Conditional average treatment effect estimation with treatment offset models

Wouter A.C. van Amsterdam* and Rajesh Ranganath 2

1 Babylon Health, *wouter.vanamsterdam@babylonhealth.com
2 Courant Institute of Mathematical Sciences, Center for Data Science, New York University

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Abstract

Treatment effect estimates are often available from randomized controlled trials as a single average treatment effect for a certain patient population. Estimates of the conditional average treatment effect (CATE) are more useful for individualized treatment decision making, but randomized trials are often too small to estimate the CATE. There are several examples in medical literature where the assumption of a known constant relative treatment effect (e.g. an odds-ratio) is used to estimate CATE models from large observational datasets. One approach to estimating these CATE models is by using the relative treatment effect as an offset, while estimating the covariate-specific baseline risk. Whether this is a valid approach in the presence of unobserved confounding is unknown.

We demonstrate for a simple example that offset models do not recover the true CATE in the presence of unobserved confounding. We then explore the magnitude of this bias in numerical experiments. For virtually all plausible confounding magnitudes, estimating the CATE using offset models is more accurate than assuming a single absolute treatment effect whenever there is sufficient variation in the baseline risk. Next, we observe that the odds-ratios reported in randomized controlled trials are not the odds-ratios that are needed in offset models because trials often report the marginal odds-ratio. We introduce a constraint to better use marginal odds-ratios from randomized controlled trials and find that the newly introduced constrained offset models have lower bias than standard offset models. Finally, we highlight directions for future research for exploiting the assumption of a constant relative treatment effect with offset models.

1 Introduction

Weighing potential benefits and harms of treatment requires knowing the treatment effect, which is the change in probability of an outcome between different treatments. The gold standard for estimating treatment effects are randomized control trials (RCT). RCTs often report the efficacy of treatments on a relative scale using for example the odds-ratio or
hazard-ratio for the entire population (e.g., Furie et al. (2020); Lean et al. (2018)). Though reported on a relative scale, the effect reported still corresponds to a single average effect, i.e., absolute change in probability of an outcome, for the whole population. Ideally, the change in probability of an outcome, rather than being known on average for a population, would be tailored to the characteristics of a patient to produce the conditional average treatment effect (CATE). To turn the population-level relative effect into a CATE estimate, several previous studies on breast cancer and cardiovascular disease used the assumption of a constant relative treatment effect to develop CATE models from observational data (Candido dos Reis et al., 2017; Ravdin et al., 2001; Alaa et al., 2021; Xu et al., 2021). We call these constant-relative CATE (CR-CATE) models. This assumption can be better contextualized by imagining studying the effect of a new type of medication, here the two “treatments” being compared are the untreated or baseline regime and that same regime plus this new medication. The assumption of a constant relative treatment effect does not preclude non-constant CATEs because even with a constant relative treatment effect, the treatment can have a varying effect on an absolute risk scale depending on the baseline risk of a patient. For instance, assume that a new cholesterol lowering drug reduces the risk of cardiovascular death within the next 10 years with an odds-ratio of 0.5. A 60-year-old male smoker with hypertension and raised cholesterol has a baseline risk of cardiovascular death of 40% and should expect a reduction in risk of 15% points. A 50-year-old female without hypertension has a baseline risk of under 1% and will have a less than 0.5% points reduction in risk. Given these widely different effects on an absolute probability scale, one may recommend the new cholesterol lowering drug to the 60-year-old male but not the 50-year-old female.

When estimating CR-CATE models from observational data where the treatment of interest was available, one approach is to use the constant relative treatment effect as an offset term, while estimating the baseline risk. By combining the estimated baseline risk model and the fixed relative treatment effect, these models estimate the absolute outcome probability under treatment or no treatment. Some CR-CATE were found to be accurate in observational validation studies, on the basis of which treatment guidelines acknowledged a place for them in clinical decision making (Cardoso et al., 2019; Gradishar, 2021). However, due to confounding, the baseline risk cannot be estimated from an observational dataset where some patients were treated and others were not (Groenwold et al., 2016; van Geloven et al., 2020).

Because CR-CATE models target interventional distributions but were developed from observational data it is implicitly assumed that using the constant relative treatment effect assumption is sufficient for controlling for any unobserved confounding. At first glance this implicit assumption may seem plausible as the constant relative treatment effect is not estimated from the observational data but is plugged in from prior RCT estimates. However, whether the assumption is correct has not been discussed or verified.

In this work we evaluate the validity of the assumption that a known constant odds-ratio for treatment allows for CATE estimation in the presence of unobserved confounding using the known odds-ratio as an offset term. We show that a known odds-ratio used as an offset is not sufficient for estimating CATEs. In spite of that, we find in numerical experiments the bias was low enough that using offset models still leads to better estimation of CATEs compared with the baseline of assuming a single risk difference for all patients. Finally, we observe that the odds-ratios reported in RCTs are not the odds-ratios that are needed for the offset method because RCTs generally report estimates of the marginal odds-ratio, whereas
We consider models that estimate the absolute difference in probability of a binary outcome \( y \) under two possible treatments \( t_x \in \{0, 1\} \) conditional on a possibly multi-dimensional pre-treatment covariate vector \( x \). This is the conditional average treatment effect (CATE), conditional on \( x \). Treatment \( t_x = 0 \) is assumed to be the baseline treatment (or no treatment depending on the clinical context) and \( t_x = 1 \) is the treatment of interest. Using Pearl’s do-operator to indicate intervening on treatment, the CATE is defined as:

\[
\text{CATE}(x) := p(y = 1|\text{do}(t_x = 1), x) - p(y = 1|\text{do}(t_x = 0), x)
\]

