Adjusting for Unobserved Confounding Using Large-Scale Propensity Scores

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Abstract
Even though observational data contain an enormous number of covariates, the existence of unobserved confounders still cannot be excluded and remains a major barrier to drawing causal inference from observational data. A large-scale propensity score (LSPS) approach may adjust for unobserved confounders by including tens of thousands of available covariates that may be correlated with them. In this paper, we present conditions under which LSPS can remove bias due to unobserved confounders. In addition, we show that LSPS may avoid bias that can be induced when adjusting for various unwanted variables (e.g., M-structure colliders). We demonstrate the performance of LSPS on bias reduction using both simulations and real medical data.

Keywords
propensity score, unobserved confounder, unmeasured confounder, observational study, causal inference, electronic health record

Introduction
Causal inference in the setting of unmeasured confounding remains one of the major challenges in observational research. In medicine, electronic health records (EHRs) have become a popular data source for causal inference, where the goal is to estimate the causal effect of a treatment on a health outcome (e.g., the effect of blood-pressure medicine on the probability of a heart attack). EHRs contain information about treatments, outcomes, and many other variables, such as patient demographics, medications, diseases, and measurements. Modern EHR datasets typically contain tens of thousands of variables.

Causal inference on these data is often carried out using propensity score adjustment¹. Researchers first select confounders among the many observed variables, either manually (based on medical knowledge) or empirically. Then they estimate a propensity model using those selected variables and employ the model in a standard causal inference method that adjusts for the propensity score (the conditional probability of treatment). While this strategy is theoretically sound, in practice researchers may miss important confounders in the selection process, which leads to confounding bias, or may include variables that induce other types of bias (e.g., a “collider” or a variable that induces "M-bias").

In this paper, we study a closely related, but different, technique, known as large-scale propensity score (LSPS) adjustment². LSPS fits an L1-regularized logistic regression with all pre-treatment covariates to estimate the propensity model. LSPS then uses standard causal inference methods, with the corresponding propensity scores, to estimate the causal effect. For example, LSPS might be used with matching³–⁵ or stratification⁶.

In contrast to the traditional approach of explicitly selecting confounders, LSPS is a "kitchen-sink" approach that includes all of the covariates. While the L1-regularization might lead to a sparse propensity model, it is not designed to select the confounders in particular. Instead, it attempts to create the most accurate propensity model based on the available data, and LSPS diagnostics (described below) use covariate balance between treatment cohorts (i.e., that covariates are distributed similarly in the two cohorts) to assess whether all covariates are in fact adjusted-for in the analysis regardless of their L1-regularization coefficient.

The discussion over how many covariates to include in a propensity model is an old one⁷–¹³ and considers—in the setting of imperfect information about variables—the tradeoff between including all measured confounders versus including variables that may increase bias and variance¹⁴,¹⁵. To address this issue, LSPS uses only pre-treatment covariates to avoid bias from mediators and simple colliders, and it uses diagnostics and domain knowledge to avoid variables highly correlated with the treatment but uncorrelated with outcomes (known as “instruments”). Including such variables can increase the variance of the estimate¹⁴–¹⁷ and can amplify bias¹⁸–²³.

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In medicine, empirical studies of the performance of LSPS have shown it to be superior to selecting confounders\textsuperscript{2,24–26}. Consequently, LSPS has been used in a number of studies, both clinical\textsuperscript{27–37} and methodological\textsuperscript{38–43}.

Further, researchers have studied whether LSPS may also address unmeasured confounders\textsuperscript{34,40,44}. The hope behind these studies is that when we adjust for many covariates, we are likely to be implicitly adjusting for the unobserved confounders that are correlated with them. Hripcsak et al.\textsuperscript{34} and Schuemie et al.\textsuperscript{40} used LSPS to estimate the causal effect of anti-hypertension drugs, adjusting for about 60,000 covariates. An important confounder, baseline blood pressure, was not contained in most of the data sources. In the one source that did contain blood pressure, adjusting for all the other covariates but no blood pressure resulted in (nearly) balancing blood pressure between propensity-score-stratified cohorts; the resulting causal inference was identical to the one obtained when including blood pressure in the propensity model.

Based on this observation, Chen et al.\textsuperscript{44} studied the effect of dropping large classes of variables from the LSPS analysis, using balance of the covariates between the treatment and control groups as a metric for successful adjustment (i.e., is every covariate in the propensity model balanced between the cohorts). If all the variables of one type were eliminated from the propensity model (e.g., medical diagnoses), then the inclusion of a large number of other variables (e.g., medications, procedures) resulted in the complete balancing of the missing variables. Even more striking, if all variables related to one medical area like cardiology were dropped from the model (e.g., all cardiology-related diagnoses, procedures, medications, etc.), then the rest of the covariates still balanced the dropped cardiology covariates. Yet if too few covariates were included, such as just demographics, then balance was not achieved on the other covariates. Based on these studies, LSPS appears to be adjusting for some unobserved variables, including some that are confounders.

In this paper, we explore conditions under which LSPS can adjust for unobserved confounding. In particular, we provide some theoretical assumptions under which LSPS is robust to some unobserved confounders. They are based on the “pinpointability” assumption used in Wang and Blei\textsuperscript{35,46}. A variable is pinpointed by others if it can be expressed as a deterministic function of them, though the function does not need to be known. In the context of causal inference from EHR data, we show that if unobserved confounders can be pinpointed by the observed confounders then LSPS implicitly adjusts for them. In a sense, the confounders are not “unobserved” because we do observe variables that could determine them. For example, if high blood pressure could be conceivably derived from the many other covariates (e.g., diagnoses, medicines, other measurements) then LSPS implicitly adjusts for high blood pressure even though it is not explicitly observed.

Of course, pinpointability is an idealized assumption and it will not hold precisely in practice. That said, there might be hope that some of the unobserved confounding is capturable by the covariates. We do not assert LSPS as a magical solution to unobserved confounding—the assumption is strong—but as an attempt to better understand the empirical observation that important unobserved or unused covariates often appear to undergo adjustment when LSPS is used. To explore this phenomenon, we use synthetic data to empirically study the sensitivity of LSPS to the degree to which pinpointability is violated. We find that under perfect pinpointability, adjusting for observed covariates removes the bias due to unobserved confounding. As the data deviates from pinpointability, adjusting for the observed covariates becomes less adequate.

Finally, we study real-world medical data to compare LSPS to other approaches to adjusting for medical confounding. We find that the unobserved confounder has a bigger impact on a traditional propensity score method than on LSPS. This finding suggests that including large-scale covariates with LSPS provides a better chance of correcting for confounders that are not observed.

