o_{P_n}(1)$.

We will first obtain the result

$$\mathbb{E}_n[\psi(W_i; \eta_n)^2] = \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2] + o_{P_n}(1)$$  \hfill (A.6)

We have

$$\mathbb{P}_{P_n}\left(\mathbb{E}_n[\psi(W_i; \eta_n)^2] - \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2] > \epsilon\right)$$

$$\leq \frac{1}{\epsilon^2}\mathbb{E}_{P_n}\left[\frac{1}{n}\sum_{i=1}^{n}\psi(W_i; \eta_n)^2 - \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2]\right]^2$$

$$\leq \frac{1}{\epsilon^2 n^2}\left(2 - \frac{1}{n}\right)\sum_{i=1}^{n}\mathbb{E}_{P_n}\left[\psi(W_i; \eta_n)^2 - \mathbb{E}_{P_n}[\psi(W_i; \eta_n)^2]\right]^2$$

where we first apply Markov’s inequality. The second uses the Von Bahr-Esseen inequality:

let $q \in [1, 2]$, then for independent mean-zero variables $X_1, ..., X_n$, we have

$$E\left[\left|\sum_{i=1}^{n}X_i\right|^q\right] \leq \left(2 - \frac{1}{n}\right)\sum_{i=1}^{n}E[|X_i|^q]$$

(von Bahr and Esseen, 1965).
Since

\[ E_P [\{ \psi(W_i; \eta_n) - \psi(W_i; \eta_n) \}^2] = \text{var}_P [\psi(W_i; \eta_n)] \]

\[ = \text{var}_P [\psi(W_i; \eta_n)^2] \]

\[ = \text{var}_P [\{A_i - \pi(L_i; \gamma_n)\}^2 E_P [\{Y_i - m(L_i; \beta_n)\}^2 | A_i, L_i]] \]

\[ + E_P [\{A_i - \pi(L_i; \gamma_n)\}^4 \text{var}_P [\{Y_i - m(L_i; \beta_n)\}^2 | A_i, L_i]] \]

then firstly

\[ \text{var}_P [\{A_i - \pi(L_i; \gamma_n)\}^2 E_P [\{Y_i - m(L_i; \beta_n)\}^2 | A_i, L_i]] \]

\[ \leq C E_P [\{A_i - \pi(L_i; \gamma_n)\}^2] = O(1) \]

where \( C \) is a constant, using Assumption 1(i). Secondly,

\[ E_P [\{A_i - \pi(L_i; \gamma_n)\}^4 \text{var}_P [\{Y_i - m(L_i; \beta_n)\}^2 | A_i, L_i]] \]

\[ \leq C E_P [\{A_i - \pi(L_i; \gamma_n)\}^4] = O(1) \]

where \( C \) is again a constant, invoking Assumptions 1(i) and 1(ii). Result (A.6) then follows.

It remains to show that

\[ E_n[\psi(W_i; \hat{\eta})^2] = E_n[\psi(W_i; \eta_n)^2] + o_P(1) \quad (A.7) \]

By adding and subtracting \( E_n[\{A_i - \pi(L_i; \hat{\gamma})\}^2 \{Y_i - m(L_i; \beta_n)\}^2] \) and applying the triangle inequality, then

\[ |E_n[\{A_i - \pi(L_i; \hat{\gamma})\}^2 \{Y_i - m(L_i; \hat{\beta})\}^2 - \{A_i - \pi(L_i; \gamma_n)\}^2 \{Y_i - m(L_i; \beta_n)\}^2]| \]

\[ \leq |E_n[\{A_i - \pi(L_i; \hat{\gamma})\}^2 - \{A_i - \pi(L_i; \gamma_n)\}^2] \{Y_i - m(L_i; \hat{\beta})\}^2| \]

\[ + |E_n[\{Y_i - m(L_i; \hat{\beta})\}^2 - \{Y_i - m(L_i; \beta_n)\}^2] \{A_i - \pi(L_i; \hat{\gamma})\}^2| \]

\[ = |R_4| + |R_5| \]