CR-CATE approaches assume that the odds-ratio for treatment is constant for the entire population. Odds are defined relative to a probability \( \pi \) as \( \text{odds}(\pi) = \frac{\pi}{1 - \pi} \). The odds-ratio of two probabilities \( \pi_0, \pi_1 \) is defined as \( \text{OR}(\pi_1, \pi_0) := \text{odds}(\pi_1)/\text{odds}(\pi_0) \). Writing \( \pi_{t_x}(x') = p(y = 1|\text{do}(t_x = t'_x), x = x') \), the assumption that the odds-ratio for treatment is constant implies that for any two possible values \( x', x'' \) for \( x \), \( \text{OR}(\pi_1(x'), \pi_0(x')) = \text{OR}(\pi_1(x''), \pi_0(x'')) \). Or equivalently, the log odds of the interventional distributions differ by a constant. Introducing \( \eta(t_x, x) \) as the log odds of \( \pi_{t_x}(x) \), the assumption implies that for each \( t_x, x \):

\[
\eta(t_x, x) = \beta_0(x) + \beta_{t_x}^* t_x
\]

2 Methods

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\eta(t_x, x) = \beta_0(x) + \beta_{t_x}^* t_x
\]

Here \( \beta_0(x) \) is the log odds of the interventional distribution with \( \text{do}(t_x = 0) \) (i.e. the baseline risk) as a function of \( x \), and \( \beta_{t_x}^* \) is the log odds-ratio for treatment, assumed to be constant for all \( x \). As we will explain later in Section \[2.2\] \( \beta_{t_x}^* \) depends on the choice for the covariate \( x \). For the moment we will assume that an estimate of \( \beta_{t_x}^* \) for the chosen \( x \) is available from prior RCTs. Later in Section \[2.2\] we discuss the more realistic setting where this is not the case. Denote \( \sigma(x) = (1 + e^{-x})^{-1} \) the sigmoid function and \( \sigma^{-1}(\pi) = \log \text{odds}(\pi); 0 < \pi < 1 \) its inverse, we can now write the CATE in terms of \( \eta \):

\[
\text{CATE}(x) = \sigma(\eta(1, x)) - \sigma(\eta(0, x))
\]

If \( \beta_{t_x}^* \) is given a priori, models for \( \eta \) of the form of Equation \[1\] can be estimated with likelihood based approaches by specifying a parametric model for \( \hat{\beta}_0(x) = f(x; \hat{\theta}) \) where \( f: \mathcal{X} \times \Theta \rightarrow \mathbb{R} \) is from a family of functions of \( x \in \mathcal{X} \) indexed by parameter vector \( \theta \in \Theta \). The full model is then given by

\[
\hat{\eta}(t_x, x) = f(x; \hat{\theta}) + \hat{\beta}_{t_x}^* t_x
\]

In the case of logistic regression, \( f(x; \theta) = \theta_0 + \theta_x x \). A fixed term in a model that is not estimated from data is called an offset term \[\text{(Watson 2007)}\]. We therefore refer to models of the from of Equation \[2\] where \( \beta_{t_x}^* \) is constant as treatment offset models or offset models for short. Offset models are a subclass of CR-CATE models.
2.1 Identification of the conditional average treatment effect

We assume we are given data from an observational distribution compatible with the Acyclic Mixed Directed Graph (AMDG) with observed multi-dimensional covariate vector \(x\) and unobserved confounder \(u\) presented in Figure 1. The AMDG is quite general in that it allows for unobserved confounding between the pairs of variables \([\{u, x\}, \{x, t\}, \{x, y\}]\). It is assumed that \(x\) is a non-descendant of \(t, y\) as implied by the assumption that \(x\) is a pre-treatment variable that may be useful for individual treatment decisions.

To prove that the CATE is identified it is sufficient to prove that the interventional distribution \(\pi_{t'x}(x')\) is identified for all \(t', x'\). Due to the unobserved confounder \(u\) in the AMDG, the interventional distribution is not identifiable from observational data without additional assumptions. The question is whether the assumption of a known constant log odds-ratio as stated in Equation 1 is sufficient for \(x\)-conditional causal effect identification from observational data when \(u\) is not observed. The known constant odds-ratio assumption implies that the query is identified when the baseline risk \(\sigma(\beta_0(x))\) is identified, as \(\pi_0(x') = \sigma(\beta_0(x'))\) and \(\pi_1(x') = \sigma(\beta_0(x') + \beta_*^t)\). We now prove with a simple counter example that offset models do not estimate the ground truth interventional distribution.

2.1.1 Example 1: Offset models do not estimate the interventional distribution

A simple example compatible with Equation 1 and the AMDG Figure 1 is where \(u\) is binary and \(\beta_0(x) = \beta_0\) for all values of \(x\), meaning that there is no variation in the baseline risk. Denoting \(B\) as the Bernoulli distribution, \(p_u = p(u = 1)\) and \(\pi_{t'u} = p(y = 1|t, u)\), then the data-generating mechanism for this example is:

\[
u \sim B(p_u), t_x \sim B(p(t_x = 1|u = u)), y \sim B(\pi_{t'u})
\]

Despite its simplicity this example is conceptually important for all cases with binary treatment and discrete \(x\) as a) when the treatment is binary, any arbitrary confounder can be modeled as a single binary variable while maintaining the same observational and interventional distributions (Ilse et al., 2023); and b) in the limit of infinite data, stratifying the population for each value of \(x\) and estimating \(\beta_0\) in each of the strata is equivalent to non-parametric estimation of \(\beta_0(x)\) in Equation 2 when \(u\) is binary and \(x\) is discrete.