The paper is organized as follows. Section 2 describes the LSPS algorithm, the pinpointability assumption, and the effect of pinpointability on M-structure colliders, instruments, and near-instruments. Section 3 compares LSPS to other unobserved confounder adjustment approaches and makes connection to other related work. Section 4 studies the impact of violations of pinpointability on the fidelity of the estimated causal effects. Section 5 presents empirical studies comparing LSPS to classical propensity-score adjustment (with manually selected covariates), and methods that do not adjust. Section 6 concludes the paper with a discussion.

The Large Scale Propensity Score Algorithm

In this section, we summarize the LSPS algorithm, describe an assumption under which LSPS will adjust for unmeasured confounding and potentially mitigate the effect of adjusting for unwanted variables, and make some remarks on the assumption.

The LSPS algorithm

We summarize the LSPS algorithm\textsuperscript{2}, including the heuristics and diagnostics that normally surround it (e.g., Weinstein\textsuperscript{25}). Consider a study where a very large number of covariates are available (e.g., over 10,000) and the problem of estimating the causal effect of a treatment. Rather than selecting confounding covariates and adjusting for them, LSPS adjusts for all of the available covariates. It uses only pre-treatment covariates to avoid adjusting for mediators and simple colliders (which induce bias), and it uses diagnostics and domain knowledge to avoid “instruments,” variables that are correlated with the treatment but do not affect the outcome. (Such variables increase the variance of the causal estimate.)

By design, LSPS includes all measured confounders. The hope is that in real-world data, such as in medicine, adjusting for all the other non-confounder variables would not impart bias, and empirical comparisons to traditional propensity approaches seem to bear that out\textsuperscript{2,24–26}. The further hope is that by balancing on a large number of covariates, other unmeasured factors would also become balanced, and this is what we address in Section .

The inputs to LSPS are observed pre-treatment covariates $X$ and binary treatment $T$. The output is the estimated causal effect $\hat{\tau}$. LSPS works in the following steps.
1. **Remove "instruments."** Remove covariates that are highly correlated with the treatment and are unlikely to be causally related to the outcome. Correlation to treatment is checked numerically, and domain expertise is used to determine if the highly correlated variables are not causally related to the outcome; if the relationship is unclear, then the variable is not removed. Note these covariates are commonly called "instruments," and used in instrumental variable analysis. LSPS, however, does not do instrumental variable analysis, and removes these variables to reduce downstream variance.

2. **Fit the propensity model and calculate propensity scores.** Given the remaining covariates, fit an L1-regularized logistic regression\(^{48}\) to estimate propensity scores \(p(t \mid x)\). The regression is

\[
p(t \mid x) = \frac{1}{1 + e^{-\theta \cdot x}},
\]

where \(\theta\) is the vector of the regression parameters.

Denote the propensity score of the \(i\)th individual as \(h_\theta(x_i) := p(t_i \mid x_i)\). L1-regularized logistic regression minimizes

\[
\mathcal{L}(\theta) = \sum_{i=1}^{N} -t_i \log(h_\theta(x_i)) - (1 - t_i) \log(1 - h_\theta(x_i)) + \lambda \sum_{j=1}^{M} |\theta_j|,
\]

where \(\lambda\) is the tuning parameter that controls the strength of the L1 penalty.

LSPS uses cross-validation to select the best regularization parameter \(\lambda\). It then refits the regression model on the entire dataset with the selected regularization parameter. Finally, it uses the resulting model to extract the propensity scores for each datapoint.

3. **Check the equipoise of the propensity model.** In this step, LSPS assesses whether the conditional distribution of assignment given by the propensity model is too certain, i.e., whether the treatment and control groups are too easily distinguishable. The reason is that a propensity model that gives assignments probabilities close to zero or one leads to high-variance estimates\(^{15}\), e.g., because it is difficult to match datapoints or create good strata.

To assess this property of the propensity model, LSPS performs the diagnostic test of Walker et al.\(^{49}\). This diagnostic assesses the overlapping support of the distribution of the preference score, which a transformation of the propensity score\(^{\ast}\), on the treatment and control groups. If there is overlapping support then the study is said to be in equipoise. If a study fails the diagnostic, then the analyst considers if an instrument has been missed and removes it, or interprets the results with caution.

4. **Stratify the dataset and check that the stratification achieves covariate balance.** Use the propensity model to stratify the dataset\(^{3}\). First, determine the number of strata \(K\) and the boundaries of the strata such that each stratum contains an equal number of treated datapoints. Each datapoint is then assigned to a stratum based on its propensity score.

Once the strata are defined, LSPS checks that the stratification achieves covariate balance. Balance is achieved if when we reweight the data according to the strata, each covariate in the treatment and control group follows the same distribution.

To check covariate balance, we first compute the weight for each datapoint \(w_i\) to be equal to the reciprocal of the number of datapoints from its treatment group within its stratum. Mathematically, that is,

\[
w_i = 1/n_s^t \quad \text{for } s = s_i \text{ and } t = t_i,
\]

where \(n_s^t\) is the number of datapoints that received treatment \(t\) in stratum \(s\). Then, the weighted mean of the covariate for treatment group \(t\) is

\[
\bar{x}_t = \frac{\sum_{i:t_i=t} w_i x_i}{\sum_{i:t_i=t} w_i}, \quad t \in \{0, 1\}.
\]

The weighted covariate variance is defined as

\[
\sigma^2_t = \frac{\sum_{i:t_i=t} w_i^2}{(\sum_{i:t_i=t} w_i)^2} \sum_{i:t_i=t} w_i (x_i - \bar{x}_t)^2.
\]

Lastly, the standardized mean difference (SMD) between the treated and the control groups is calculated as

\[
\text{SMD} = \frac{\bar{x}_{t=1} - \bar{x}_{t=0}}{\sqrt{(\sigma^2_{t=1} + \sigma^2_{t=0})/2}}.
\]

Following Austin\(^{50}\), if any covariate has a SMD over 0.1\(^{50}\), then the comparison is said to be out of balance, and the study needs to be discarded (or interpreted with caution).

Alternatively, matching on propensity scores\(^{3-5}\) can also be used to create balanced groups.

5. **Estimate the causal effect.** The last step is to use the stratified data to estimate the causal effect. In the simulations Section, the causal effect of interest is the average treatment effect

\[
\text{ATE} = E[Y^1(1) - Y^0(0)],
\]

where \(Y^t(1)\) and \(Y^t(0)\) are the potential outcomes for a subject under treatment and under control.

