Treatment Effect Bias from Sample Snooping: Blinding Outcomes is Neither Necessary nor Sufficient

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Abstract

Popular guidance on observational data analysis states that outcomes should be blinded when determining matching criteria or propensity scores. Such a blinding is informally said to maintain the “objectivity” of the analysis, and to prevent analysts from fishing for positive results by exploiting chance imbalances. Contrary to this notion, we show that outcome blinding is not a sufficient safeguard against fishing. Blinded and unblinded analysts can produce bias of the same order of magnitude in cases where the outcomes can be approximately predicted from baseline covariates. We illustrate this vulnerability with a combination of analytical results and simulations. Finally, to show that outcome blinding is not necessary to prevent bias, we outline an alternative sample partitioning procedure for estimating the average treatment effect on the controls, or the average treatment effect on the treated. This procedure uses all of the the outcome data from all partitions in the final analysis step, but does not require the analysis to not be fully prespecified.

Keywords: confounder selection; fishing; objective design; propensity score; p-hacking.

1 Introduction

One of the central goals in statistics is to develop rigorous standards of evidence in order to protect the conclusions of a study from being influenced by the incentives or preconceptions of the researchers involved. This goal arguably drives the popularity of prespecified analysis plans (Mathieu et al., 2009; Humphreys et al., 2013; Gelman and Loken, 2013); of p-value tests and objective Bayesian inference, in contrast to subjective priors (see Chapter 13 of Efron and Hastie, 2016); and of reproducible research practices concerning data management (Wickham, 2014; Wilkinson et al., 2016; Weiskopf et al., 2017) and data analysis (Peng and Hicks, 2021).
Within the field of causal inference, outcome blinding forms an additional, popular approach for generating credible evidence (Rubin, 2001, 2007). This approach was partly motivated by the author’s role as a litigation consultant for the tobacco industry (Rubin, 2001, 2002), an industry whose objectivity is frequently called into question.

Under the outcome blinding workflow, researchers are permitted to view covariate data while applying matching criteria, propensity scores or other balancing techniques, but must finalize their analysis plan before observing outcome data. The rationale offered for outcome blinding is that (1) viewing covariates allows researchers to adjust their propensity score model if the covariate distributions are still not well balanced across exposure groups after weighting based on an initial model; (2) observational data analysis should mimic randomized controlled trials, which generally require the final analysis plan to be specified before the outcomes are observed; and (3) masking outcomes prevents researchers from (subconsciously) tinkering until a significant result is produced (Rubin, 2001, 2007; Rubin et al., 2008).

Outcome blinding has been widely endorsed and adopted over the past two decades (Shadish and Steiner, 2010; Yue, 2012; Yue et al., 2014; Kainz et al., 2017; Ding and Lu, 2017; Lu et al., 2019; King and Nielsen, 2019; Chen et al., 2021). In particular, outcome blinding was recently cited as a regulatory necessity by the Real World Evidence Scientific Working Group, under the Biopharmaceutical Section of the American Statistical Association (Ho et al., 2021). This group’s members include leading scientists from across academia, industry and government.

Still, certain questions and debates about outcome blinding remain open. Rubin (2001; 2007; 2008) summarizes the benefits of outcome blinding by saying that it maintains “objectivity,” but this conceptualization of objectivity has not yet been formalized as a property that can be proven or disproven. The notion of mimicking randomized trials presents similar ambiguities, as many randomized trials (e.g., those with rolling enrollment) require committing to an analysis plan before seeing outcomes or covariates. Related questions also arise in discussions of propensity scores and other balancing methods, which are commonly recommended because of their compatibility with outcome blinding. Here, the effectiveness of outcome blinding is implicitly assumed, but not directly investigated (Steiner et al., 2010; Li et al., 2016; Levenson et al., 2021). Moreover, blinding outcomes is not universally encouraged, as an inability to view outcomes can impede confounder selection, limiting the effectiveness of matching or weighting (McCandless et al., 2009; De Luna et al., 2011; Zigler and Dominici, 2014; Shortreed and Ertefaie, 2017; D’Amour and Franks, 2019). To our knowledge, deeper study of these issues is still desired (Varadhan et al., 2012). This work aims to provide such a study.

Namely, we demonstrate that outcome blinding does not preclude analysts from fishing for desired results. Even a blinded analyst can produce intentionally biased estimators as long as some prior knowledge is available that links covariates to outcomes (see discussion in Section 2.1). We begin with a notation framework for comparing the biases of blinded and unblinded analysts. To form an initial, tractable model of analysts’ behavior, we start by assuming that analysts are fully aware of the underlying relationships between covariates and outcomes in the population. We then show that, in many scenarios, the
resulting bias from blinded and unblinded analysts is on the same order of magnitude. In sufficiently large samples, the choices of these two analysts can even converge to each other. Building on this base case, we show that similar results hold for analysts who only have an approximate knowledge of the relationships between covariates and outcomes (Section 3). We supplement these theoretical results with simulations over a wide range of scenarios, which point to the same conclusion (Section 4).

To highlight that outcome blinding is not necessary for preventing bias, we discuss a sample partitioning method for estimating the average treatment effect on the controls (ATC) or the average treatment effect on the treated (ATT). This partitioning procedure avoids bias without “throwing away” any of the outcome data from any of the partitions, and without fully prespecifying all stages of the analysis (Section 5). We close with a discussion (Section 6). All proofs are provided in the supplementary materials.

2 Notation & assumptions

We consider the scenario where analysts must choose one of several treatment effect estimators. We will generally use boldface to denote matrices or vectors, uppercase letters to denote random variables, lowercase letters to denote realized values of random variables, and a subscript $i$ to denote the index of the $i^{th}$ individual in the sample.