Let \(l(y, \hat{\pi})\) denote the Bernoulli log-likelihood of outcome \(y\) conditional on estimated probability \(\hat{\pi}\). We derive a closed-form expression for the expected log-likelihood depending on the single parameter of the offset model \(\beta_0\): \(L(\beta_0) = E_{p(y,t,u)}[l(y, \hat{\pi}(t, u, \beta_0))]\) in the
Appendix A.1. Taking the derivative with respect to $\beta_0$ and plugging in the ground truth value for $\beta_0^*$ we find the following expression:

$$\frac{\partial L}{\partial \beta_0}(\beta_0 = \beta_0^*) = p_u(1 - p_u)\left[ (\pi_{01} - \pi_{00}) (p(t_x = 0|u = 1) - p(t_x = 0|u = 0)) + \right. \\
\left. (\pi_{11} - \pi_{10}) (p(t_x = 1|u = 1) - p(t_x = 1|u = 0)) \right]$$

In general this expression is non-zero, meaning that the ground truth solution $\beta_0^*$ is not a stationary point of the expected log-likelihood. This proves that the offset method does not recover the true baseline risk in the presence of confounding. In the case of no confounding when $\pi_{t_x,0} = \pi_{t_x,1}$ or $p(t_x|u = 1) = p(t_x|u = 0)$, the derivative is zero at $\beta_0^*$ meaning $\beta_0^*$ is a stationary point of the expected log-likelihood. The question is now how important this bias is and whether offset models can be used if the constant odds-ratio assumption is tenable, or if offset models should be avoided altogether. We study this later in with numerical experiments in Section 3.1.

### 2.2 Collapsibility

An important consideration for offset models is the difference between the marginal odds-ratio and the conditional odds-ratio. In a sufficiently large RCT where treatment $t_x$ is randomized and binary covariate $x$ is observed, two different models may be estimated: one that does not condition on $x$ and estimates the marginal log odds-ratio $\gamma_{t_x}$:

$$p(y = 1|do(t_x = t'_x)) = \sigma(\gamma_0 + \gamma_{t_x} t'_x)$$

and one that estimates the conditional log odds-ratio $\beta_{t_x}$:

$$p(y = 1|do(t_x = t'_x), x = x') = \sigma(\beta_0 + \beta_{t_x} t'_x + \beta_x x')$$

Note that the model with the conditional odds-ratio does not include an interaction term between $t_x$ and $x$, as implied by the constant odds-ratio assumption. In contrast with linear regression, in general $\beta_{t_x} \neq \gamma_{t_x}$. This means that the odds-ratio for treatment is different if the model conditions on the covariate $x$ or not. This property of the odds-ratio is called non-collapsibility (Greenland et al. 1999, Burgess 2017). To illustrate non-collapsibility, consider the extreme example with binary covariate $x$ where $\pi_{x,0}(x = 0) = \{0.01, 0.02\}$ and $\pi_{x,1}(x = 1) = \{0.98, 0.99\}$. For both $x \in \{0, 1\}$, the $x$-conditional log odds-ratio $\beta_{t_x} \approx \log(2.0)$. However, when grouping patients with different values of $x$ together we see that, assuming $p(x = 1) = 0.5$, $p(y = 1|do(t_x = \{0, 1\}) = \{0.495, 0.505\}$, thus the marginal log odds-ratio $\gamma_{t_x} \approx \log(1.0)$. In most RCTs the marginal log odds-ratio $\gamma_{t_x}$ is estimated. When $\gamma_{t_x} \neq \beta_{t_x}$ the trials do not provide the information required to use the offset method as defined in Equation 2. The stronger the $t_x$-conditional association between $x$ and $y$, the greater the difference between $\gamma_{t_x}$ and $\beta_{t_x}$ (Hauck et al. 1991). For an illustration, see Appendix A.2. This is an important drawback as at the same time, a stronger association between $x$ and $y$ conditional on $t_x$ results in more variation in the baseline risk and thus more variation in the $x$-conditional treatment effect. So in the situation where offset models have
more potential added value (when $x$-conditional treatment effects differ substantially), the estimate of the marginal log odds-ratio $\gamma_{t_x}$ from RCTs becomes a less accurate approximation of the $\beta_{t_x}$ needed for the offset model.

Having defined $\beta_{t_x}$ and $\gamma_{t_x}$ we can now refine the assumptions underlying binary treatment
gen given in the hypothetical RCT. This leads to:

$$x$$

mechanism of this hypothetical RCT is:

$$\text{are:}$$

The maximum likelihood estimate of the marginal log odds-ratio $\gamma_{t_x}$ in the data generating

mechanism of this hypothethical RCT is:

$$\gamma_{t_x} = \sigma^{-1}(\mathbb{E}_{p_{\text{RCT}}(y = 1 | t_x = 1)} - \sigma^{-1}(\mathbb{E}_{p_{\text{RCT}}(y = 1 | t_x = 0)})$$

We can use Equations 3 and 4 to calculate $\mathbb{E}_{p_{\text{RCT}}(y = 1 | t_x = 0)}$ by averaging over

observed values $x_i$ of $x$ from the empirical distribution and arrive at our estimate of the

implied marginal odds-ratio:

$$\gamma_{t_x} = \frac{1}{N} \sum_{i=1}^{N} \sigma(f(x_i; \hat{\beta}_{t_x}; \hat{\theta})) - \frac{1}{N} \sum_{i=1}^{N} \sigma(f(x_i; \hat{\beta}_{t_x}; \hat{\theta}))$$

(8)
Given an estimate of the marginal odds-ratio $\gamma_{t_x}^*$ from RCTs, we can now formulate a new objective that includes both the likelihood of the observed data and a constraint defined by the known versus implied marginal odds-ratio. Denote the Bernoulli log-likelihood of an individual observation as $l(y_i, x_i; \hat{\beta}_{t_x}, \hat{\theta})$ and $L(\hat{\beta}_{t_x}, \hat{\theta}) = \sum_{i=1}^{N} l(y_i, x_i; \hat{\beta}_{t_x}, \hat{\theta})$ the total log-likelihood of the observed data. We formulate the following Lagrangian:

$$L(\hat{\beta}_{t_x}, \hat{\theta}) = L(\hat{\beta}_{t_x}, \hat{\theta}) + \lambda \left( \gamma_{t_x} - \gamma_{t_x}^* \right)$$

(9)

The optimal set of parameters maximizes the likelihood of the observed data while adhering to the constraint on the implied marginal odds-ratio. Finding these parameters given data can be done with constrained optimization algorithms, for example an Augmented Lagrangian Algorithm (Madsen et al., 2004).