To estimate the ATE, we first fit a linear regression within each stratum,

\[
E[Y^t | s] = \alpha_s + \nu_s T_t,
\]

where \(\nu_s\) and \(\alpha_s\) are the stratum-specific treatment effect and intercept. Then pool the stratum-specific treatment effects to obtain the average treatment effect,

\[
E[Y^t(1) - Y^t(0)] = E[E[Y^t(1) - Y^t(0) \mid s]] = \sum_s \nu_s \omega_s,
\]

where \(\omega_s\) is the weight for stratum \(s\) and proportional to the size of stratum.

In the empirical studies of Section, we will use a Cox proportional hazards model\(^{51}\) to estimate a (causal) hazard

\[
\ln[f(x)/(1 - f(x))] = \ln[p(t \mid x)]/(1 - p(t \mid x)) - \ln[p(t = 1)/(1 - p(t = 1))].
\]

\(^{\ast}\) Define the preference score \(f(x)\) as a transformation of the propensity score \(p(t \mid x)\) that adjusts for the probability of treatment \(p(t = 1)\),
ratio (the outcome \( Y \) is time to event). The Cox model is expressed by the hazard function denoted by \( h(t) \). Within a stratum \( s \), the stratum-specific hazard function \( h^s(t) \) is estimated as,

\[
h^s(t) = h_0^s(t) \exp(\zeta^s t),
\]

where \( \tau \) is the survival time, \( h_0^s(\tau) \) is the baseline hazard at time \( \tau \), \( t \) is the treatment, and \( \exp(\zeta^s) \) is the stratum-specific hazard ratio of the treatment. This expression gives the hazard function at time \( \tau \) for subjects with treatment \( t \) in stratum \( s \).

The parameters in the Cox model are estimated by optimizing the likelihood

\[
L(\zeta^s) = \prod_{i:C_i=1 \cap s_i=s} \frac{\exp(\zeta^s t_i)}{\sum_j Y_i \geq y_i \exp(\zeta^s t_j)},
\]

where \( C_i = 1 \) indicates the occurrence of the outcome.

The hazard ratio can be obtained by reweighting \( \exp(\zeta^s) \) by the size of the stratum. However, in practice, due to within-strata zero counts and finite machine precision, the hazard ratio is estimated by optimizing the Cox partial conditional across strata as in the Cyclops R package.

**Adjusting for unobserved confounders**

As noted in the introduction, LSPS has been found to adjust for known but unmeasured confounders\(^{34,40} \) and a large number of unused covariates\(^{41} \). We describe here an assumption under which LSPS will adjust for unmeasured confounding.

Consider the causal graph in Fig.1 for an individual \( i \) (the subscript is omitted in the graph), where \( T_i \in \{0, 1\} \) is a binary treatment, \( Y_i \) is the outcome (either binary or continuous), \( X_i \in \{0, 1\}^M \) is a high-dimensional vector of observed pre-treatment covariates with length \( M \) (which includes observed confounders and other variables), and \( U \in \mathbb{R} \) is the unobserved confounder. The goal is to estimate the causal effect of treatment \( T \) on the outcome \( Y \). To do so, we need to adjust for both pre-treatment covariates \( X \) (observed) and \( U \) (unobserved), because the treated subjects often differ systematically from untreated subjects in observational studies. In studies where unobserved confounders are assumed not to be present, under the ignorability assumption, propensity score adjustment\(^{1} \) can be applied directly to obtain unbiased causal effects. But, what if there are unobserved confounders? We found that empirically, LSPS can adjust for unobserved confounders by adjusting for large-scale observed covariates.

In the following sections, we will demonstrate that LSPS can still produce unbiased causal estimates even in the presence of unobserved confounders. We first introduce Assumption 1, which indicates the relationship between observed covariates and unobserved confounders.

**ASSUMPTION 1 (Pinpointability of unobserved confounder) Unobserved confounders \( U \) are said to be pinpointable by observed covariates if**

\[
p(u \mid x) = \delta(f(x)) \tag{1}
\]

where \( \delta(\cdot) \) denotes a point mass at \( f(\cdot) \).

In other words, the unobserved confounder \( U \) can be represented by a deterministic function \( f \) of the observed covariates \( X \). Theorem 1, building upon Assumption 1, formally states the conditions that LSPS needs in order to obtain unbiased causal estimates by only conditioning on observed covariates. We use the potential outcome framework by Rubin\(^{53} \). Let \( Y_i(1) \) and \( Y_i(0) \) denote the potential outcome under treatment and under control respectively for an individual \( i \).

**THEOREM 1** The treatment and the potential outcomes are independent conditioning on all confounders, both the observed \((X)\) and unobserved \((U)\),

\[
T_i \perp Y_i(1), Y_i(0) \mid X, U. \tag{2}
\]

Under the pinpointability assumption, the above conditional independence can be reduced to only conditioning on the observed covariates,

\[
T_i \perp Y_i(1), Y_i(0) \mid X. \tag{3}
\]

In other words, the causal effect of the treatment on the outcome is identifiable by only adjusting for the observed covariates \( X \). We do not need to know the unobserved confounders \( U \) or their functional form \( f(\cdot) \).

**PROOF.** Theorem 1 relies on the marginalization over \( U \) in computing the propensity score using high-dimensional observed covariates,

\[
p(t \mid x) = \int p(t \mid u, x)p(u \mid x)du \tag{4}
\]

\[
= p(t \mid u^*, x), \tag{5}
\]

where \( u^* = f(x) \).

**Effect of pinpointing on instruments and M-bias**

Because LSPS uses a large number of covariates, there is a concern that adjusting for these covariates will induce bias due to M-structure colliders, instrumental variables (IVs), and near instrumental variables (near-IVs). As noted above, our goal is not to do instrumental variable analysis but rather to remove their potential effect of increasing variance and amplifying bias. IVs are addressed in part by domain knowledge and diagnostics, but some IVs may remain. In this section, we discuss how LSPS in the setting of pinpointing may address them.
Effect on IV and near-IV Instrumental variables may persist despite LSPS’s procedures. In the setting of unmeasured confounding, IV can cause bias amplification as shown numerically and proved theoretically in various scenarios. Insofar as pinpointing adjusts for unobserved confounding (Fig. 2a), even if there are IVs in the propensity score model, they will not produce bias amplification.

Near-instrumental variables (near-IVs) are weakly related to the outcome and strongly related to the treatment, may also lead to bias amplification, and the bias amplification or the confounding may dominate. Just as for IVs, pinpointing (Fig. 2b) may reduce bias amplification by reducing unmeasured confounding, while the confounding is eliminated by adjusting for the near-IV.