Let $n$ denote the sample size, where each individual in the sample is drawn independently from a common distribution. Let $X$ denote a random $(n \times p)$ matrix of covariates, where $X_{i\cdot}$, $X_{\cdot j}$, and $X_{ij}$ respectively denote the $i^{th}$ row, the $j^{th}$ column, and the $i^{th}$ element of the $j^{th}$ column. Let $\tilde{Y}_{treat}$ and $\tilde{Y}_{control}$ be $n$-length, latent, random vectors representing potential outcomes on treatment and control respectively. Here, higher values of $\tilde{Y}_{treat}$ and $\tilde{Y}_{control}$ denote better outcomes. Let $\Delta = E(\tilde{Y}_{treat} - \tilde{Y}_{control})$ be the causal effect being estimated; let $A \in \{0, 1\}^n$ be a vector of treatment indicators; let $Y = (Y_1, \ldots, Y_n)$ be the observed outcomes, where $Y_i = A_i \tilde{Y}_{treat} + (1 - A_i) \tilde{Y}_{control}$; and let $Y$ and $X$ denote the domain of $Y_i$ and $X_{i\cdot}$ respectively. We assume throughout that $0 < P(A_i = 1) < 1$.

Let $D$ be a set of estimating functions for $\Delta$. That is, let each $d \in D$ be a mapping from $Y^n \times X^n \times \{0, 1\}^n$ to the real line, such that $d(Y, X, A)$ produces an estimate of $\Delta$. For example, we may set $D = \{d_{OLS,1}, \ldots, d_{OLS,p}\}$, where $d_{OLS,j}(y, x, a)$ returns the ordinary least squares (OLS) coefficient from the linear regression model that adjusts for the $j^{th}$ covariate $x_j$:

$$d_{OLS,j}(y, x, a) = \arg \min_{b_a} \left[ \min_{b_0, b_j} \|y - (b_0 + b_j x_j + b_a a)\|_2^2 \right]. \quad (1)$$

Here, $\{y, x, a\}$ denotes a realization of the random variables $\{Y, X, A\}$. In the results below, we will generally assume that each $d \in D$ is linear in $Y$. 

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2.1 Problem statement: comparing blinded and unblinded malicious analysts

This section introduces a notation framework to study the objectivity arguments in Section 1. Analogous to the problem framing used by King and Nielsen (2019), we say that an analyst is malicious if they adaptively choose an estimator \( d \) in a way that maximizes bias. This means that an unblinded, malicious analyst produces an estimate equal to
\[
\hat{\Delta}_{\text{snoop}} = \max_{d \in D} d(Y, X, A),
\]
after “snooping” by looking at the outcome data. Even if each estimator \( d \in D \) is unbiased for \( \Delta \), the maximum across \( D \) will generally not be unbiased (see similar discussion in King and Nielsen [2019]). The larger the set of candidates \( D \) is, the more opportunities the analyst affords themself to exploit chance imbalances in pursuit of a high estimated effect. Thus, by changing the size of the set \( D \), we can represent analysts with different degrees of maliciousness.

Unfortunately, similar bias can still exist even if the outcomes are blinded, so long as they can be predicted. Suppose that some of the variables in \( X \) are known to be correlated with \( Y \), and let \( \mu(X, A) = E(Y | X, A) \) be the expected outcomes given the covariates and exposures. By replacing \( Y \) with its proxy \( \mu(X, A) \), a blinded malicious analyst can select the estimator \( D^\star \in D \) that is expected to produce the highest bias after the outcomes are revealed. That is, they select the estimator function
\[
D^\star = \arg \max_{d \in D} E_{Y|X,A} \{d(Y, X, A)\}
= \arg \max_{d \in D} d \{\mu(X, A), X, A\}.
\]
The analyst then commits to using \( D^\star \) in their final analysis of the outcomes, ultimately producing the estimate
\[
\hat{\Delta}_{\text{blind}} = D^\star(Y, X, A).
\]
As with unblinded analysts, the extent of a blinded analyst’s maliciousness can be moderated by changing the size of the candidate set \( D \). Above, Line [3] comes the linearity of \( d(y, x, a) \) with respect to \( y \). The uppercase notation \( D^\star \) captures the fact that the estimator selection is random, as it depends on the random variables \( A \) and \( X \). Hereafter, because the terms \( d \{Y, X, A\} \) and \( d \{\mu(X, A), X, A\} \) in Eqs (2) & (3) differ only in their first argument, we will omit the dependence of \( d \) on \( X, A \). Instead, for any random variable \( Z \in Y^n \), we will write \( d(Z) \) to represent \( d(Z, X, A) \), and will write \( D^\star(Z) \) to represent \( D^\star(Z, X, A) \).

The conditional expectation \( \mu(X, A) \) does not always need to be particularly predictive. In some cases, we will see that even weak associations between \( X \) and \( Y \) can have a dramatic effect on blinded bias (Section 3.1).

In many research settings, the function \( \mu \) can be approximately learned from previous studies, or from the related literature. This is true, for example, in Rubin’s study of medical expenses for smokers and similar nonsmokers (Rubin [2001, 2007]). Indeed, many
scientific best practices implore quantitative researchers to consult with domain experts before beginning an analysis (VanderWeele, 2019). If no existing domain expertise is available, initial pilot studies are typically run in order to determine which variables are worth measuring, and to estimate power for larger followup studies. As a result of these pilot studies and consultations, analysts may already know an approximation of $\mu$ before seeing the main dataset.

Even in cases where no prior knowledge or pilot studies are available, an analyst might still learn comparable information about $\mu$ via sample splitting. That is, an analyst may reasonably choose to split the data into two partitions, using one for informal exploration and one for formal analysis. In the first partition, the analyst can attempt to identify important prognostic variables (i.e., $\mu(X, A)$). The second partition can then be used to estimate the effect of treatment. However, even after the initial exploration, the analyst may opt to continue to explore the distribution of covariates in the second data partition before choosing an estimator, under the pretense of ensuring that balance has been achieved. Thus, while balance checks would be considered prudent under the outcome blinding paradigm (see Section 1), they would also allow an ill-intentioned analyst to overfit within the second partition, and to increase bias.