### 2.3 Metric

CATE models estimate the difference in outcome probability under hypothetical interventions on treatment conditional on covariates. A common metric for CATE estimation is the root-mean-squared error of the predicted difference in outcome probability versus the actual difference in outcome probability, also known as the “Precision in Treatment Effect Heterogeneity” (PEHE, Hill (2011)). If $\pi_1(x), \pi_0(x)$ denote the interventional distributions, and $\hat{\pi}_1(x), \hat{\pi}_0(x)$ the estimated interventional distributions, the PEHE is calculated as:

$$PEHE = \sqrt{\frac{1}{N} \sum_{i}^N ((\pi_1(x_i) - \pi_0(x_i)) - (\hat{\pi}_1(x_i) - \hat{\pi}_0(x_i)))}^2$$

CATE models are generally motivated to enable more individualized treatment decisions as opposed to using a single average treatment effect estimate for all patients. This means that the baseline for CATE models is using a single average treatment effect on the absolute probability scale for all patients (ATE-baseline).

### 3 Experiments

We evaluate the amount of bias when estimating CATE models from observational data using the offset method in the presence of unobserved confounding with numerical experiments. First, we investigate Example 1 (Equation 3) and find that the bias of offset models is small even for large confounding magnitudes. Finally we study in what situations offset models have better PEHE than the ATE-baseline when there are measured covariates, comparing different offset model variants.

#### 3.1 Example 1 examined

To evaluate the amount of bias in offset models in Example 1, we parameterize the magnitude of confounding using log odds-ratios $\beta_{u \rightarrow t_x}, \beta_{u \rightarrow y}$ so that $p(t_x = 1|u) = \sigma(\frac{1}{2} \beta_{u \rightarrow t_x}(2u - 1))$ and $p(y = 1|t_x, u) = \sigma(\frac{1}{2} (\beta_{t_x}(2t_x - 1) + \beta_{u \rightarrow y}(2u - 1)))$. Note that because there is no variation in baseline risk $\gamma_{t_x}^* = \beta_{t_x}^*$. We plot different solutions and the log-likelihood contours for different values of $\beta_{u \rightarrow t_x} = \beta_{u \rightarrow y}$ in Figure 2 setting $\beta_{t_x} = 1$ and $p_u = 0.5$. Even in
Figure 2: Solutions for different methods on Example 1 with different amounts of confounding, indexed by OR_{uf} = OR_{uy}, the odds-ratios from confounder u to treatment t_x and outcome y respectively. The contour lines indicate solutions with the same log-likelihood of the observational data. As visualized with the horizontal line, the offset method finds the β_0 that maximizes the observational likelihood while keeping β_{t_x} = β_{t_x}^∗. Fully observational: estimate β_0 and β_{t_x} from observational data, RCT: ground truth values of β_0 and β_{t_x}, offset: offset method.

extreme cases of confounding when β_{u→t_x} = β_{u→y} = log 10, the offset solution is close to the ground truth, while the observational estimate becomes more and more biased. This indicates that when β_{t_x}^∗ is known, the bias in offset models induced by the unobserved confounder u is small.

3.2 Numerical experiments with a binary covariate

The bias induced by the confounding in Example 1 seems minor even for extreme magnitudes of confounding when β_{t_x}^∗ is known. However, a more important metric is whether the PEHE of the offset model is better than that of the ATE-baseline when γ_{t_x}^∗ is known instead of β_{t_x}^∗ and there is variation in the baseline risk, which means that γ_{t_x}^∗ ≠ β_{t_x}^∗. To investigate this, we extend the example by introducing a marginally independent binary covariate x with non-zero effect on the outcome. The updated data generating mechanism is:

\[ u \sim \mathcal{B}(p_u), t_x \sim \mathcal{B}(p(t_x = 1 | u = u)), x \sim \mathcal{B}(p_x), y \sim \mathcal{B}(\pi_{t_x xu}) \]

where

\[ \pi_{t_x xu} = p(y = 1 | t_x, x, u) = \sigma\left(\frac{1}{2}(\beta_{t_x}(2t_x - 1) + \beta_x(2x - 1) + \beta_{u→y}(2u - 1))\right) \quad (10) \]