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Looking first at $|R_0|$, after some algebra we have

$$
|\mathbb{E}_n[(Y_i - m(L_i; \hat{\beta}))^2 - (Y_i - m(L_i; \beta_n))^2] A_i - \pi(L_i; \hat{\gamma})|^2 |
\leq \mathbb{E}_n[\{m(L_i; \hat{\beta}) - m(L_i; \beta_n)\}^2 A_i - \pi(L_i; \hat{\gamma})]^2]
+ 2\mathbb{E}_n[\{Y_i - m(L_i; \beta_n)\} \{m(L_i; \hat{\beta}) - m(L_i; \beta_n)\} A_i - \pi(L_i; \hat{\gamma})]^2] \tag{A.8}
$$

Then for (A.8),

$$
\mathbb{E}_n[\{m(L_i; \hat{\beta}) - m(L_i; \beta_n)\}^2 A_i - \pi(L_i; \hat{\gamma})]^2
\leq \max_{i \leq n} \{A_i - \pi(L_i; \hat{\gamma})\}^2 \mathbb{E}_n[\{m(L_i; \hat{\beta}) - m(L_i; \beta_n)\}^2] = o_P(1)
$$

following (A.5), the fact that $A$ is binary and sparsity condition \textit{(ii)}. Furthermore, for (A.9),

$$
|2\mathbb{E}_n[\{Y_i - m(L_i; \beta_n)\} \{m(L_i; \hat{\beta}) - m(L_i; \beta_n)\} A_i - \pi(L_i; \hat{\gamma})|^2]|
\leq 2 \max_{i \leq n} \{A_i - \pi(L_i; \hat{\gamma})\}^2 \mathbb{E}_n[\{Y_i - m(L_i; \beta_n)\}^2]^{1/2} \mathbb{E}_n[\{m(L_i; \hat{\beta}) - m(L_i; \beta_n)\}^2]^{1/2}
\leq 2 \max_{i \leq n} \{A_i - \pi(L_i; \hat{\gamma})\}^2 \mathbb{E}_n[\{Y_i - m(L_i; \beta_n)\}^2]^{1/2} = o_P(1)
\text{ by (A.5). For } \mathbb{E}_n[\{Y_i - m(L_i; \beta_n)\}^2]^{1/2}, \text{ note that by Assumption } \textit{(ii)} \mathbb{E}_P_n[|Y_i - m(L_i; \beta_n)|^4] = O(1) \text{ and hence } \mathbb{E}_P_n[\{Y_i - m(L_i; \beta_n)\}^2]^{1/2} = O(1). \text{ Then to bound the sample average, by the Von Bahr-Esseen inequality:}

$$
\mathbb{P}_P_n\left(\frac{\mathbb{E}_n[|Y_i - m(L_i; \beta_n)|^4] - \mathbb{E}_P_n[|Y_i - m(L_i; \beta_n)|^4]|^q}{\epsilon^{n^q}} > \epsilon\right)
\leq \frac{1}{\epsilon^{n^q}} \left(2 - \frac{1}{n}\right) \sum_{i=1}^{n} \mathbb{P}_n\left[|Y_i - m(L_i; \beta_n)|^4 - \mathbb{E}_P_n[|Y_i - m(L_i; \beta_n)|^4]\right]^q
$$

for $q \in [1, 2]$. Applying Minkowski’s inequality and using Assumption \textit{(ii)}

$$
\mathbb{E}_P_n\left[|Y_i - m(L_i; \beta_n)|^4 - \mathbb{E}_P_n[|Y_i - m(L_i; \beta_n)|^4]\right]^q
\leq \left[\mathbb{E}_P_n[|Y_i - m(L_i; \beta_n)|^4q] + \mathbb{E}_P_n\left\{\mathbb{E}_P_n[|Y_i - m(L_i; \beta_n)|^4q]^{1/q}\right\}^q\right]^q
= O(1),
$$
hence $\mathbb{E}_n[|Y_i - m(L_i; \beta_n)|^4] = O_{P_n}(1)$ and also $\mathbb{E}_n[|Y_i - m(L_i; \beta_n)|^2]^{1/2} = O_{P_n}(1)$. Therefore $|R_5| = o_{P_n}(1)$.