We close this section by noting that, as one reviewer has pointed out, readers should be careful not to overinterpret the term “outcome blinding.” This term is of course based on terminology from randomized controlled trials (RCTs) in which patients and clinicians are blinded to a patient’s treatment. However, while treatment randomization hinders a RCT participant’s ability to guess their treatment at baseline, no comparable randomization can be done to prevent an analyst from approximating participants’ outcomes. For this reason, it could perhaps be appropriate to rename “outcome blinding” as “approximate outcome blinding,” or even “covariate-exposure previewing.” Still, we keep the term “outcome blinding” for consistency with Rubin (2001; 2007; 2008). The terminology of “blinding” also does not imply that no outcomes have ever been observed from prior studies, as evidenced from Rubin’s example of medical expenses (Rubin, 2001, 2007), as well as the examples studied by Rubin et al. (2008).

3 Analytical comparisons of blinded and snooping bias

Next, we present analytical comparisons of the biases produced by blinded and unblinded analysts. Our ultimate goal will be to offer insight into the simulation results in Section 4 below.

Section 3.1 examines large sample settings, where, remarkably, the actions of blinded and unblinded analysts can converge to each other. Section 3.2 examines the finite sample setting, where $E[\hat{\Delta}_{\text{blind}}]$ can be proportional to $E[\hat{\Delta}_{snoop}]$. Section 3.3 relaxes the assumption that analysts know the conditional expectation function $E(Y|X, A)$ exactly, and shows that versions of the previously discussed results still hold under this relaxed setting.
3.1 Preference agreement in large samples

In this section, beyond looking at each analyst’s most preferred estimator, we also consider their preference ordering for all of the available estimators. For any two estimators \( d, d' \in \mathcal{D} \), we say that a snooping analyst prefers \( d \) to \( d' \) if \( d(Y) > d'(Y) \). Likewise, we say that a blind analyst prefers \( d \) to \( d' \) if \( d(\mu(X, A)) > d'(\mu(X, A)) \), or, equivalently, if \( E[d(Y, X, A)|X, A] > E[d'(Y, X, A)|X, A] \). Our first result gives conditions under which the preferences of blinded and snooping analysts converge to each other in large samples.

**Theorem 1.** (Asymptotic preference agreement) Let \( d_j, d_k \in \mathcal{D} \) be two candidate estimators, where \( j, k \in \{1, \ldots, p\} \). Suppose that the following conditions hold.

1. (OLS estimators) The two estimator functions \( d_j, d_k \) are equal to \( d_{OLS,j} \) and \( d_{OLS,k} \) respectively (see Eq (1)).

2. (Informative covariates) \( X_{ij} \) and \( X_{ik} \) satisfy \( |\text{Cor}(X_{ij}, \mu(X, A))|, |\text{Cor}(X_{ik}, \mu(X, A))| \in (0, 1], \text{ and Cor}(\mu(X, A), Y) \in (0, 1]\).

3. (No observed confounders) \( X \perp A \).

Under these conditions,

\[
P(d_j(Y) < d_k(Y) \text{ and } d_j(\mu(X, A)) > d_k(\mu(X, A)) \rightarrow 0 \quad (4)
\]

as \( n \rightarrow \infty \).

It follows from Theorem 1 that, if each estimator in \( \mathcal{D} \) takes the form of Eq (1) and Conditions 2,3 hold for all \( j, k \in \{1, \ldots, p\} \), then all preferences expressed by snooping and blinded analysts will likely be identical in sufficiently large samples. Thus, we would expect the selections of snooping and blinded analysts to converge in large samples. This holds even if these analysts do not always select the max estimator (e.g., Eq (2)), so long as their selection depends only on their preference ranks for estimators in \( \mathcal{D} \).

The intuition behind Theorem 1 is that the preferences of the snooping analyst depend on the chance associations between features and treatment, as well as associations between features and outcomes. Specifically, these preferences depend on \( \frac{1}{n}A^\top X \) and \( \frac{1}{n}Y^\top X \). The first quantity (\( \frac{1}{n}A^\top X \)) is also available to the blinded analyst, and the second quantity (\( \frac{1}{n}Y^\top X \)) converges to the same limit as \( \frac{1}{n}\mu(X, A)^\top X \). Thus, in large samples, blinded analysts see information that is comparable to what snooping analysts see, and so they can approximate the preferences of snooping analysts.

While it is troubling to see how the behavior of our two analysts align, we have not yet incorporated the effect of a potentially increasing number of covariates \( p \). This is a meaningful gap, as the bias of both analysts will tend to decrease in large samples with fixed \( p \), as each estimator \( d \in \mathcal{D} \) becomes less and less variable. Thus, it will be important to be able to describe bias both in finite samples and in samples with arbitrarily large \( p \). These settings are considered in the next subsection.
3.2 Bias comparisons in finite samples

Here, we study the relative bias of \( \hat{\Delta}_{\text{blind}} \) and \( \hat{\Delta}_{\text{snoop}} \) in finite samples. Our main result states that, on expectation, the blinded estimate can be proportional to the snooping estimate. This result holds for any combination of \( n \) and \( p \), and for any set of estimators \( D \) that are linear in \( Y \).

**Theorem 2.** (Finite sample expectation ratio) Let \( \epsilon_{Y,i} = Y_i - \mu(X_{i*}, A_i) \), let \( \epsilon_Y = (\epsilon_{Y,1}, \ldots, \epsilon_{Y,n}) \), and let \( \rho = \sqrt{\frac{\text{Var}(\mu(X_{i*}, A_i))}{\text{Var}(Y_i)}} \) be the proportion of variance in outcomes that is explained by \( X \) and \( A \).

Suppose that

1. (Linearity) Each estimator function \( d_j(Y) \) is linear in \( Y \) (see example in Section 2).
2. (Higher signal-to-noise ratios increase bias) We assume that

\[
E \left[ \max_{d \in D} d \left( \frac{Y}{\text{Var}(Y_i)^{1/2}} \right) \right] \leq E \left[ \max_{d \in D} d \left( \frac{Y - \epsilon_Y}{\text{Var}(Y_i - \epsilon_{Y,i})^{1/2}} \right) \right].
\]

That is, the more that variance in \( Y \) can be explained by \( X \), the higher the unblinded bias will tend to be (see discussion below).