Addressing M-bias Despite the use of pre-treatment variables, bias through colliders is still possible due to causal structures like the one in Fig. 2c, known as an M-structure, causing M-bias. In this case, two unobserved underlying causes create a path from T to Y via a collider that can precede T in time. If the collider is included in the many covariates, then this can induce bias. LSPS may be able to address M-bias in the following way. If the common cause between the treatment and the collider (Z₁) can be pinpointed by the observed confounders, then this will block the back-door path from T to Y. Similarly, the common cause between the outcome and the collider (Z₂) could be pinpointed, also blocking the path. The assertion that one or both of these common causes is pinpointed is similar to the assertion that U is pinpointed.

Some remarks on pinpointing

We clarify here what needs to be pinpointed. U refers to the true confounder that underlies potentially measured (but currently missing) covariates. In the example from the Introduction, baseline measured blood pressure is referred to as a “confounder,” but in fact it is a proxy to some true confounder. There is some physiological state, perhaps mean blood pressure or perhaps severity of illness that underlies blood pressure, that serves as the true confounder. Baseline measured blood pressure is a measured variable that depends on the true confounder. It does not generally affect outcomes like stroke directly, although it is on the causal pathway from the true confounder to the doctor’s decision of which medication to use. LSPS need not pinpoint measured blood pressure accurately, but instead must pinpoint the latent underlying true confounder. Assuming that medicine is relatively low rank, the prospect of pinpointing a smaller number of such states appears more feasible than hoping to pinpoint a vast array of potentially measured variables.

Pinpointing is a strong assumption. In practice, we are likely to capture varying degrees of the confounding information in the observed confounders. Therefore in the simulations of Section , we assess sensitivity to the strength of the pinpointing.

Related methods

We describe here the methods that are related to LSPS. These methods are related to LSPS in different ways. Section compares and contrasts LSPS to other methods that also address unmeasured confounding in causal effect estimation. Section compares LSPS to another propensity score-based method that also uses large-scale covariates. Section draws similarity between LSPS and another method for causal effect estimation in the presence of unobserved confounding where pinpointability is a required assumption.

Relation to proxy variable, multiple imputation and residual bias detection

Studies such as those by Kuroki and Pearl, Miao et al., and Tchetgen Tchetgen et al. have shown that causal effects can be identified by observing proxy variables of unmeasured confounders. In this case, the confounder is known but not measured, there is sufficient knowledge of the
structural causal model such that proxies can be selected, and there is the knowledge that there are no other unmeasured confounders.

Another approach is to use measured covariates to explicitly model unmeasured confounders using multiple imputation. While it differs from our approach, it exploits the same phenomenon, that some covariates contain information about unmeasured confounders. This is in contrast to LSPS, where there is no explicit model of unmeasured confounders; adjusting for measured covariates is should be effective for causal inference as long as the observed covariates pinpoint the unobserved confounders.

Given the need to assume no additional unmeasured confounding—additional in the sense of not being pinpointed or not having proxies—a complementary approach is to estimate the degree of residual bias, potentially including additional unmeasured confounding. Large-scale use of negative and synthetic positive controls can additionally be used to calibrate estimates to assure appropriate coverage of confidence intervals. LSPS is usually coupled with such empirical calibration.

Relation to high-dimensional propensity score adjustment

LSPS adjusts for all available pre-treatment covariates. In practice, because the sample size is limited, regularized regression selects a subset of variables to represent the information contained in the whole set of covariates, but the goal is to represent all the information nonetheless. Therefore, LSPS diagnostics test balance not just on the variables that regularized regression included in the model, but on all the covariates. All covariates are retained because even those that are not direct confounders may still contribute to the pinpointing of the unobserved confounders. Therefore, LSPS is not a variable selection technique.

LSPS is distinct from techniques that attempt to select confounders empirically. Some of these techniques also start with large numbers of covariates, but they attempt to find the subset that are confounders using information about the treatment and outcome. They then adjust for the selected covariates. As long as all confounders are observed and then selected, adjusting for them should eliminate confounding. It may not, however, benefit from the pinpointing that we identify in this paper. Empirical studies show that adjusting for a small number of confounders does not successfully adjust for unobserved confounders, and an empirical comparison of the methods favored LSPS.

Relation to the deconfounder

LSPS and the deconfounder are distinct but share several features. The deconfounder is a causal inference algorithm that estimates unbiased effects of multiple causes in the presence of unobserved confounding. Under the pinpointability assumption (unobserved confounders are pinpointable by multiple causes), the deconfounder can infer unobserved confounders by fitting a probabilistic low-rank model to capture the dependencies among multiple causes. Both methods thus rely on pinpointing to address unobserved confounders.

Simulations

We conduct two simulations to show that, under the assumption of pinpointability, LSPS can adjust for some of the unobserved confounding. In both simulations, we assume that the large number of covariates is derived from a smaller number of underlying latent variables. This low-rank structure induces dependencies among the observed covariates, mimicking the dependencies observed in EHR, in which the observed covariates are driven by a smaller number of physiological and procedural processes.

The two simulations differ in the creation of the unmeasured confounder. The first simulation illustrates direct pinpointability, where the unobserved confounder is pinpointed by observed covariates because it is simulated as a function of the latent variable and unobserved covariates. This low-rank structure induces dependencies among the observed covariates, mimicking the dependencies observed in EHR, in which the observed covariates are driven by a smaller number of physiological and procedural processes.

Simulation 1: direct pinpointability

Each simulated data set contains $N = 5,000$ patients, $M = 10,000$ observed covariates, 1 unobserved confounder, $K = 10$ latent variables, a treatment and an outcome. The data set is $D = \{v_i, x_i, u_i, t_i, y_i\}_{i=1}^N$, where $v_i$ is a vector of latent variables, $v_i = (v_{i1}, \ldots, v_{iK})$; $x_i$ is a vector of observed covariates, $x_i = (x_{i1}, \ldots, x_{iM})$; $u_i$, $t_i$ and $y_i$ are all scalar, representing the unobserved confounder, treatment and outcome respectively.

Below are the steps to simulate data for patient $i$.

1. Simulate the latent variable $v_i$ as $v_i \sim \text{Bernoulli}(p_i)$.
where \( p_i \sim \text{Beta}(2, 5)^K \).

2. Simulate observed covariates \( x_i \) as

\[
x_i \sim \text{Bernoulli}(\text{sigmoid}(\mathbf{v}_i^T \mathbf{\beta}_x)),
\]

where \( \mathbf{\beta}_x \sim \mathcal{N}(0, 10)^K \times M \).