Similarly, for $R_4$ we have

$$|R_4| \leq \mathbb{E}_n[\{\pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n)\}^2\{Y_i - m(L_i; \beta_n)\}^2]$$

$$+ 2 \max_{i \leq n} |A_i - \pi(L_i; \gamma_n)| \mathbb{E}_n[|Y_i - m(L_i; \beta_n)|^4]^{1/2} \mathbb{E}_n[\{\pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n)\}^2]^{1/2}$$

By invoking Assumption (ii), (A.4) and the sparsity condition (i), one can show that the second term on the right hand side of the inequality is $o_{P_n}(1)$. Regarding the first term,

$$\mathbb{E}_n[\{\pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n)\}^2\{Y_i - m(L_i; \beta_n)\}^2]$$

$$\leq \max_{i \leq n} |\pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n)| \mathbb{E}_n[\{\pi(L_i; \hat{\gamma}) - \pi(L_i; \gamma_n)\}^2]^{1/2} \mathbb{E}_n[|Y_i - m(L_i; \beta_n)|^4]^{1/2}$$

$$= o_{P_n}(1)$$

using Holder’s inequality, Assumption (ii), the previous result that $\mathbb{E}_n[|Y_i - m(L_i; \beta_n)|^4] = O_{P_n}(1)$, (A.4) and the sparsity condition (i). We have shown (A.7) and result (A.3) follows.

**Step 4**

Consider a sequence $P_m \in P$ such that for each $m$, 

$$\lim_{m \to \infty} |P_{P_m}(T_n \leq t) - \Phi(t)| > 0$$

This directly contradicts the results given above that the test statistic $T_n$ converges to a normal distribution with mean 0 and variance 1 under any subsequence $P_m$ in $P$. \qed
A.2.2 Proof of Theorem 2

In this section, we now make use of the rates

\[ ||\gamma_n - \hat{\gamma}_{BR}||_1 = O_{P_n} \left( s_{\gamma} \frac{\sqrt{\log(p \vee n)}}{n} \right) \]  \hspace{1cm} (A.10)

\[ ||\beta_n - \hat{\beta}_{BR}||_1 = O_{P_n} \left( s_{\beta} \frac{\sqrt{\log(p \vee n)}}{n} \right) \]  \hspace{1cm} (A.11)

\[ ||\gamma_n - \hat{\gamma}_{BR}||_2 = O_{P_n} \left( \frac{s_{\gamma} \log(p \vee n)}{n} \right) \]  \hspace{1cm} (A.12)

\[ ||\beta_n - \hat{\beta}_{BR}||_2 = O_{P_n} \left( \frac{s_{\beta} \log(p \vee n)}{n} \right) \]  \hspace{1cm} (A.13)

Our proposed nuisance parameter estimators are obtained via (weighted) $\ell_1$ penalized regression. Results (A.10)-(A.13) follow from the results of Belloni et al. (2016) on weighted $\ell_1$-penalized regression (e.g. their Theorem 4). We also make use of the conditions

\[ \mathbb{E}_n \left[ \pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma}_{BR}) \right]^2 = O_{P_n} \left( \frac{s_{\gamma} \log(p \vee n)}{n} \right) \]  \hspace{1cm} (A.14)

\[ \mathbb{E}_n \left[ m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR}) \right]^2 = O_{P_n} \left( \frac{s_{\beta} \log(p \vee n)}{n} \right) \]  \hspace{1cm} (A.15)

that are equivalent to (A.4) and (A.5); these again follow from Belloni et al. (2016).