Under these conditions,

\[
E \left[ \hat{\Delta}_{\text{blind}} \right] \geq \rho E \left[ \hat{\Delta}_{\text{snoop}} \right].
\]

Eq (5) states that, on expectation, the blinded estimate is at least proportional to the snooping estimate, with a proportionality constant (\( \rho \)) that depends on how well \( Y \) can be predicted from \( X \). For example, any addition to the candidate set \( D \) will necessarily increase the bias of a snooping analyst, but it will also lead to proportionate increase in the bias of a blinded analyst. In other words, in cases where the bias caused by viewing outcomes is large, Theorem 2 suggests that the bias caused by merely observing \( X \) and \( A \) can be large as well.

Roughly speaking, Condition 2 means that the noisier the relationship is between \( X \) and \( Y \), the harder it is for an unblinded analyst to amplify the treatment effect by exploiting chance imbalances. We expect this condition to hold in many cases, as adjusting for a chance imbalance in any given covariate \( X_{i*} \) is relatively ineffectual when \( X_{i*} \) is not prognostic of \( Y \). For example, consider the estimator \( d_{\text{OLS},j} \) that linearly adjusts for \( X_{i*} \).

The value of \( |d_{\text{OLS},j}(Y, X, A)| \) depends on four factors: the unadjusted average difference in \( Y \) across treatment arms; the imbalance in \( X_{i*} \) across treatment arms; the scale of \( Y \); and the correlation between \( Y_i \) and \( X_{ij} \). For \( |d_{\text{OLS},j}(Y, X, A)| \) to be large, at least one of these four factors must be large. Increasing the signal-to-noise ratio in the manner of Condition 2 (i.e., removing noise) will increase the correlation between \( Y_i \) and \( X_{ij} \), but leave the first three factors unchanged. Thus, if \( D = \{d_{\text{OLS},1}, \ldots, d_{\text{OLS},p}\} \), then we would...
expect higher signal-to-noise ratios to be associated with larger values of $E_{\max_{d \in D}} d(Y)$. Indeed, Condition 2 held over the wide range of simulation settings we explored in Section 4 below.

Alternatively, in the special case where Condition 2 holds with equality, Eq (5) also holds with equality (see Section D.1 of the supplementary materials). This case is especially relevant when $X$ contains a large number of “noisy” covariates that are independent of $\mu(X, A)$. For example, suppose that $D = \{d_{\text{OLS},1}, \ldots, d_{\text{OLS},p}\}$, such that analysts select a single covariate to adjust for. Suppose also that $\mu(\mu_*, A_i)$ and $\epsilon_{Y,i}$ are both normal variables with mean zero. Here, removing signal from $Y$ will only affect the estimators $d_{\text{OLS},j}(Y)$ for which $X_{\cdot,j}$ is predictive of $Y$. If almost none of the covariates are predictive of $Y$, then removing noise from $Y$ in the manner of Condition 2 will have minimal effect on $\max_{d \in D} d(Y)$, since signal variables will rarely be selected anyway. As a result, Condition 2 and Eq (5) will both hold with approximate equality. We will refer back to this special case when discussing simulation results.

3.3 Analysts with imperfect knowledge of $E(Y|X, A)$

In this section we relax assumption that analysts know the conditional expectation function $\mu(X, A) = E(Y|X, A)$ exactly, and instead assume that they know only a rough approximation denoted by $\hat{\mu}$. We will refer to blinded analysts who base their decisions on the imperfect proxy function $\hat{\mu}$ as misinformed. The approximation $\hat{\mu}$ can be determined from an pilot study, from consultations with domain experts, or from a sample splitting procedure (see Section 2.1). We will see below that Theorems 1 & 2 can be extended to describe bias of misinformed analysts, and that degree to which such analysts can produce bias depends on the fidelity of the approximation $\hat{\mu}$.

Before discussing these results, we first introduce more precise notation to describe the behavior of a misinformed analyst. Given a prespecified approximation $\hat{\mu}$, let $D^*_{\hat{\mu}} = \arg\max_{d \in D} d(\hat{\mu}(X, A))$ be the estimator that the misinformed analyst believes will be the largest after $Y$ is revealed, and let $\hat{\Delta}_{\text{blind},\hat{\mu}} = D^*_{\hat{\mu}}(Y)$ be their resulting estimate. Let $\epsilon_d = d(\hat{\mu}(X, A)) - d(\mu(X, A))$ be the error that a misinformed analyst incurs by not knowing $\mu$, for a given estimation function $d$. It is straightforward to show that, if $d(Y)$ is linear in $Y$ for each $d \in D$, then

$$E[\hat{\Delta}_{\text{blind},\hat{\mu}}] \geq E[\hat{\Delta}_{\text{blind}}] - E[\epsilon_{D^*_{\hat{\mu}}} - \epsilon_{D^*}],$$

(6)

where $D^*$ is the function chosen by a blinded analyst with perfect knowledge of $\mu$ (see Eq (3) and Section D.2 of the supplementary materials). That is, the difference between the bias of a misinformed blinded analyst and the bias of a blinded analyst who knows the true function $\mu$ depends on the accuracy of the proxy function $\hat{\mu}$ (via $E[\epsilon_{D^*_{\hat{\mu}}} - \epsilon_{D^*}]$).

Under assumptions similar to those used in Section 3.2, the next corollary simplifies Eq (6) into a more interpretable statement about the extent to which misinformation about $\mu$ reduces an analyst’s ability to bias their results.
Corollary 1. Let $\hat{\mu}(X, A) = \mu(X, A) + W$ be noise-corrupted version of $\mu(X, A)$ that is available to a misinformed, malicious, blinded analyst, where $W = (W_1, \ldots, W_n)$ is a vector of random prediction errors.

Suppose that the following conditions hold.