3. Simulate the unobserved confounder \( u_i \) as

\[
u_i = x_i^T \mathbf{\beta}_u,
\]

where \( \mathbf{\beta}_u \sim \mathcal{N}(0, 1)^M \). Notice that \( u \) is a deterministic function of \( x \). To allow only a small subset of the covariates pinpoint, we randomly select 99% of the \( \mathbf{\beta}_u \) and set their value to 0.

4. Simulate the treatment \( t_i \) as

\[
t_i \sim \text{Bernoulli}(\text{sigmoid}(x_i^T \gamma_x + u_i \gamma_u)),
\]

where the effect of the unobserved confounder on the treatment \( \gamma_u = 1 \) and \( \gamma_x \sim \mathcal{N}(0, 1) \). To allow a small subset of the covariates serve as observed confounders, we randomly select 99% of the \( \gamma_x \) and set their value to 0.

5. Simulate the outcome \( y_i \) as

\[
y_i \sim \mathcal{N}(x_i^T \eta_x + u_i \eta_u + t_i \nu, 0.1),
\]

where the true causal effect \( \nu = 2 \), the effect of the unobserved confounder on the outcome \( \eta_u = 1 \), \( \eta_x \sim \mathcal{N}(0, 1) \) for the covariates serve as observed confounders and 0 otherwise.

The above steps illustrate the simulation under pinpointability. To increase the degree of violation of pinpointability, we add an increasing amount of random noise to the unobserved confounder. To do so, we modify the simulation of \( u_i \) in Step 3 to be

\[
u_i = u_i^\det + u_i^\dim
\]

\[
u_i^\det = x_i^T \mathbf{\beta}_u
\]

\[
u_i^\dim \sim \mathcal{N}(0, \sigma^2)
\]

where \( u_i^\det \) is the deterministic component of \( u_i \), and \( u_i^\dim \) is the random component of \( u_i \). To increase the degree of violation of pinpointability, we increase \( \sigma^2 \), the variance of \( U^\dim \). Specifically, we set the variance of the random component to be proportional to the variance of the deterministic component, that is, \( \sigma^2 = c \text{Var}[U^\det] \), where \( \text{Var}[U^\det] = \frac{\sum_i (u_i^\det - \bar{u}^\det)^2}{N-1} \), \( \bar{u}^\det \) is the sample mean, and \( c \) is the sensitivity parameter. When \( c = 0 \), the pinpointability assumption is satisfied (\( U \) is pinpointed by \( X \)). When \( c > 0 \), the larger the value of \( c \), the more variance in \( U \) is attributable to the random component. The degree of pinpointability can be expressed as below:

\[
\text{degree of pinpointability (\%)} = 1/(c + 1) \times 100\
\]

The range of degree of pinpointability we test is

\[
\text{degree of pinpointability (\%)} \in \{0, 20, 40, 60, 80, 99\}
\]

by setting \( c \) to its corresponding value.

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### Simulation 2: pinpointability through a factor model

Each simulated data set contains \( N \) patients, \( M \) observed covariates, \( K \) latent variables, a treatment and an outcome. The data set is \( D = \{ \mathbf{v}_i, x_i, u_i, t_i, y_i \}_{i=1}^N \), where \( \mathbf{v}_i \) is a vector of latent variables, \( \mathbf{v}_i = (v_{i1}, \ldots, v_{iK}) \); \( x_i \) is a vector of observed covariates, \( x_i = (x_{i1}, \ldots, x_{iM}) \); \( u_i, t_i \) and \( y_i \) are all scalar, representing the unobserved confounder, treatment and outcome respectively.

Below are the steps to simulate data for patient \( i \).

1. Simulate the latent variable \( \mathbf{v}_i \) as

\[
\mathbf{v}_i \sim \text{Bernoulli}(0.5)^K.
\]

2. Simulate the unobserved confounder \( u_i \) as

\[
u_i = \mathbf{v}_i^T \mathbf{\beta}_u,
\]

where \( \mathbf{\beta}_u \sim \mathcal{N}(0, 1)^K \). Notice that \( u \) is a deterministic function of \( \mathbf{v} \).

3. Simulate observed covariates \( x_i \) as

\[
x_i \sim \text{Bernoulli}(\mathbf{v}_i^T \mathbf{\beta}_x),
\]

where \( \mathbf{\beta}_x \sim \mathcal{N}(0, 1)^K \times M \).

4. Simulate the treatment \( t_i \) as

\[
t_i \sim \text{Bernoulli}(\text{sigmoid}(x_i^T \gamma_x + u_i \gamma_u)),
\]

where \( \gamma_u = 1 \) and \( \gamma_x \sim \mathcal{N}(0, 1) \) for the covariates serve as observed confounders and 0 otherwise.

5. Simulate the outcome \( y_i \) as

\[
y_i = x_i^T \eta_x + u_i \eta_u + t_i \nu,
\]

where the true causal effect \( \nu = 2 \), \( \eta_u = 1 \) and \( \eta_x \sim \mathcal{N}(0, 1) \) for the covariates serve as observed confounders and 0 otherwise. That is, only the first 10 covariates in \( x_i \) have non-zero coefficients, meaning that only the first 10 covariates in \( x_i \) are causally associated with the treatment assignment.

In contrast to Simulation 1 where the unobserved confounder is generated as a function of the observed covariates, here the unobserved confounder and the observed covariates are both generated from the same latent variables. The function generating \( U \) from \( \mathbf{V} \) is deterministic (step 2), but the function generating \( X \) from \( \mathbf{V} \) is not (step 3). So we need a measure to quantify how pinpointable \( U \) is (see Sec.).