For different values of β_x, β_{u→t_x}, β_{u→y} in Equation (10) we calculated the PEHE of the ATE-baseline. We contrast this PEHE with 5 different approaches. As we are investigating the amount of bias due to unobserved confounding, the reference is (1) a logistic regression model based on data where there is no confounding as in RCTs, with \( p_{\text{RCT}}(t_x = 1 | u = 0) = p_{\text{RCT}}(t_x = 1 | u = 1) = 0.5 \), but the rest of the data generating mechanism remains the same (RCT). We then compare 4 different approaches using observational data: (2) a logistic regression model where β_0, β_{t_x}, β_x are estimated from the observational data (full). (3) An
Figure 3: Three different approaches to estimating a model for data with a binary covariate $x$. Each image is a hyperplane of the parameter cube $(\beta_0, \beta_t, \beta_x)$ dissected at a specific value of $\beta_x$ corresponding to the solution of the respective method. The ground truth solution, indicated with the black asterix lies in none of the shown hyperplanes. The contour lines indicate solutions with the same log-likelihood of the observational data. In the marginal offset method, the solution for $(\beta_0, \beta_t)$ maximizes the log-likelihood on the line with $\beta_x = \gamma^*_t$, as indicated with the orange horizontal line in the second plot. Because of non-collapsibility, this is a suboptimal solution as $\gamma^*_t \neq \beta^*_t$. In the constrained offset method (third plot), reference lines are added that are dissections of level sets defined by equal values of the constraint on the implied marginal odds-ratio $\gamma_t(x)(\beta_0, \beta_t, \beta_x) - \gamma^*_t$. Here, the solution $(\beta_0, \beta_t, \beta_x)$ maximizes the log-likelihood on the level set defined by $\gamma_t(x)(\beta_0, \beta_t, \beta_x) - \gamma^*_t = 0$, which is a saddlepoint of the Lagrangian as formulated in Equation 9.

offset model where $\beta_0, \beta_x$ are estimated while plugging in the ground truth $\beta^*_t$ as obtained by the RCT in model (1) (conditional). (4) An offset model where the marginal $\gamma^*_t$ is available from RCTs and is used as an offset in place of $\beta_t$ (marginal). (5) An offset model where the implied marginal $\gamma_t(x)(\hat{\beta}_t, \theta)$ is constrained to be $\gamma^*_t$ as in Equation 9 (constrained). For these experiments we set $\beta_{u \rightarrow t} = \beta_{u \rightarrow y} = \beta_u$ to four different values and varied $\beta_x$, keeping $\beta_t = 1$ and $p_u = p_x = 0.5$. As for these experiments the expected log-likelihood is available in closed-form, we optimize the expected log-likelihood directly instead of generating random samples. We implemented the constrained offset model using a gradient-based augmented Lagrangian optimizer implemented in the R package ‘alabama’. The code to replicate these results is available at www.github.com/vanamsterdam/binaryoffsetmodels. The constrained offset method applied to this setting is illustrated in Figure 3 and contrasted with the fully observational baseline and the marginal offset method.

As a first observation from the results shown in Figure 4 whenever the baseline risk varies with $x$, the ATE-baseline has sub optimal PEHE. Also, the PEHE of the fully observational logistic regression model becomes worse than the ATE-baseline for higher magnitudes of confounding. Whenever the estimated $\overline{OR}_x > 1$, offset models are better than the ATE-baseline with respect to PEHE. For larger magnitudes of $\overline{OR}_x$ the performance of the marginal offset model degrades because the issue of non-collapsibility becomes more pronounced. Of note, the constrained offset model is always better than the ATE-baseline whenever $\overline{OR}_x > 1$, and always better than the fully observational baseline. Finally, we observe that even the
Figure 4: PEHEs for different strategies, indexed by $\text{OR}_{ut} = \text{OR}_{uy}$, the odds-ratios from confounder $u$ to treatment $t_x$ and outcome $y$ respectively. The shaded areas indicate whether the chosen approach improves upon the ATE-baseline of assuming a single predicted difference in outcome for all patients. In the right most plot the fully observational baseline has higher PEHE than the maximum $y$-value of the plot.

A logistic regression model estimated from RCT data has non-zero PEHE which increases when the confounding increases. The reason for this not confounding but parametric form bias. The data were generated according to a simple logistic regression setup, linear in $t_x, x, u$. When fitting a logistic model conditional on $t_x, x$ in this data, marginalizing out $u$, simple logistic regression is no longer sufficient. Specifically, the model now requires an added interaction term between $t_x$ and $x$ to be unbiased.

We further expanded this example with numerical experiments where $x$ and $u$ are no longer marginally independent. Details of these experiments are described in the Appendix A.3. Except in some extreme settings when there is very little variation in baseline risk, the constrained offset models have better PEHE than the ATE-baseline. Overall, constrained offset models perform most stable across all settings and have better PEHE than the fully observational baseline and the marginal offset models.

4 Discussion

We evaluated whether the offset method provides valid CR-CATE models for binary outcomes in the presence of unobserved confounding. Though not exact, offset models still have better PEHE than the baseline of using the average treatment effect for all patients even for large confounding magnitudes. In our numerical experiments, this holds even if an estimate of the marginal odds-ratio is used from randomized trials instead of the conditional odds-ratio. We introduced a new way of using estimates of the marginal odds-ratio to address the issue of non-collapsibility of the odds-ratio and find that it gives the best performance overall in terms of PEHE.

An important question for practical applications is when it is valid to assume that the relative treatment effect is indeed constant. There is some evidence from meta-analyses that treatment effect estimates on a relative scale are more stable across different RCTs than treatment effects on an absolute scale (Engels et al., 2000; Sterne and Egger, 2001). However, in some settings there may clear indications for differences in treatment effect on a relative
scale. This could hold for example for therapies whose mechanism of action depends on certain genetic mutations. If this is the case and the difference in relative treatment effect is known, this difference could be accounted for accordingly in offset models.

Recent work has studied combining observational data and data from randomized trials for CATE estimation (Rosenman et al., 2020; Ilse et al., 2022). Under relatively mild assumptions, estimates from combined datasets yield more efficient estimates of CATEs than using RCT data alone. However, these methods require access to the individual-patient data from the RCT, whereas offset methods only rely on a single effect estimate from RCTs. Gaining access to individual-patient data from RCTs is often challenging due to data-access restrictions.