1. (Linearity) $d(Y)$ is linear in $Y$ for each $d \in D$.
2. (Independent, homogeneous errors) $W \perp Y, X, A$.
3. (Normality) $W$ and $\mu(X, A)$ are both normally distributed with mean zero.
4. (Higher signal-to-noise ratios increase bias) $E[\max_{d \in D} d(U)] \leq E[\max_{d \in D} d(\mu(X, A))]$, where $U$ is an independent copy of $\mu(X, A)$ with the same marginal distribution, but with $U \perp X, A$.

Under the above conditions

$$E \left[ \frac{\hat{\Delta}_{\text{blind}, \hat{\mu}}}{\hat{\Delta}_{\text{blind}}} \right] \geq 1 - 2 \sqrt{\frac{\text{Var}(W_i)}{\text{Var}(\mu(X_i, A_i))}}. \quad (7)$$

Eq (7) states that the extent to which bias is reduced by misinformation (the left-hand side) is limited by the magnitude of misinformation (as represented by $\text{Var}(W_i)$). As $\text{Var}(W_i)$ approaches zero, $\hat{\mu}$ becomes more accurate, and the expectation of the estimator from a blinded, misinformed analyst approaches the expectation of the estimator from a blinded analyst with full knowledge of $E(Y|X, A)$. The required Condition 4 is analogous to Condition 2 of Theorem 2 (see discussion in Section 3.2).

Similarly, Theorem 1 can also be extended to the setting where $\mu$ is unknown, but where an increasingly accurate proxy $\hat{\mu}$ is available. Suppose that $\hat{\mu}$ is learned from an independent pilot study of size $n_{\text{train}}$, such that $\hat{\mu}$ becomes more accurate as $n_{\text{train}}$ increases. Equivalently, given a sufficient amount of data, $\hat{\mu}$ can be learned using a sample splitting approach. For any two functions $d, d' \in D$, we will say that the blinded, misinformed analyst prefers $d$ to $d'$ if $d(\hat{\mu}(X, A)) \geq d'(\hat{\mu}(X, A))$. A simple corollary of Theorem 1 is that, if $\hat{\mu}$ approaches $\mu$ in large samples, then the preference convergence shown in Eq (4) still holds.

Corollary 2. (Preference agreement with learned outcome proxies) If the conditions of Theorem 1 hold and $E \left[ \{\hat{\mu}(X_i, A_i) - \mu(X_i, A_i)\}^2 \right] \to 0$ as $n_{\text{train}} \to \infty$, then

$$P(d_j(\hat{\mu}(X, A)) < d_k(\hat{\mu}(X, A)) \text{ and } d_j(Y) > d_k(Y)) \to 0 \quad (8)$$

as $n, n_{\text{train}} \to \infty$.

In words, Eq (8) states that, when given enough data, a blinded analyst who can effectively learn $\mu(X, A)$ will likely make decisions that are similar to those of snooping analysts.
4 Simulated comparisons of blinded and unblinded bias

While the analytical results in Section 3 paint a worrisome picture of blinded bias, several questions warrant deeper exploration. For Theorem 1, we have not yet examined how quickly the blinded analyst’s behavior converges to that of the snooping analyst, especially when the blinded analyst must learn the conditional expectation function $\mu$ (see Corollary 2). For Theorem 2, we have not examined how conservative the lower bound on $E[\hat{\Delta}_{\text{blind}}]$ is (Eq (5)). It will also be beneficial to check how often the signal-to-noise condition in Theorem 2 holds (Condition 2 of Theorem 2).

To inform these questions, we simulate data under a variety of settings. We set $D = \{d_{\text{OLS},1}, \ldots, d_{\text{OLS},p}\}$ (see Eq (1)) and set $Y = X\beta + \epsilon$, but vary the sample size ($n$), the sample dimension ($p$), and the variance in $Y$ explained by $X$ (see Eq (1)). Here, each row $X_i$ follows an independent, standard normal distribution, regardless of the value of $A_i$; $\beta = (\beta_1, \beta_2, \ldots, \beta_p)$ is a $p$-length vector with $\beta_j = 2$ for $j \in [1, 5]$, $\beta_j = -1$ for $j \in [6, 10]$, and $\beta_j = 0$ for $j > 10$; and $\epsilon_i$ is normally distributed with mean zero and variance calibrated to achieve the desired value for $\rho^2$. To avoid degenerate estimates in small samples, we fix $A$ so that the two treatment arms are the same size (i.e., we set $A_i = 1(i < n/2)$). Under this model, we simulate all combinations of $n \in \{30, 100, 250, 500\}$; $p \in \{10, 30, 100, 500\}$; $\rho^2 \in \{0.25, 0.5, 0.75\}$. In each setting, we simulate 2500 draws.

We also consider two levels of knowledge regarding the conditional expectation function $\mu$. In the first setting, we assume $\mu$ is known to the blinded analyst. In the second setting, we assume that the blinded analyst estimates $\mu$ by fitting a lasso regression on an independent dataset of size $n_{\text{train}} = n$ (see Section 3.3), with a penalty parameter determined from cross-validation (Friedman et al., 2010).

Figures 1 & 2 display the results of our simulations. Figure 1 shows the bias for three types of analysts: (1) snooping analysts who observe $Y$, (2) blinded analysts who know the function $\mu(X, A)$ a priori, and (3) blinded analysts who estimate $\mu(X, A)$ using an independent dataset. In the first two settings, bias decreases as $n/p$ increases. This is as expected, since each estimate $d_{\text{OLS},j}(Y)$ approaches zero in large samples. The trend is more complex in the third setting however, where larger values of $n/p$ also facilitate learning the function $\mu$. Across all settings we considered, changes in $n$ generally produced more dramatic effects than changes in $p$.

To explicitly compare blinded and snooping analysts, Figure 2 displays the bias ratio $E[\hat{\Delta}_{\text{blind}} - \Delta] / E[\hat{\Delta}_{\text{snoop}} - \Delta]$. That is, Figure 2 divides the second and third rows of Figure 1 by the first row of Figure 1. Since $\Delta = 0$ in our simulations, the bias ratio depicted in Figure 2 is also equal to the ratio of expectations described in Eq (5). This ratio is substantial in many cases. For example, in settings where $\mu$ must be estimated and $n = n_{\text{train}} \geq 100$, we observe that the bias ratio is similar to or larger than $\rho^2$.