Repeating the previous decomposition of $\sqrt{n}\mathbb{E}_n[\psi(W_i; \hat{\eta}_{BR})] - \sqrt{n}\mathbb{E}_n[\psi(W_i; \eta_n)]$, for $R_1$, we now have

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{A_i - \pi(L_i; \gamma_n)\} \{m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR})\} \\
= \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{A_i - \pi(L_i; \hat{\gamma}_{BR})\} \{m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR})\} \\
+ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{\pi(L_i; \hat{\gamma}_{BR}) - \pi(L_i; \gamma_n)\} \{m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR})\} \]  \hspace{1cm} (A.16)

(A.17)
Then for (A.16), note that following a Taylor expansion,

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ A_i - \pi(L_i; \hat{\gamma}_{BR}) \right\} \left\{ m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR}) \right\} = \sqrt{n} \mathbb{E}_n \left[ \frac{\partial \psi(W_i; \hat{\eta}_{BR})}{\partial \beta} \right] (\beta_n - \hat{\beta}_{BR}) + O_P(\sqrt{n} \| \beta_n - \hat{\beta}_{BR} \|_2^2)
\]

and by Hölder’s inequality,

\[
\left| \sqrt{n} \mathbb{E}_n \left[ \frac{\partial \psi(W_i; \hat{\eta}_{BR})}{\partial \beta} \right] (\beta_n - \hat{\beta}_{BR}) \right| \leq \sqrt{n} \left\| \mathbb{E}_n \left[ \frac{\partial \psi(W_i; \hat{\eta}_{BR})}{\partial \beta} \right] \right\|_\infty \| \beta_n - \hat{\beta}_{BR} \|_1 \leq \sqrt{n} \lambda \gamma \delta |\hat{\gamma}_{BR}|^{\delta - 1} \text{sign}(\hat{\gamma}_{BR}) \| \beta_n - \hat{\beta}_{BR} \|_1
\]

since \( \| \delta |\hat{\gamma}_{BR}|^{\delta - 1} \text{sign}(\hat{\gamma}_{BR}) \|_\infty \leq \delta \). Therefore, given Assumption 2 (A.11), (A.13) and sparsity condition (iii)

\[
\left| \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ A_i - \pi(L_i; \hat{\gamma}_{BR}) \right\} \left\{ m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR}) \right\} \right| = o_P(1)
\]

Considering the other term (A.17), along the same lines as in the proof of Theorem I, one can show that

\[
\left| \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ \pi(L_i; \hat{\gamma}_{BR}) - \pi(L_i; \gamma_n) \right\} \left\{ m(L_i; \beta_n) - m(L_i; \hat{\beta}_{BR}) \right\} \right| = o_P(1)
\]

using Hölder’s inequality, sparsity condition (iii) and results (A.14) and (A.15). Therefore

\[ |R_1| = o_P(1). \]

One can re-apply the argument given immediately above to show that

\[ |R_3| = o_P(1). \]

By noting that

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \left\{ Y_i - m(L_i; \hat{\beta}_{BR}) \right\} \left\{ \pi(L_i; \gamma_n) - \pi(L_i; \hat{\gamma}_{BR}) \right\} = \sqrt{n} \mathbb{E}_n \left[ \frac{\partial \psi(W_i; \hat{\eta}_{BR})}{\partial \gamma} \right] (\gamma_n - \hat{\gamma}_{BR}) + O_P(\sqrt{n} \| \gamma_n - \hat{\gamma}_{BR} \|_2^2)
\]