The pinpointability of \( U \) could potentially depend on the number of patients \( N \), the number of observed covariates \( M \), and the number of latent variables \( K \). We simulated data with \( N \in \{1000, 10000\} \), \( M \in \{10, 100, 10, 1000, 1000, 10, 100, 1000, 10, 100\} \), and \( K \in \{1, 10, 10, 100\} \). Notice that even though the number of observed covariates increases, the number of observed confounders is always 10. This allows the confounding due to observed versus unobserved to stay the same. This allows us to rule out the possibility of any changes in effect estimation due to the diminishing of unobserved confounding.
Evaluation metrics

In both simulations, we compared the root-mean-squared error (RMSE) of causal effect estimated by LSPS to that estimated by the oracle (LSPS with access to the unobserved confounder). RMSE is defined as follows.

$$\text{Bias}(\hat{\nu}) = E[\hat{\nu} - \nu]$$
$$\text{Var}[\hat{\nu}] = E[(\hat{\nu} - \nu)^2]$$
$$\text{RMSE}(\hat{\nu}) = \sqrt{\text{Var}[\hat{\nu}] + \text{Bias}(\hat{\nu})^2}$$

To quantify the degree of pinpointability in Simulation 2, we fit a Ridge regression with $U$ as the dependent variable and $X$ as independent variables, $U = f(X)$. We use the R-squared ($R^2$) to determine the pinpointability of $U$.

$$R^2 = 1 - \frac{\text{residual sum of squares}}{\text{total sum of squares}} = 1 - \sum_{i=1}^{N}(u_i - f(x_i))^2 \sum_{i=1}^{N}(u_i - \bar{u})^2$$

where $\bar{u} = \frac{1}{N} \sum_{i=1}^{N} u_i$. R-squared is a statistical measure that represents the proportion of the variance for a dependent variable that is explained by independent variables in a regression model. Because $R^2$ is bounded between 0 and 1, it can be interpreted as a percentage. An R-squared of 100% means that all of the variance of the dependent variable is completely explained by the independent variables in the regression model. Given the dependent variable $U$ and independent variables $X$ in our case, $R^2$ represents the variance of the unobserved confounder $U$ that is explained by the observed covariates $X$. When $R^2 = 1$, the unobserved confounder can be predicted without uncertainty by the observed covariates, which coincide with our definition of pinpointability. As $R^2$ decreases, the degree of pinpointability decreases.

Results

Fig. 4 shows the results of Simulation 1. Under perfect pinpointability (% of unexplainable variation in $U = 0$), the causal effect estimated by LSPS had nearly identical RMSE compared to that of the oracle, suggesting that under perfect pinpointability, LSPS can correct for the unobserved confounders by only including observed covariates. As the unobserved confounders become less pinpointable (% of unexplainable variation increases), the bias and RMSE of the estimated causal effect increase, suggesting that adjusting for observed covariates alone becomes less adequate for adjusting for the bias due to the unobserved confounder.

Fig. 5 shows the results of Simulation 2. The goal of Simulation 2 is to explore the performance of LSPS under different degrees of pinpointability. In contrast to Simulation 1 where the degree of pinpointability is varied by changing the variance of random noise in $U$, the degree of pinpointability in this simulation is varied by changing the number of observed covariates in the data set. First, pinpointability ($R^2$) strengthens as the number of observed covariates increases. Second, stronger pinpointability in general leads to better estimates. For example, at $N = 10,000$, both the RMSE of propensity scores ($\text{RMSE}(\hat{p})$) and the RMSE of causal effects ($\text{RMSE}(\hat{\nu})$) decrease as pinpointability strengthens. However, when the sample size is not large enough, for example, when the sample size $N = 1,000$, pinpointability improves the estimates up until when the number of covariates and sample size is approximately equal. Including much more covariates than the sample size does not further reduce the RMSE of estimates, which could be even higher than when $N$ and $M$ are approximately equal.
Empirical studies

We now use real data to compare LSPS to other approaches to adjusting for confounding. With an EHR database, we compared the effect of two anti-hypertension drugs, hydrochlorothiazide and lisinopril, on two clinical outcomes, acute myocardial infarction (AMI) and chronic kidney disease (CKD). A detailed cohort definition is provided in Supplement S1.

For both outcomes, type 2 diabetes mellitus (T2DM) is a known confounder. Thus, by including or excluding T2DM in an adjustment model while keeping other covariates the same, we can assess a method’s capacity in adjusting for unobserved confounding.

We compared LSPS to propensity score adjustment that included confounding variables that were previously selected by experts for inclusion in related hypertension drug studies. The list of manually selected confounders is provided in Supplement S2.

We studied the following five methods:

- unadjusted: no covariate was adjusted for.
- manual: adjust for a list of manually selected confounders.
- manual without T2DM: adjust for a list of manually selected confounders without T2DM-related confounders.
- LSPS: adjust for all pre-treatment covariates in the database.
- LSPS without T2DM: adjust for all pre-treatment covariates in the database except covariates related to T2DM.

For the four methods that adjust for confounders, we estimated propensity scores with Lasso logistic regression (and selected the regularization with cross-validation). To estimate the treatment effect, we fit a Cox proportional-hazards model to estimate the (causal) hazard ratio (HR). We then calculated the mean and 95% confidence interval of the HR.

Results

Fig. 6 shows the results of empirical studies. These results show that the unobserved (or unused) confounder had a bigger impact on the manual methods than on the LSPS methods. The impact was determined by comparing the absolute difference in effect estimates between the two manual models versus the two LSPS-based models. In the CKD study, the absolute difference between the two manual methods was 0.09 (Manual without T2DM: HR 0.77 [95% CI, 0.71-0.83]; Manual: HR 0.86 [95% CI, 0.79-0.93]), higher than the absolute difference between the two LSPS-based methods, which was 0.05 (LSPS without T2DM: HR 0.84 [95% CI, 0.77-0.92]; LSPS: HR 0.89 [95% CI, 0.82-0.97]). In fact, the estimates for manual with T2DM, LSPS with T2DM, and LSPS without T2DM were all closer to each other than to manual without T2DM. Therefore, whether manual with T2DM or LSPS with T2DM is actually closer to ground truth, LSPS without T2DM is closer to either one than is manual without T2DM.

This finding suggests that by including large-scale covariates, one has a better chance of correcting for confounders that are not explicitly observed. The pinpointability assumption is more likely to hold when there are many observed covariates.

Discussion

We have illustrated conditions under which LSPS adjusts for unobserved confounding and the impact of violations of such conditions on effect estimation. We have found in previous practice, in our current simulations, and in our current real-world study that unmeasured (or unused) confounding can be adjusted for in LSPS, apparently working better than smaller, manually engineered sets of covariates that are also missing the confounder.

The success of LSPS in adjusting for unobserved confounders relies on the unobserved confounder being pinpointable, so one may ask the question: can we assess the soundness of the pinpointability assumption for a given dataset through modeling? If a domain area of interest can be expressed as a low-rank model, and observed covariates and unobserved confounders depend on that model, then the assertion that the observed covariates pinpoint the unobserved confounders becomes more credible because it is then known that there is a function (through the low-rank model) linking them.

In medicine, it is possible that the physiology and the environment relevant to some hypothesis of interest has some finite number of degrees of freedom, say perhaps hundreds. If many more covariates are observed, it may be possible to pinpoint the model and the unobserved confounders associated with it, just as shown in the simulation. Therefore,
confirming that a dataset is in fact representable as a low-rank model adds credibility to the pinpointing assumption.