When $\mu$ is known a priori, the bias ratio in Figure 2 is at least $\rho$ (dashed horizontal line), as suggested by Theorem 2. Condition 2 of Theorem 2 is difficult to confirm analytically, but was satisfied empirically in every simulation setting we considered. The lower bound
in Theorem 2 appears to hold with approximate equality only when $n \ll p$, and to be conservative otherwise. This trend is consistent with our result in Section 3.1 stating that blinded and unblinded analysts tend to agree in large samples, as well as with the discussion at the end of Section 3.2.

In addition to the simulations described above, we also implemented estimators based on inverse propensity score weighting (IPW). Like the OLS estimators described in this section, each IPW estimator adjusted for a different covariate. The results were almost identical, and are described in detail in the supplementary materials. Condition 2 of Theorem 2 held in each of these simulation settings as well.

5 Outcome blinding is not necessary: other methods to avoid bias

Thus far, we have shown that outcome blinding is not sufficient for preventing bias. In this section, we discuss simple strategies that can prevent the bias incurred by adaptively selecting an estimator. Of course, one valid, conventional approach is to determine an estimator from a subsample and apply this estimator in a separate subsample to estimate treatment effects. Unfortunately, this requires that we “throw away” half of the outcome data in the final estimation step.

As a related approach, we now introduce a procedure that applies unblinded sample splitting while still allowing all data points to be used in the final treatment effect estimation, so long as the final estimand is either the ATT or the ATC. As an illustration, we focus on estimating the ATT:

$$E(\tilde{Y}_i^{\text{treat}} - \tilde{Y}_i^{\text{control}} | A_i = 1) = E(\tilde{Y}_i^{\text{treat}} | A_i = 1) - E(\tilde{Y}_i^{\text{control}} | A_i = 1).$$

We will see that, while our proposed procedure does not reproduce all properties of traditional sample splitting, it is sufficient to allow data exploration without incurring bias.

In the same way that $\mathcal{D}$ denotes a set of estimators for $\Delta$, let $\mathcal{F}$ denote a set of estimators for $E(\tilde{Y}_i^{\text{control}} | A_i = 1)$. That is, if $f \in \mathcal{F}$ and $\mathcal{I} \subseteq \{1, \ldots, n\}$, then $f (\{Y_i, X_i \cdot, A_i\}_{i \in \mathcal{I}})$ represents an estimate of $E(\tilde{Y}_i^{\text{control}} | A_i = 1)$. This set $\mathcal{F}$ may be arbitrarily large, or even infinite in size. Different estimators in $\mathcal{F}$ may be used to represent screening out different subsets of covariates, different methods for feature generation, or different styles of parametric modeling (see, for example, Lee et al., 2010; Hill, 2011; Wang et al., 2017; Dorie et al., 2019).

Given a set of candidate estimator functions $\mathcal{F}$, we propose the following interactive procedure.

**Algorithm 1. (Sample splitting for the ATT)**

1. (Partition) The researcher partitions the treated data into two parts, $\mathcal{T}_1^{\text{treat}}$ and $\mathcal{T}_2^{\text{treat}}$. 

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Figure 1: Simulated bias from snooping and blinded analysts using \( d_{\text{OLS}} \) – Columns of plots show different values for the variance in outcomes that is explained by covariates, \( \rho^2 = \frac{\text{Var}(\mu(X_{i\cdot}, 0))}{\text{Var}(Y_i - A_i \Delta)} \). The first row of plots shows the bias of snooping analysts. The second row shows the bias of blinded analysts who know the conditional expectation function \( \mu(X, A) \) a priori. The third row shows the bias of blinded analysts who must estimate \( \mu(X, A) \) from an independent training sample (see Section 3.3). The y-axis shows the bias of each analyst, scaled by the standard deviation of \( Y_i \). This scaling is done to account for the fact that \( \text{Var}(\epsilon_i) \) changes in order to achieve each desired value for \( \rho^2 \).
Figure 2: Comparison of bias from simulated snooping and blinded analysts, each using \( d_{\text{OLS}} \) – Columns of plots show different values for the variance in outcomes that is explained by covariates, \( \rho^2 = \frac{\text{Var}(\mu(X_i, 0))}{\text{Var}(Y_i - A_i \Delta)} \). Rows of plots indicate whether or not \( \mu(X, A) \) is known to the blinded analyst, or must be estimated from an independent training sample (see Section 3.3). The y-axis shows the bias ratio between blinded and snooping analysts, \( \frac{E[\hat{\Delta}_{\text{blind}} - \Delta]}{E[\hat{\Delta}_{\text{snoop}} - \Delta]} \). Since \( \Delta = 0 \) in our simulations, this bias ratio is also equal to the ratio of expectations described in Theorem 2. For cases where \( \mu(X, A) \) is known (top row), the dashed, gray line shows the lower bound on the bias ratio suggested by Theorem 2(\( \rho \)).
2. (Explore) The researcher freely explores $\{Y_i, X_i\}_{i \in I_{\text{treat}}}$. Based on insights from this exploration, as well as on prior knowledge, the researcher uses their personal judgment to select a function $f \in \mathcal{F}$ for estimating $E(Y_i^{\text{control}} | A_i = 1)$. Up until this point, the researcher has only had access to data from $I_{\text{treat}}^1$.

3. (Fit) After committing to a particular estimator $f \in \mathcal{F}$, the researcher applies $f$ to the remaining data from $I_{\text{treat}}^2$ and from the control arm, and returns the following estimate of the ATT.

$$\hat{\Delta}_{\text{ATT}, f} = \left( \sum_{i=1}^{n} Y_i A_i \right) - f \left( \{Y_i, X_i, A_i\}_{i \in I_{\text{treat}}^2 \text{ or } A_i = 0} \right).$$ (9)

Before discussing formal properties of this algorithm, we illustrate the steps above using a hypothetical data example.