A limitation of our work is the relatively restricted set of experiments. Future work could experiment with higher dimensional, mixed-type covariates and different functional relationships between the variables. In higher dimensions, the constraint on the implied marginal odds-ratio restricts a lower fraction of the degrees of freedom. It is unknown whether the constraint will effectively reduce confounding bias in higher dimensions. One potential solution for this would be to first learn a scalar function from all covariates, for example with a fully observational model or a marginal offset model. The constrained offset method can then be applied using this scalar as the single covariate.

Future work could extend our experiments to relative treatment effect estimates in the form of hazard-ratios, or to the setting of time-varying confounding. Furthermore, Bayesian extensions of our constrained offset model can be investigated to account for uncertainty in marginal odds-ratio estimates from RCTs. Finally, finite-sample characteristics of our estimator for the implied marginal odds-ratio in terms of bias and variance could be studied further. We leave these extensions for future work.

In conclusion, we find that offset models do not correctly estimate CATEs in the presence of unobserved confounding. However, from our experiments it may still be justified to use offset models in practice as they often have better PEHE than the ATE-baseline. The newly introduced constraint on the implied marginal odds-ratio improved the PEHE even more. Further extensions of the offset method for CR-CATE models remain for future work.

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We now prove that the assumption expressed in Equation 1 is not sufficient for identifying the following expression for $\beta$ the observational distribution in this example. Then we show that the ground truth solution for the expected log likelihood as a function of $\beta$ amounts to estimating the log odds of the untreated risk that the untreated risk does not vary with $x$. In this setting, estimating an offset model amounts to estimating the log odds of the untreated risk $\beta_0$. We first derive an expression for the expected log likelihood as a function of $\beta_0$ $L(\beta_0) = E_{\pi_{\text{obs}}(y,t,u)}[l(y,\hat{\pi}(t,u),\beta_0)]$ under the observational distribution in this example. Then we show that the ground truth solution $\beta_0^*$ is not a stationary point, proving our claim. Writing

$$p_u = p(u = 1)$$
$$p_{t_x, u'} = p(t_x = t_x', u = u') = p(t_x = t_x'|u = u')p(u = u')$$
$$\pi_{t_x, u'} = p(y = 1|t_x = t_x', u = u')$$

Then the data generating mechanism is:

$$u, t_x \sim \mathcal{B}(p_{t_x, u'}), y \sim \mathcal{B}(\pi_{t_x, u})$$

The ground truth solutions $\beta_0^*$ and $\beta_*^t$ are:

$$p(y = 1|do(t_x = 0)) = (1 - p_u)\pi_{00} + p_u\pi_{01} = \sigma(\beta_0^*)$$  \hspace{1cm} (11)
$$p(y = 1|do(t_x = 1)) = (1 - p_u)\pi_{10} + p_u\pi_{11} = \sigma(\beta_0^* + \beta_*^t)$$  \hspace{1cm} (12)

The Bernoulli log-likelihood is

$$l(y|t_x, \beta_0, \beta_*) = y \log \sigma(\beta_0 + \beta_*^t) + (1 - y) \log(1 - \sigma(\beta_0 + \beta_*^t))$$

In offset models $\beta_*^t$ is assumed given a priori and $\beta_0$ is the only parameter, resulting in the following expression for $L(\beta_0)$:

$$L(\beta_0) = p_{00} \left[ \pi_{00} \log \sigma(\beta_0) + (1 - \pi_{00}) \log(1 - \sigma(\beta_0)) \right] + p_{01} \left[ \pi_{01} \log \sigma(\beta_0) + (1 - \pi_{01}) \log(1 - \sigma(\beta_0)) \right] + p_{10} \left[ \pi_{10} \log \sigma(\beta_0 + \beta_*^t) + (1 - \pi_{10}) \log(1 - \sigma(\beta_0 + \beta_*^t)) \right] + p_{11} \left[ \pi_{11} \log \sigma(\beta_0 + \beta_*^t) + (1 - \pi_{11}) \log(1 - \sigma(\beta_0 + \beta_*^t)) \right]$$

Taking the derivative with respect to $\beta_0$, noting that $(\log \sigma(x))' = 1 - \sigma(x)$, we get:

$$\frac{\partial L}{\partial \beta_0} = p_{00} \left[ \pi_{00}(1 - \sigma(\beta_0)) - (1 - \pi_{00})\sigma(\beta_0) \right] + p_{01} \left[ \pi_{01}(1 - \sigma(\beta_0)) - (1 - \pi_{01})\sigma(\beta_0) \right] + p_{10} \left[ \pi_{10}(1 - \sigma(\beta_0 + \beta_*^t)) - (1 - \pi_{10})\sigma(\beta_0 + \beta_*^t) \right] + p_{11} \left[ \pi_{11}(1 - \sigma(\beta_0 + \beta_*^t)) - (1 - \pi_{11})\sigma(\beta_0 + \beta_*^t) \right]$$  \hspace{1cm} (13)
We now plug in the ground truth solutions for $\beta_0^*, \beta_{tx}^*$.

\[
\frac{\partial L}{\partial \beta_0}(\beta_0 = \beta_0^*) = p_{00}[\pi_{00}(1 - p_u \pi_{01} - (1 - p_u)\pi_{00}) - (1 - \pi_{00})(p_u \pi_{01} + (1 - p_u)\pi_{00})] \\
+ p_{01}[\pi_{01}(1 - p_u \pi_{01} - (1 - p_u)\pi_{00}) - (1 - \pi_{01})(p_u \pi_{01} + (1 - p_u)\pi_{00})] \\
+ p_{10}[\pi_{10}(1 - p_u \pi_{11} - (1 - p_u)\pi_{10}) - (1 - \pi_{10})(p_u \pi_{11} + (1 - p_u)\pi_{10})] \\
+ p_{11}[\pi_{11}(1 - p_u \pi_{11} - (1 - p_u)\pi_{10}) - (1 - \pi_{11})(p_u \pi_{11} + (1 - p_u)\pi_{10})]
\]