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and

\[ \sqrt{n} E_n \left[ \frac{\partial \psi(W_i; \hat{\gamma}_{BR})}{\partial \gamma} \right] (\gamma_n - \hat{\gamma}_{BR}) \leq \sqrt{n} \left\| E_n \left[ \frac{\partial \psi(W_i; \hat{\gamma}_{BR})}{\partial \gamma} \right] \right\|_\infty \| \gamma_n - \hat{\gamma}_{BR} \|_1 \]

\[ \leq \sqrt{n} \lambda \| \gamma_n - \hat{\gamma}_{BR} \|_1 \]

one can also repeat the above arguments to show that \( |R_2| = o_{P_n}(1) \), given Assumption 2 (A.11), (A.13), (A.14), (A.15) and sparsity condition (iii). Result (A.1) follows immediately and the main result follows by essentially repeating Steps 2-4 from the proof of Theorem 1.

A.2.3 Proof of Corollary 1

Proof. As discussed in the main paper, when \( E(A|L) = \pi(L; \gamma^*) \) and \( \gamma^* \) is known, the proposal in Section 5 for estimating \( \beta \) reduces to standard (unweighted) PMLE. Then repeating Step 1 of the previous proof,

\[ \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{A_i - \pi(L_i; \gamma^*)\} \{Y_i - m(L_i; \beta)\} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{A_i - \pi(L_i; \gamma^*)\} \{Y_i - m(L_i; \beta_n)\} + \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{A_i - \pi(L_i; \gamma^*)\} \{m(L_i; \beta_n) - m(L_i; \hat{\beta})\} \]

Let us define \( R_1^* = \sqrt{n} E_n [\{A_i - \pi(L_i; \gamma^*)\} \{m(L_i; \beta_n) - m(L_i; \hat{\beta})\}] \).

Then,

\[ E_{P_n} [R_1^2 | Y_i, L_i \}_{i=1}^{n}] = E_n \left[ \{E_{P_n} [\{A_i - \pi(L_i; \gamma^*)\} ^2 | \{L_i\}_{i=1}^{n}] \{m(L_i; \beta_n) - m(L_i; \hat{\beta})\} \}^2 \right] \]

\[ \leq C E_n [\{m(L_i; \beta_n) - m(L_i; \hat{\beta})\}^2] \]

where \( C \) is a constant. Invoking (A.5) and sparsity condition (i) we have

\[ C E_n [\{m(L_i; \beta_n) - m(L_i; \hat{\beta})\}^2] = o_{P_n}(1) \]

hence \( E_{P_n} [R_1^2] = o(1) \) and \( |R_1^*| = o_{P_n}(1) \) using Markov’s Inequality. Note that sparsity condition (iii) has not been invoked.
Proof. Decomposing \( \sqrt{nE_n[\psi(W_i; \hat{\eta}_{BR})]} - \sqrt{nE_n[\psi(W_i; \eta_n)]} \) as above, one can show \( |R_2| = o_P(n) \) along the lines of the proof of Theorem 1 appealing to Assumption 1(i), (A.4) and sparsity condition (i). Similarly, one can show that \( R_3 \) is \( o_P(n) \) using the joint sparsity condition (ii) and results (A.4) and (A.15).

In this setting, note that \( \hat{\gamma}_{BR} = \hat{\gamma} \), since no weights are used in estimating this parameter. Furthermore, in order to make transparent the dependence of the estimator \( \hat{\beta}_{BR} \) on the weights, we introduce the notation \( \hat{\beta}(\hat{\gamma}) \) for when \( \gamma \) (required for the weights) is estimated from the data and \( \hat{\beta}(\gamma_n) \) otherwise. Then for \( R_1 \),

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ A_i - \pi(L_i; \gamma_n) \} \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}(\gamma_n)) \} = \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ A_i - \pi(L_i; \gamma_n) \} \{ m(L_i; \hat{\beta}(\gamma_n)) - m(L_i; \hat{\beta}(\hat{\gamma})) \} + \frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ A_i - \pi(L_i; \gamma_n) \} \{ m(L_i; \hat{\beta}(\gamma_n)) - m(L_i; \hat{\beta}(\hat{\gamma})) \} = R_{1a} + R_{1b}
\]