In summary, LSPS is a confounding adjustment approach that includes large-scale pre-treatment covariates in estimating propensity scores. It has previously been demonstrated that LSPS balances unused covariates and can adjust for an unobserved confounder. This paper contributes to understanding conditions under which LSPS adjusts for unobserved confounders, and how causal effect estimation by LSPS is impacted when such conditions are violated. We demonstrated the performance of LSPS on both simulated and real medical data.

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References

1. Rosenbaum PR and Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika 1983; 70(1): 41–55.
2. Tian Y, Schuemie MJ and Suchard MA. Evaluating large-scale propensity score performance through real-world and synthetic data experiments. International Journal of Epidemiology 2018; 47(6): 2005–2014.
3. Rubin DB. Matching to Remove Bias in Observational Studies. Biometrics Journal of the International Biometric Society 1973; 29(1): 159.
4. Rubin DB. The Use of Matched Sampling and Regression Adjustment to Remove Bias in Observational Studies. Biometrics Journal of the International Biometric Society 1973; 29(1): 185.
5. Stuart EA. Matching Methods for Causal Inference: A Review and a Look Forward. Statistical Science 2010; 25(1): 1–21.
6. Rosenbaum PR and Rubin DB. Reducing Bias in Observational Studies Using Subclassification on the Propensity Score. Journal of the American Statistical Association 1984; 79(387): 516.
7. Rubin DB. The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. Statistics in Medicine 2007; 26(1): 20–36.
8. Shrier I. Re: The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. Statistics in Medicine 2008; 27(14): 2740–2741.
9. Rubin DB. Author’s reply re: The design versus the analysis of observational studies for causal effects: parallels with the design of randomized trials. Statistics in Medicine 2008; 27(14): 2741–2742.
10. Shrier I. Propensity scores. Statistics in Medicine 2009; 28(8): 1317–1318.
11. Sjölander A. Propensity scores and M-structures. Statistics in Medicine 2009; 28(9): 1416–1420.
12. Pearl J. Remarks on the method of propensity score. Statistics in Medicine 2009; 28(9): 1415–1416.
13. Rubin DB. Should observational studies be designed to allow lack of balance in covariate distributions across treatment groups? Statistics in Medicine 2009; 28(9): 1420–1423.
14. Rubin DB. Estimating causal effects from large data sets using propensity scores. Annals of Internal Medicine 1997; 127(8 Pt 2): 757–763.
15. Myers JA, Rassen JA, Gagne JJ et al. Effects of Adjusting for Instrumental Variables on Bias and Precision of Effect Estimates. American Journal of Epidemiology 2011; 174(11): 1213–1222.
16. Brookhart MA, Schneeweiss S, Rothman KJ et al. Variable selection for propensity score models. American Journal of Epidemiology 2006; 163(12): 1149–1156.
17. Austin PC, Grootendorst P and Anderson GM. A comparison of the ability of different propensity score models to balance measured variables between treated and untreated subjects: a Monte Carlo study. Statistics in Medicine 2007; 26(4): 734–753.
18. Pearl J. On a Class of Bias-Amplifying Variables that Endanger Effect Estimates. In Proceedings of the Twenty-Sixth Conference on Uncertainty in Artificial Intelligence. pp. 417–424.
19. Pearl J. Invited Commentary: Understanding Bias Amplification. American Journal of Epidemiology 2011; 174(11): 1223–1227.
20. Pearl J. Linear Models: A Useful “Microscope” for Causal Analysis. Journal of Causal Inference 2013; 1(1): 155–170.
21. Wooldridge JM. Should instrumental variables be used as matching variables? Research in Economics 2016; 70(2): 232–237.
22. Steiner PM and Kim Y. The Mechanics of Omitted Variable Bias: Bias Amplification and Cancellation of Offsetting Biases. Biometrika 2017; 104(2): 291–302.
23. Ding P, Vanderweele TJ and Robins JM. Instrumental variables as bias amplifiers with general outcome and confounding. Biometrika 2017; 104(2): 291–302.
24. Ryan PB, Schuemie MJ, Gruber S et al. Empirical Performance of a New User Cohort Method: Lessons for Developing a Risk Identification and Analysis System. Drug Safety 2013; 36(Suppl 1): 59–72.
25. Weinstein RB, Ryan P, Berlin JA et al. Channeling in the Use of Nonprescription Paracetamol and Ibuprofen in an Electronic Medical Records Database: Evidence and Implications. Drug Safety 2017; 40(12): 1279–1292.
26. Weinstein RB, Ryan PB, Berlin JA et al. Channeling Bias in the Analysis of Risk of Myocardial Infarction, Stroke, Gastrointestinal Bleeding, and Acute Renal Failure with the Use of Paracetamol Compared with Ibuprofen. Drug Safety 2020; 43(9): 927–942.
27. Lane JCE, Weaver J, Kostka K et al. Risk of hydroxychloroquine alone and in combination with azithromycin in the treatment of rheumatoid arthritis: a multinational, retrospective study. The Lancet Rheumatology 2020; 2(11): e698–e711.
28. Duke JD, Ryan PB, Suchard MA et al. Risk of angioedema associated with leviracetam compared with phenytoin: Findings of the observational health data sciences and informatics research network. Epilepsia 2017; 58(8): e101–e106.
29. Morales DR, Conover MM, You SC et al. Renin–angiotensin system blockers and susceptibility to COVID-19: an international, open science, cohort analysis. *The Lancet Digital Health* 2021; 3(2): e98–e114.

30. Burn E, Weaver J, Morales D et al. Opioid use, postoperative complications, and implant survival after unicompartimental versus total knee replacement: a population-based network study. *The Lancet Rheumatology* 2019; 1(4): e229–e236.

31. Wilcox MA, Villasis-Keever A, Sena AG et al. Evaluation of disability in patients exposed to fluoroquinolones. *BMC Pharmacology and Toxicology* 2020; 21(1): 40.

32. Suchard MA, Schuemie MJ, Krumholz HM et al. Comprehensive comparative effectiveness and safety of first-line antihypertensive drug classes: a systematic, multinational, large-scale analysis. *The Lancet* 2019; 394(10121): 1816–1826.

33. You SC, Jung S, Sverdlen JD et al. Comparison of First-Line Dual Combination Treatments in Hypertension: Real-World Evidence from Multinational Heterogeneous Cohorts. *Korean Circulation Journal* 2019; 50(1): 52–68.