Removing terms that cancel out in each line results in

\[
= p_{00}[p_u(\pi_{00} - \pi_{01})] \\
+ p_{01}[(1 - p_u)(\pi_{01} - \pi_{00})] \\
+ p_{10}[p_u(\pi_{10} - \pi_{11})] \\
+ p_{11}[(1 - p_u)(\pi_{11} - \pi_{10})]
\]

Substituting back $p_{tx} = p(t_x = t_x'|u = u')p(u = u')$:

\[
= p(t_x = 0|u = 0)(1 - p_u)[p_u(\pi_{00} - \pi_{01})] \\
+ p(t_x = 0|u = 1)p_u[(1 - p_u)(\pi_{01} - \pi_{00})] \\
+ p(t_x = 1|u = 0)(1 - p_u)[p_u(\pi_{10} - \pi_{11})] \\
+ p(t_x = 1|u = 1)p_u[(1 - p_u)(\pi_{11} - \pi_{10})]
\]

Factoring out $p_u(1 - p_u)$ and re-arranging we arrive at our result:

\[
\frac{\partial L}{\partial \beta_0}(\beta_0 = \beta_0^*) = p_u(1 - p_u)[(\pi_{01} - \pi_{00})(p(t_x = 0|u = 1) - p(t_x = 0|u = 0)) + \\
(\pi_{11} - \pi_{10})(p(t_x = 1|u = 1) - p(t_x = 1|u = 0))]
\]

If there is no confounding this expression is zero, but in general it is not which means that the ground truth solution $\beta_0^*$ is not an optimum of the expected log-likelihood in the observational data distribution. This proves our claim that the offset model does not recover the interventional distribution in the presence of confounding. \( \square \)

Of note, the fact that the interventional distribution is not identified does not automatically imply that the CATE is not identified as there may be another $\beta_0' \neq \beta_0^*$ such that $\text{CATE}(\beta_0 = \beta_0', \beta_{tx} = \beta_{tx}' = \beta_{tx}^*) = \text{CATE}(\beta_0 = \beta_0^*, \beta_{tx} = \beta_{tx}^*)$. To investigate this, assume that for some $\beta_0^* = a$ and $\beta_{tx}^* = b$ we have that:

\[
\delta := \text{CATE}(\beta_0 = a, \beta_{tx} = b) = \sigma(a + b) - \sigma(a) = \frac{e^{a+b}}{1 + e^{a+b}} - \frac{e^a}{1 + e^a}
\]

\[15\]
Again, treating $\beta^*_{t_x}$ as fixed, we will now prove that this equation has at most two solutions for $\beta_0 = a$ by noting that:

$$\frac{e^{a+b}}{1+e^{a+b}} - \frac{e^a}{1+e^a} = \frac{e^{a+b}(1+e^a) - (1+e^{a+b})e^a}{(1+e^{a+b})(1+e^a)} = \frac{e^a(e^b - 1)}{(1+e^{a+b})(1+e^a)}$$

Introducing $y := e^a$ and cross-multiplying we get:

$$\delta = \frac{y(e^b - 1)}{(1+e^b)(1+y)} \iff \delta(1+e^b)(1+y) = y(e^b - 1) = \delta + \delta(1+e^b)y + \delta e^b y^2 = y(e^b - 1) \iff \delta e^b y^2 + (\delta(1+e^b) - e^b + 1) y + \delta = 0$$

Depending on the values of $\delta$ and $b$ this quadratic equation in $y$ has 0, 1 or 2 real-valued solutions, yielding 0, 1 or 2 real-valued solutions for $a = \log y = \beta_0$. This implies that there exists utmost one alternative solution $\beta^*_0 \neq \beta^*_0$ such that CATE($\beta_0 = \beta^*_0, \beta_{t_x} = \beta^*_x$) = CATE($\beta_0 = \beta^*_0, \beta_{t_x} = \beta^*_x$).

In fact, we can explicitly compute this alternative solution by exploiting the symmetry of the sigmoid function: $\sigma(x) = 1 - \sigma(-x)$. Whenever it is true that:

$$\sigma(\beta^*_0 + \beta^*_x) - \sigma(\beta^*_0) = \delta$$

It must simultaneously be true that, writing $\beta'_0 := -(\beta^*_0 + \beta^*_x)$:

$$\sigma(\beta'_0 + \beta^*_x) = \sigma(\beta'_0) = \sigma(-\beta^*_0 + \beta^*_x) = \sigma(-\beta'_0 + \beta^*_x) = (1 - \sigma(\beta'_0)) = \sigma(\beta'_0 + \beta^*_x) - \sigma(\beta'_0) = \delta$$

This means that except in the trivial case when $\beta'_0 = \beta^*_x = 0$ there always exists a second solution $\beta'_0$ that has the same CATE $\delta$ but a different interventional distribution $p(y|do(t_x))$. We can check whether this coincidentally coincides with the maximum likelihood solution for $\beta_0$ in the offset model on the observational data by plugging in $\beta'_0 := -(\beta^* + \beta^*_x)$ in the expression of the gradient of the likelihood (Equation $13$). Again we remove terms that cancel out and substitute back $p_{t_x,u'} = p(t_x = t_x' | u = u')p(u = u')$ to arrive at:
\[
\frac{\partial L}{\partial \beta_0} (\beta_0 = \beta_0') = p_u (1 - p_u) (p(t_x = 0|u = 1) - p(t_x = 0|u = 0)) \left( (\pi_{10} - \pi_{11}) + (\pi_{01} - \pi_{00}) \right)
\]

\[+ p_u ((\pi_{11} - \pi_{10}) + (\pi_{01} - \pi_{00})) \]  

\[+ 2\pi_{10} + \pi_{11} - 1 \]  

(14)

(15)

(16)

Analyzing this expression line-by-line we see that the first two lines are non-zero in general when there is confounding such that \( p(t_x = 0|u = 1) \neq p(t_x = 0|u = 0) \) and \( \pi_{t_x1} \neq \pi_{t_x0} \). The last line is also non-zero in general as \( \pi_{t_xu} \) are free parameters.