One can show \( |R_{1a}| = o_P(n) \) using (A.15) and sparsity condition (i). For \( R_{1b} \),

\[
\frac{1}{\sqrt{n}} \sum_{i=1}^{n} \{ A_i - \pi(L_i; \gamma_n) \} \{ m(L_i; \hat{\beta}(\gamma_n)) - m(L_i; \hat{\beta}(\hat{\gamma})) \} = \sqrt{nE_n[\{ A_i - \pi(L_i; \gamma_n) \} L_i]} \{ \hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma}) \} \leq \max_{1 \leq j \leq p} \| \mathbb{E}_n[\{ A_i - \pi(L_i; \gamma_n) \} L_{ij}] \| \sqrt{n} \| \hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma}) \|_1
\]

Given Assumption 1(iii) we have

\[
\max_{1 \leq j \leq p} \| \mathbb{E}_n[\{ A_i - \pi(L_i; \gamma_n) \} L_{ij}] \| \leq \max_{1 \leq j \leq p} \mathbb{E}_n[\| A_i - \pi(L_i; \gamma_n) \| L_{ij}] = O_P(n)
\]
Then it remains to bound $||\hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma})||_1$.

Let us define the weights $w(L; \gamma_n) = \pi(L; \gamma_n)\{1 - \pi(L; \gamma_n)\}$, and likewise for $w(L; \hat{\gamma})$. We have that

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} w(L_i; \gamma_n)\{Y_i - m(L_i; \hat{\beta}(\gamma_n))\}L_i$$

(A.18)

$$= \frac{1}{\sqrt{n}} \sum_{i=1}^{n} w(L_i; \gamma_n)\{Y_i - m(L_i; \hat{\beta}(\gamma_n))\}L_i$$

(A.19)

$$+ \sqrt{n} \mathbb{E}_n \left[ \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \{Y_i - m(L_i; \hat{\beta}(\gamma_n))\}L_i \right] (\hat{\gamma} - \gamma_n)$$

(A.20)

$$+ \sqrt{n} \mathbb{E}_n [L_i w(L_i; \gamma_n)L_i^T] \{\hat{\beta}(\hat{\gamma}) - \hat{\beta}(\gamma_n)\}$$

(A.21)

Beginning with (A.18) and (A.19),

$$\frac{1}{\sqrt{n}} \sum_{i=1}^{n} w(L_i; \gamma_n)\{Y_i - m(L_i; \hat{\beta}(\gamma_n))\}L_i - \frac{1}{\sqrt{n}} \sum_{i=1}^{n} w(L_i; \hat{\gamma})\{Y_i - m(L_i; \hat{\beta}(\hat{\gamma}))\}L_i$$

$$= \sqrt{n} \lambda_\beta \delta ||\hat{\beta}(\gamma_n)||^{\delta - 1} \circ \text{sign}(\hat{\beta}(\gamma_n)) - ||\hat{\beta}(\hat{\gamma})||^{\delta - 1} \circ \text{sign}(\hat{\beta}(\hat{\gamma}))$$

$$= \sqrt{n} \lambda_\beta \delta (\delta - 1)||\hat{\beta}(\hat{\gamma})||^{\delta - 2} \circ \text{sign}(\hat{\beta}(\hat{\gamma})) \{\hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma})\} + O_{P_n}(\sqrt{n}||\hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma})||_2^2)$$

where the final equality follows from a Taylor expansion around $\hat{\beta}(\hat{\gamma})$. For any finite $n$, we can choose $\delta$ to be close enough to 1 such that

$$\sqrt{n} \lambda_\beta \delta (\delta - 1)||\hat{\beta}(\hat{\gamma})||^{\delta - 2} \circ \text{sign}(\hat{\beta}(\hat{\gamma})) \{\hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma})\}$$

is negligible.