5.1 Example application

Consider a hypothetical, observational study of vaccine efficacy. For a given individual $i$, let $A_i$ represent their exposure to a vaccine, let $X_i$ denote their age, and let $Y_i$ be an indicator of infection within 1 year. Let $n = 1000$ be the number of study participants.

The following workflow exemplifies how one might implement Algorithm 1 to estimate the average effect of the vaccine on those who received it. First, the researcher defines a set of candidate estimators $\mathcal{F}$. In this case, they choose the set of stratified estimators formed by using no more than 10 age-specific strata (example to follow). Next, the researcher defines data partitions (Step 1). For ease of notation, we will assume that half of the study participants received the vaccine, with $A_i = 0$ for $i \leq 500$ and $A_i = 1$ for $i > 500$. Suppose that the researcher sets $I_{\text{treat}}^2 = \{501, 502, \ldots, 750\}$ and $I_{\text{treat}}^1 = \{751, 752, \ldots, 1000\}$. The researcher then performs an exploratory analysis of data from participants in $I_{\text{treat}}^1$ by plotting infections status against age, producing Figure 3 (Step 2). Upon seeing this plot, the researcher informally concludes that younger children and older adults have higher infection risks, and so they decide to stratify individuals according to three age intervals: $(0, 18], (18, 55]$, and $(55, \infty)$. That is, the researcher commits to use strata boundaries equal to $\{u_1, u_2, u_3, u_4\} = \{0, 18, 55, \infty\}$, and to estimate $E(Y_i^{\text{control}} | A_i = 1)$ using the stratified estimator

$$f_{18,55} \left( \{Y_i, X_i, A_i\}_{i=1}^{750} \right) = \sum_{k=2}^{4} \left\{ \frac{\sum_{i=1}^{750} Y_i (1 - A_i) 1(X_i \in (u_{k-1}, u_k])}{\sum_{i=1}^{750} (1 - A_i) 1(X_i \in (u_{k-1}, u_k])} \times \frac{\sum_{i=1}^{750} A_i 1(X_i \in (u_{k-1}, u_k])}{\sum_{i=1}^{750} A_i} \right\}. \quad (10)$$

Note that, above, $\{1, \ldots, 750\}$, is equivalent to the set $\{i : i \in I_{\text{treat}}^2 \text{ or } A_i = 0\}$ mentioned in Algorithm 1. Each summation term in Eq (10) involves taking the mean control outcome in one of the age strata, and weighting it according to the prevalence of that strata among the treated.
Finally, the researcher returns
\[
\left( \frac{\sum_{i=1}^{1000} Y_i A_i}{\sum_{i=1}^{1000} A_i} \right) - f_{18,55} \left( \{Y_i, X_i, A_i\}_{i=1}^{750} \right)
\]  
(11)
as their estimate of the ATT (Step 3). Importantly, the first term in Eq (11) was unaffected by the qualitative choices made by the researcher in selecting \( f_{18,55} \), and the researcher’s selection was required to be completed before they had access to the data on which \( f_{18,55} \) was applied (\( \{Y_i, X_i, A_i\}_{i=1}^{750} \), in Step 3).

5.2 Properties of Algorithm 1

All outcomes from the dataset are used in the final estimate from Algorithm 1 in Eqs (9) & (11). However, the first term in Eq (9) is not influenced by the exploratory procedures in Step 2. Likewise, the data used to select \( f \) is independent of the data that is plugged into \( f \), in the second term. As we will see below, this means that the exploratory steps do not inject additional bias. Roughly speaking, an analyst who learns about the data generating distribution from exploratory analyses, using Algorithm 1, will be no more biased than an analyst who learns the same information from external sources.

To formalize this statement, we will treat the researcher’s choice of estimator as a random variable, denoted by \( F_{\text{split}} \in \mathcal{F} \) (Step 2). That is, \( F_{\text{split}} \) is a random selection from \( \mathcal{F} \) that can depend only on \( \{Y_i, X_i\}_{i \in \mathcal{I}_{\text{treat}}} \). In our notation, we will also take special care to account for the fact that the partition itself, \( \mathcal{I}_{\text{treat}} \subseteq \{1, \ldots, n\} \), is also a random variable, as it depends on \( A \).
By definition, we know that $F_{\text{split}} \perp \{Y_i, X_i, A_i\}_{i \notin I^{\text{treat}}_1}$. From this conditional independence statement, it follows immediately that

$$E\left(\hat{\Delta}_{\text{ATT}, F_{\text{split}} | I^{\text{treat}}_1}, F_{\text{split}} = f\right) = E\left(\hat{\Delta}_{\text{ATT}, f | I^{\text{treat}}_1}\right)$$

(12)

for any $f \in F$. Roughly speaking, this means if a researcher following Algorithm 1 selects $F_{\text{split}} = f$, then the expectation of their resulting estimate $\hat{\Delta}_{\text{ATT}, f}$ can be interpreted as if the function $f$ were chosen a priori, based on only the indices $I^{\text{treat}}_1 \subseteq \{1, \ldots, n\}$ but not the values $\{Y_i, X_i\}_{i \notin I^{\text{treat}}_1}$ associated with those indices. For example, in the scenario described in Section 5.1 knowing the indices $I^{\text{treat}}_1 \subseteq \{1, \ldots, n\}$ means only that a researcher observes that $I^{\text{treat}}_1 = \{751, 752, \ldots, 1000\}$. Within Eq (12), conditioning on $I^{\text{treat}}_1$ is necessary due to the fact that the expectation of some functions $f \in F$ may depend on the number of observations used as input ($n - |I^{\text{treat}}_1|$). Such a dependency holds, for example, if $f$ involves shrinkage.

One implication of Eq (12) is that, given a particular way of partitioning the dataset, if each estimator in $F$ is unbiased for $E(Y_{i|^\text{control}} | A_i = 1)$ then $\hat{\Delta}_{\text{ATT}, F_{\text{split}}}$ is unbiased for the ATT. Such a property is not true of the blinded procedures discussed above. As King and Nielsen (2019) point out, even if $d(Y)$ is unbiased for all $d \in D$, the estimator $\hat{\Delta}_{\text{blind}} = D^*(Y)$ will generally not be. The key difference is that the data used to select $F_{\text{split}}$ (Step 2) is independent of the data that is plugged into $F_{\text{split}} (\{Y_i, X_i, A_i\}_{i \notin I^{\text{treat}}_1})$, while the data used to select $D^*$ is not independent of the data that is plugged into $D^*(Y)$.