### A.2 Non-Collapsibility

Here we provide an example and intuition on what non-collapsibility of the odds-ratio is and why it increases when the association between \( x \) and \( y \) becomes greater. Consider the following data-generating mechanism for binary \( x \) with \( p(x = 1) = 0.5 \), binary treatment \( t_x \), and outcome mechanism \( p(y = 1|do(t_x), x) = \sigma(\beta_0(x) + t_x) \), so that the conditional odds-ratio \( e^1 \approx 2.72 \) is constant. As we will see, depending on how \( \beta_0 \) depends on \( x \), the marginal log odds-ratio \( \gamma_{t_x} \) will vary. For two settings of \( \beta_0(x) \) we calculate the resulting marginal odds-ratio \( \gamma_{t_x} \) in a few simple steps. The calculations are visualized in Figure 5.

Let \( \pi_{t_x}(x) = p(y = 1|do(t_x), x) \):

\[
\pi_0(0) = \sigma(\beta_0(x = 0)) \\
\pi_0(1) = \sigma(\beta_0(x = 1)) \\
\pi_1(0) = \sigma(\beta_0(x = 0) + 1) \\
\pi_1(1) = \sigma(\beta_0(x = 1) + 1) \\
\eta_0 = \sigma^{-1}(\pi_0) \\
\eta_1 = \sigma^{-1}(\pi_1) \\
\gamma_{t_x} = \eta_1 - \eta_0
\]

This leads to the following numerical results in Table 1 where we see that \( \beta_{t_x} > \gamma_{t_x} > 0 \) and \( \gamma_{t_x} \to 0 \) when the difference between \( \pi_0(0), \pi_0(1) \) becomes bigger, despite \( \beta_{t_x} = 1 \) remaining constant.
Figure 5: Illustration of non-collapsibility. For fixed $p(x = 1) = 0.5$ and $\beta_1 = 1.0$, the marginal log odds-ratio $\gamma_{\ell_x}$ of treatment becomes closer to 0 when the difference in the untreated risks $\pi_0(0), \pi_0(1)$ becomes larger.
A.3 Additional Experiments

Extending the experiments in 3.2, we investigate the situation where x and u are correlated. Specifically, \( p(x,u) = p(u|x)p(x) \) with \( p(u|x = 0) = 1 - p(u|x = 1) = \alpha \) and \( \alpha \in [0.1,0.3,0.5,0.7,0.9] \), \( p(x) = 0.5 \). As seen in Figure 6 whereas the PEHE for the marginal offset model increases with \( \hat{\beta}_x \), the constrained offset model remains relatively unbiased in a wide range of settings. Again, the PEHE of the constrained offset model is always better than the fully observational baseline. In the areas with very high confounding (\( \beta_u \rightarrow y \geq \log(5) \)) and strong negative correlation between u and x (\( \alpha \geq 0.7 \)) there are some settings where the constrained offset models perform worse than the ATE-baseline. As x and u both increase the probability of y but x and u are anti-correlated in these settings, we get close to the situation that \( p(y|\text{do}(t_x), x = 0) \approx p(y|\text{do}(t_x), x = 1) \). This means that in these cases, the ATE-baseline has low PEHE as there is no actual difference in baseline risk depending on x. Whether this situation is relevant in actual applications will depend on the available background knowledge. The implication would be that the entire population under study would have the same outcome probability if they were included in a RCT and were assigned to the control arm. This total lack of variation in baseline risk may be deemed implausible in many concrete applications. Outside of these settings, the constrained offset models have better PEHE than the ATE-baseline whenever \( \hat{\beta}_x \neq 1 \).

| setting | \( x \) | \( \eta_0(x) \) | \( \eta_1(x) \) | \( \beta_{tx} \) | \( \pi_0(x) \) | \( \pi_1(x) \) | \( \pi_0 \) | \( \pi_1 \) | \( \eta_0 \) | \( \eta_1 \) | \( \gamma_{tx} \) |
|---------|------|----------------|----------------|--------------|-------------|-------------|--------|--------|--------|--------|--------|
| a       | 0    | -1.5           | -0.5           | 1            | 0.182       | 0.378       | 0.402  | 0.598  | -0.395 | 0.395  | 0.791  |
|         | 1    | 0.5            | 1.5            | 1            | 0.622       | 0.818       |         |         |         |         |         |
| b       | 0    | -3.5           | -2.5           | 1            | 0.029       | 0.076       | 0.477  | 0.523  | -0.093 | 0.093  | 0.186  |
|         | 1    | 2.5            | 3.5            | 1            | 0.924       | 0.971       |         |         |         |         |         |

Table 1
Figure 6: PEHEs for different offset models, indexed by $\text{OR}_{ut} = \text{OR}_{uy}$, the odds-ratios from confounder $u$ to treatment $t_x$ and outcome $y$ respectively, and $p(u|x=0) = 1 - p(u|x=1)$. The fully observational baseline is sometimes not visible because the PEHE is higher than the maximum value on the y-axis.