Moving onto (A.20), note that

$$\sqrt{n} \mathbb{E}_n \left[ \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \{Y_i - m(L_i; \hat{\beta}(\gamma_n))\}L_i \right] (\hat{\gamma} - \gamma_n)$$

$$= \sqrt{n} \mathbb{E}_n \left[ \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \{Y_i - m(L_i; \hat{\beta}_n)\} (\gamma^T L_i - \gamma_n^T L_i) \right]$$

$$+ \sqrt{n} \mathbb{E}_n \left[ \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \{m(L_i; \beta_n) - m(L_i; \hat{\beta}(\gamma_n))\} (\gamma^T L_i - \gamma_n^T L_i) \right]$$

$$= R_6 + R_7$$
Then we have

\[ \mathbb{E}_P [R_6 | \{A_i, L_i\}_{i=1}^n] = \frac{1}{\sqrt{n}} \sum_{i=1}^n \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \{ \mathbb{E}_P [Y_i | \{A_i, L_i\}_{i=1}^n] - m(L_i; \beta_n) \} (\hat{\gamma}^T L_i - \gamma_n^T L_i) = 0 \]

and

\[
\mathbb{E}_P[\| R_6 \|_2^2 | \{A_i, L_i\}_{i=1}^n] \\
= \sum_j \frac{1}{n} \mathbb{E}_P \left[ \left\{ \sum_{i=1}^n \left( \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \right) \{ Y_i - m(L_i; \beta_n) \} (\hat{\gamma}^T L_i - \gamma_n^T L_i) \right\}^2 \right] \{A_i, L_i\}_{i=1}^n \\
= \sum_j \mathbb{E}_n \left[ \mathbb{E}_P \left[ \left( \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \right)^2 \{ Y_i - m(L_i; \beta_n) \}^2 (\hat{\gamma}^T L_i - \gamma_n^T L_i)^2 \right] \{A_i, L_i\}_{i=1}^n \right] \\
= \sum_j \mathbb{E}_n \left[ \left( \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \right)^2 \mathbb{E}_P \left[ \{ Y_i - m(L_i; \beta_n) \}^2 (\hat{\gamma}^T L_i - \gamma_n^T L_i)^2 \right] \right] \\
\leq C \mathbb{E}_n [(\hat{\gamma}^T L_i - \gamma_n^T L_i)^2] = o_P(1)
\]

where \( C \) is a constant; this follows from Assumptions [ii(i)] and Assumption [ii(ii)] (A.4) and sparsity condition [i]. Note that the second equality follows since

\[
\mathbb{E}_P \left[ \sum_{i=1}^n \sum_{k=1, i \neq k}^n \left( \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \right) \{ Y_i - m(L_i; \beta_n) \} (\hat{\gamma}^T L_i - \gamma_n^T L_i) \right. \\
\times \left( \frac{\partial w(L_k; \gamma_n)}{\partial \gamma} \right) \{ Y_k - m(L_k; \beta_n) \} (\hat{\gamma}^T L_k - \gamma_n^T L_k) \right] \{A_i, L_i\}_{i=1}^n \\
= \sum_{i=1}^n \sum_{k=1, i \neq k}^n \mathbb{E}_P \left[ \left( \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \right) \{ Y_i - m(L_i; \beta_n) \} (\hat{\gamma}^T L_i - \gamma_n^T L_i) \right] \{A_i, L_i\}_{i=1}^n \\
\times \left( \frac{\partial w(L_k; \gamma_n)}{\partial \gamma} \right) \{ Y_k - m(L_k; \beta_n) \} (\hat{\gamma}^T L_k - \gamma_n^T L_k) = 0.
\]