34. Hripcsak G, Suchard MA, Shea S et al. Comparison of Cardiovascular and Safety Outcomes of Chlorthalidone vs Hydrochlorothiazide to Treat Hypertension. *JAMA Internal Medicine* 2020; 180(4): 542–551.

35. Kim Y, Tian Y, Yang J et al. Comparative safety and effectiveness of alendronate versus raloxifene in women with osteoporosis. *Scientific Reports* 2020; 10(1): 11115.

36. You SC, Rho Y, Bäckdeli B et al. Association of Ticagrelor vs Clopidogrel With Net Adverse Clinical Events in Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention. *JAMA : the Journal of the American Medical Association* 2020; 324(16): 1640–1650.

37. Vashisth R, Jung K, Schuler A et al. Association of Hemoglobin A1c Levels With Use of Sulfonylureas, Dipeptidyl Peptidase 4 Inhibitors, and Thiazolidinediones in Patients With Type 2 Diabetes Treated With Metformin: Analysis From the Observational Health Data Sciences and Informatics Initiative. *JAMA Network Open* 2018; 1(4): e181755.

38. Schuemie MJ, Weinstein R, Ryan PB et al. Quantifying bias in epidemiologic studies evaluating the association between acetaminophen use and cancer. *Regulatory Toxicology and Pharmacology* 2021; 120: 104866.

39. Schuemie MJ, Cepede MS, Suchard MA et al. How Confident Are We About Observational Findings in Health Care: A Benchmark Study. *Harvard Data Science Review* 2020; 2(1).

40. Schuemie MJ, Ryan PB, Pratt N et al. Large-scale evidence generation and evaluation across a network of databases (LEGEND): assessing validity using hypertension as a case study. *Journal of the American Medical Informatics Association* 2020; 27(8): 1268–1277.

41. Schuemie MJ, Ryan PB, Hripcsak G et al. Improving reproducibility by using high-throughput observational studies with empirical calibration. *Philosophical Transactions Series A, Mathematical, Physical, and Engineering Sciences* 2018; 376(2128): 20170356.

42. Schuemie MJ, Hripcsak G, Ryan PB et al. Empirical confidence interval calibration for population-level effect estimation studies in observational healthcare data. *Proceedings of the National Academy of Sciences* 2018; 115(11): 2571–2577.

43. Schuemie MJ, Ryan PB, Pratt N et al. Principles of Large-scale Evidence Generation and Evaluation across a Network of Databases (LEGEND). *Journal of the American Medical Informatics Association* 2020; 27(8): 1331–1337.

44. Chen R, Schuemie M, Suchard M et al. Evaluation of large-scale propensity score modeling and covariate balance on potential unmeasured confounding in observational research (abstract). In *Proceedings of the AMIA Symposium*.

45. Wang Y and Blei DM. The Blessings of Multiple Causes. *Journal of the American Statistical Association* 2019; 114(528): 1574–1596.

46. Wang Y and Blei DM. Towards Clarifying the Theory of the Deconfounder. *ArXiv* 2020; .

47. Hernán MA and Robins JM. Instruments for Causal Inference. *Epidemiology (Cambridge, Mass)* 2006; 17(4): 360–372.

48. Haste T, Tibshirani R and Friedman J. *The elements of statistical learning: data mining, inference and prediction* 2 ed. Springer, 2009.

49. Walker A, Patrick, Lauer et al. A tool for assessing the feasibility of comparative effectiveness research. *Comparative Effectiveness Research* 2013; Volume 3: 11–20.

50. Austin PC. Using the standardized difference to compare the prevalence of a binary variable between two groups in observational research. *Communications in Statistics - Simulation and Computation* 2009; 38(6): 1228–1234.

51. Cox DR. Regression Models and Life-Tables. *JSTOR* 1972; 2(4): 187–220.

52. Suchard MA, Simpson SE, Zorych I et al. Massive parallelization of serial inference algorithms for complex generalized linear models. *ACM Transactions on Modeling and Computer Simulation* 2013; 23: 10.

53. Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology* 1974; 66(5): 688.

54. Bhattacharya J and Vogt WB. Do Instrumental Variables Belong in Propensity Scores? Working Paper, National Bureau of Economic Research, 2007.

55. Middleton JA, Scott MA, Diakov R et al. Bias Amplification and Bias Unmasking. *Political Analysis* 2016; 24(3): 307–323.

56. Kuroki M and Pearl J. Measurement bias and effect restoration in causal inference. *Biometrika* 2014; 101(2): 423–437.

57. Miao W, Geng Z and Tchetgen Tchetgen EJ. Identifying causal effects with proxy variables of an unmeasured confounder. *Biometrika* 2018; 105(4): 987–993.

58. Tchetgen Tchetgen EJ, Ying A, Cui Y et al. An Introduction to Proximal Causal Learning. *ArXiv* 2020; .

59. Albogami Y and Winterstein AG. Plasmode simulation of multiple imputation performance using internal validation data to adjust for unmeasured confounders. In *Pharmacoepidemiology and Drug Safety*, volume 29. pp. 414–414.

60. Albogami Y, Cusi K, Daniels MJ et al. Glucagon-like peptide 1 receptor agonists and chronic lower respiratory disease exacerbations among patients with type 2 diabetes. *Diabetes Care* 2021; .

61. Schneeweiss S, Rassen JA, Glynn RJ et al. High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. *Epidemiology* 2009; 20(4): 512.

62. Chien SC, Ou SM, Shih CJ et al. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Receptor Blockers in Terms of Major Cardiovascular Disease Outcomes in Elderly Patients. *Medicine* 2015; 94(43): e1751.

63. Hicks BM, Filion KB, Yin H et al. Angiotensin converting enzyme inhibitors and risk of lung cancer: population based
cohort study. *BMJ (Clinical Research Ed)* 2018; 363: k4209.

64. Ku E, McCulloch CE, Vittinghoff E et al. Use of Antihypertensive Agents and Association With Risk of Adverse Outcomes in Chronic Kidney Disease: Focus on Angiotensin-Converting Enzyme Inhibitors and Angiotensin Receptor Blockers. *Journal of the American Heart Association* 2018; 7(19): e009992.

65. Magid DJ, Shetterly SM, Margolis KL et al. Comparative Effectiveness of Angiotensin-Converting Enzyme Inhibitors Versus Beta-Blockers as Second-Line Therapy for Hypertension. *Circulation: Cardiovascular Quality and Outcomes* 2010; 3(5): 453–458.

66. Hasvold LP, Bodegård J, Thuresson M et al. Diabetes and CVD risk during angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker treatment in hypertension: a study of 15 990 patients. *Journal of Human Hypertension* 2014; 28(11): 663–669.