Although Algorithm 1 can prevent bias, it does not completely undo all effects of exploration. For example, p-values produced by Step 3 may be miscalibrated, as these values depend on an estimate’s entire sampling distribution, not simply its expectation. The sampling distribution of Algorithm 1’s output, conditional on a particular choice of $f$, is not necessarily equivalent to the distribution that would result from choosing $f$ a priori. Thus, Algorithm 1 is not strictly superior to the traditional sample splitting methods described above, but rather has different benefits and drawbacks.

Several open research questions remain in terms of how to implement procedures such as Algorithm 1 efficiently, and how to account for exploration more deeply. For example, consider the case where $D = \{d_{\text{OLS}, 1}, \ldots, d_{\text{OLS}, p}\}$, and the analyst must choose a single feature to adjust for. An alternative approach could involve allowing data exploration (either blinded or unblinded), but also requiring a subsequent test for overfitting based on how much the distribution of the selected feature changes when moving to a holdout dataset of covariates. Large changes would indicate overfitting and potential bias. Approaches in this vein would have the benefit of not requiring additional outcome data, but also the drawback of not offering a way to fix the bias that they identify. Procedures for teams of analysts could be also explored. For example, each team member could be allowed to explore a different partition of the data, in isolation, before validating results on the partitions explored by their peers. Developing such procedures and studying their formal properties could be a fruitful direction for future research.
6 Discussion

Rigorous standards of evidence and objectivity are crucial for the regulatory and litigation settings that motivate outcome blinding. Unfortunately, and contrary to conventional guidance, we have shown that the bias incurred by blinded analysts can be on the same order of magnitude as the bias incurred by unblinded analysts. We have also outlined a simple, alternative, unblinded procedure for avoiding such forms of bias, which does not require any outcome data to be discarded in the final analysis.

An important caveat is that bias from blinded analysts appears to require that analysts either be explicitly malicious, or have tendencies towards self-interest. Bias in unblinded scenarios however might plausibly be the result of well-intentioned analysts second guessing their methods after seeing a surprising result. For this reason, the insufficiencies of outcome blinding are most concerning when analysts present reports to external decision makers with conflicting incentives (e.g., journal editors, regulatory agencies, or judges). Here, the external decision makers may wish to enforce safeguards that protect against bias regardless of its cause. On the other hand, outcome blinding may still be a useful tool for an analyst reporting to internal decision makers, as the analyst’s team will bear the cost of any poorly informed decision, and there is less incentive to mislead.

One significant remaining problem manifests under repeated analyses of shared data. Many observational, retrospective data analyses in the literature are conducted on common datasets that are either publicly available, or available for a fee. Examples range from modern databases such as the UKbiobank (Sudlow et al., 2015) and the SEER Databases on Cancer Statistics (www.seer.cancer.gov), to the 1987 National Medical Expenditure Survey used by Rubin (2001; 2007), which describes as being reused across many litigation cases. For such datasets, partial information about in-sample data is already in the public domain via published articles. Even if a researcher fully prespecifies their analysis, it may not be realistic to assume that the specified analysis was not influenced by previously published analyses of the same dataset by different labs. This problem is sometimes referred to as the challenge of developing quality preserving data (Aharoni et al., 2011; Aharoni and Rosset, 2014; Woodworth et al., 2018; see also Dwork et al., 2015). Exploring whether methods for controlled reuse of datasets can be meaningfully combined with some form of blinding or data partitioning is an important area of future work.

While outcome blinding has become a dominant take-away from Rubin (2001, 2007); Rubin et al. (2008), and is now somewhat widespread (Steiner et al., 2010; Shadish and Steiner, 2010; Yue et al., 2012; Yue et al., 2014; Li et al., 2016; Ding and Lu, 2017; Kainz et al., 2017; Lu et al., 2019; King and Nielsen, 2019; Chen et al., 2021; Levenson et al., 2021; Ho et al., 2021), it was never meant to stand in isolation. Rubin et al. (2008) also argued that, in addition to blinding outcomes, analysts should appeal to domain experts when identifying confounders to adjust for. This advice is vital, since identifying confounders fundamentally requires knowledge of the underlying causal pathways (Pearl, 2012; VanderWeele, 2019). Unfortunately, we have also seen that domain expertise can contribute to the bias of blinded, ill-intentioned analysts who choose to use that expertise.
to serve their own interests. In this way, involving domain experts in the analysis does prevent outcome blinding from being subverted.

Indeed, many modern causal inference approaches do not use blinding, and instead study the treatment mechanism and the outcome mechanism simultaneously (De Luna et al., 2011; Zigler and Dominici, 2014; Shortreed and Ertefaie, 2017; D’Amour and Franks, 2019). When applied as prespecified procedures, any such method can be studied through theory and simulation, and should not be dismissed simply because it does not relegate outcome analysis to a separate stage.

Our general approach is similar in spirit to other quantitative models of researcher behavior (Coker et al., 2018; Fisher et al., 2019) and of the publication system that researchers inhabit (Miller and Ulrich, 2016, 2019; Patil et al., 2016). We recommend that similar models continue to be examined when establishing best practices for statistical analyses. For example, agent-based approaches could be relevant when studying publication bias; publication races between competing labs; the likelihood of a given result being the subject of a replication study; how data sharing requirements may change the results that researchers submit; how prediction model comparisons are presented (see also Hand, 2006); or how courtroom evidence is presented by competing sides. Such studies could form a valuable complement to empirical studies of how analysts are observed to behave (e.g., Leek et al., 2011; Jager and Leek, 2014; Fisher et al., 2014; Silberzahn et al., 2018; Auspurg and Brüderl, 2021).

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