by the i.i.d. structure of the data, under model \( \mathcal{B} \). Hence by Markov’s inequality, \( \| R_6 \|_2 = \)
$o_{P_n}(1)$. Furthermore, for $R_7$, 
\[
\left\| \sqrt{n} \mathbb{E}_n \left[ \frac{\partial w(L_i; \gamma_n)}{\partial \gamma} \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}(\gamma_n)) \} (\hat{\gamma}^T L_i - \gamma_n^T L_i) \right] \right\|_2^2 \\
\leq n \sum_j \mathbb{E}_n \left[ \frac{\partial w(L_i; \gamma_n)}{\partial \gamma_j} \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}(\gamma_n)) \} (\hat{\gamma}^T L_i - \gamma_n^T L_i) \right]^2 \\
\leq nC \mathbb{E}_n \{ m(L_i; \beta_n) - m(L_i; \hat{\beta}(\gamma_n)) \}^2 \mathbb{E}_n [(\hat{\gamma}^T L_i - \gamma_n^T L_i)^2] = o_{P_n}(1)
\]

where $C$ is a constant, using Hölder’s inequality, Assumption (ii), (A.4), (A.15) and sparsity condition (ii).

Finally, given assumption (ii) it follows that
\[
\left\| \mathbb{E}_n [L_i w(L_i; \gamma_n) L_i^T] \right\|_\infty \leq C \mathbb{E}_n [w(L_i; \gamma_n)] = O_{P_n}(1)
\]

Note that by a sparse eigenvalue condition (Belloni et al., 2016), in the limit the above matrix is positive definite and hence can be inverted (restricting to columns corresponding to non-zero entries of $\beta$). Combining the above results,
\[
\sqrt{n} \| \hat{\beta}(\gamma_n) - \hat{\beta}(\hat{\gamma}) \|_1 = \{ o_{P_n}(1) + o_{P_n}(1) \} / O_{P_n}(1).
\]

so we have that $R_{1b} = o_{P_n}(1)$ and thus $R_1 = o_{P_n}(1)$. By then repeating Steps 2-4 from the proof of Theorem I, the main result follows.

\[\square\]

B Appendix B

B.1 Sparse misspecified models

We will partition $L$ as $L = (L^*, Z')$, where $L^*$ includes the true confounders of the $A - Y$ association and $Z$ is independent of $Y$ and $A$, conditionally on $L^*$ a.k.a. $(Y, A) \independent Z | L^*$. Hence the true regression functions $E(A|L)$ and $E(Y|L)$ depend only on $L^*$ but not $Z$;
we will assume that the dimension of $L^*$ is sufficiently small such that sparsity holds in both models.

We will assume that model $\mathcal{A}$ is correctly specified and also sparse in $L^*$. Furthermore, we will assume that model $E(Z|L^*)$ is linear in $L^*$ in the sense that $E(Z|L^*) = \alpha^T L^*$. Then, if we consider the weighted estimating equations used in estimating $\beta$, sparsity will hold in the potentially misspecified model $\mathcal{B}$ if

$$E \left[ w(L^*; \gamma) \left( \frac{Z}{L^*} \right) \{Y - m(L^*; \beta)\} \right] = 0$$

Here; $w(L^*; \gamma)$ are the weights obtained via model $\mathcal{A}$ (as in our proposal) that depend only on $L^*$ (since we also assume model $\mathcal{A}$ does not depend on $Z$). Since by virtue of how $\beta$ is estimated, $E[w(L^*; \gamma)L^*\{Y - m(L^*; \beta)\}] = 0$ at the limiting value of the proposed estimator of $\beta$, and it remains to show that $E[w(L^*)Z\{Y - m(L^*; \beta)\}] = 0$. Using the law of iterated expectation and the fact that $Y \perp Z|L^*$, we have

$$E[w(L^*; \gamma)Z\{Y - \pi(L^*; \beta)\}] = E[w(L^*; \gamma)E(Z|L^*)\{Y - m(L^*; \beta)\}]$$

$$= E[w(L^*; \gamma)\alpha^T L^*\{Y - m(L^*; \beta)\}] = 0$$

A similar argument can be used if model $\mathcal{A}$ is misspecified.

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