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Covariate Adjustment for Logistic Regression Analysis of Binary Clinical Trial Data

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Abstract

In linear regression models covariate adjusted analysis is not expected to change the estimates of the treatment effect in the clinical trials with randomized treatment assignment but rather to increase the precision of the estimates. However, the covariate adjusted treatment effect estimates are generally not equivalent to the unadjusted estimates in logistic regression analysis for binary clinical trial data. In this paper we report the results of a simulation study conducted to quantify the magnitude of difference between the estimands underlying the two estimators in logistic regression. The simulation results demonstrated that both unadjusted and adjusted analyses preserved type I error at the nominal level. The covariate adjusted analysis produced unbiased, larger treatment effect estimates, larger standard error, and increased power compared with the unadjusted analysis when the sample size was large. The unadjusted analysis resulted in biased estimates of treatment effect. Analysis results for five phase 3 diabetes trials of the same compound were consistent with the simulation findings. Therefore, covariate adjusted analysis is recommended for evaluating binary outcomes in clinical data.

Key Words

Biased estimates ; Type I error; Power; Estimands

1. Introduction

Binary outcomes are commonly assessed in clinical trials to compare treatment groups. For example, in neuroscience trials, a binary outcome of whether a 50% or greater decrease in scores on the Young Mania Rating Scale from baseline to any evaluation during the treatment (Yong et al. 1978; and Lipkovich et al. 2005) is often evaluated. In diabetes trials, a clinically meaningful outcome is whether glycated haemoglobin (HbA1c) reaches the target of < 7.0 (ADA 2013; Jiang et al. 2015a; and Jiang et al. 2015b); another important safety outcome is whether the patient experiences hypoglycemia (low blood glucose) during the study (Holman et al. 2007). In oncology trials, medically relevant beneficial changes are often associated with experiencing a 30% or greater decline in tumor size (Eisenhauer et al. 2009). Common estimates of treatment effect include the risk difference (RD), relative risk (RR), and odds ratio (OR) in the analysis of binary data. Generalized linear models (GLM) with an identity or log link function are often used for estimation of RD or RR, respectively. However, these two methods may result in estimated probabilities outside of $[0, 1]$ interval, and the log binomial model (for RR) often experiences convergence issues (Blizzard and Hosmer 2006; and Deddens and Peterson 2008). As a result, logistic regression using GLM with a logit link for estimation of OR remains more popular for analysis of binary data in clinical trials (Agresti and Hartzel 2000).

In clinical trials, treatment effect can be estimated either as a covariate adjusted effect or as an unadjusted effect. When modeling the relationship between the outcome and treatment variable using a non-linear link, the estimands underlying the two estimators are different despite the fact that treatment is assigned independently of covariates. The unadjusted estimate is marginal or

population-averaged, whereas the adjusted estimate is conditional on subject-specific characteristics included in the model. It is of interest to quantify the magnitude of the difference between the two estimands for binary data analysis with logistic regression.

In randomized clinical trials, baseline covariates are not expected to be correlated with treatment assignment. Therefore, in linear regression models covariate adjustment is not expected to change estimates of the treatment effect, but rather to increase the precision of the estimate.

However, this is not the case for nonlinear regression models (Gail et al. 1984; Hauck et al. 1991; Canner 1991; Robinson and Jewell 1991; Hauck et al. 1998; Kernan et al. 1999; Steyerberg et al. 2000; Raab et al. 2000; Pocock et al. 2002; Ford and Norrie 2002; Hernandez et al. 2004)

The covariate adjusted treatment effect estimates are generally not equivalent to the unadjusted treatment effect estimates in logistic regression models (Gail et al. 1984). Robinson and Jewell (1991) and Begg and Lagakos (1993) showed that adjustment for prognostic covariates always results in an increase in the standard error as well as the treatment effect estimate compared to the unadjusted analysis. However, the efficiency with adjustment for covariates is at least as high as without adjustment.

Hernandez et al. (2004) and Nicholas et al. (2015) conducted simulation studies to compare logistic regression analyses with or without adjustment for one dichotomous covariate. Hernandez et al. (2004) showed that covariate adjusted analysis increased power to detect the treatment effect without inflation of type I error. Nicholas et al. (2015) showed that in both superiority and noninferiority settings, unadjusted analysis resulted in biased treatment effect estimates and deflated standard errors, and decreased power and nominal or conservative type I error in the

context of superiority. They did not study the effect of covariate adjustment with continuous covariates.

Jiang et al. (2015a, 2015b) conducted simulation studies to compare different methods for analysis of repeated binary data with or without adjustment for one continuous covariate. They showed that adjusted analyses were associated with larger estimates of treatment effect, larger standard errors, and increased power without inflation of the type I error. However, they did not evaluate the bias due to the nature of data generation. Ciolino et al (2013) evaluated the effect of adjusting one continuous covariate in the analysis of binary outcome. But they focused on the estimates of relative risk, not odds ratio.

To fix ideas, consider a simple adjusted model where the binary clinical outcome depends on treatment (T) and a single covariate (X) through the inverse logit link:

$$P(Y = 1|X, T) = 1/[1 + \exp(-\beta_0 - \beta_1 T - \beta_2 X)] \quad (1)$$

Then, our covariate-adjusted treatment effect (estimand) is simply defined by the model parameter β_1 . This is because $\beta_1 = \log \left(\frac{P(Y=1|X,T=1)}{1-P(Y=1|X,T=1)} \frac{1-P(Y=1|X,T=0)}{P(Y=1|X,T=0)} \right)$, regardless of the marginal distribution of covariate X, assuming that model (1) is correctly specified.

Now we define an unadjusted estimate as $\tilde{\beta}_1 = \log \left(\frac{P(Y=1|T=1)}{1-P(Y=1|T=1)} \frac{1-P(Y=1|T=0)}{P(Y=1|T=0)} \right)$, where the probabilities have to be computed under model (1). Therefore the marginal probability of response can be obtained by integration:

$$P(Y = 1|T = 1) = \int P(Y = 1|X = x, T = 1)f(x)dx.$$

As a result, the unadjusted treatment effect $\tilde{\beta}_1$ expected in a given population of patients will depend on the distribution of covariate X in that population.

Our algebra shows the relationship between the model formulation conditional on X on the one hand and marginal over X on the other (see the appendix), for a number of scenarios. First, when a probit rather than a logit link is assumed and X is assumed standard normally distributed, then the model marginal over X is of a probit nature as well, but with attenuation of the other two regression coefficients, by the amount $\sqrt{\beta_2^2 + 1}$. Second, a similar result is found for a logit link and X following the bridge distribution proposed by Wang and Louis (2003, 2004). The attenuation factor then is $\sqrt{1 + \frac{3}{\pi^2}\beta_2^2}$. It is important to see that, in both cases, there is no shift, merely attenuation. Also, the attenuation effect depends solely on the β_2^2 , and hence is independent of its sign. Calculations were done with the bridge rather than the normal distribution, because a logit link and a normally distributed X does not allow for a closed-form solution. Third, when X is uniform over an interval $[-k/2, k/2]$, then the marginalized model allows for a closed form, but is no longer of a logistic type. Also here, though, dependence is on $|\beta_2|$ only, not on its sign.

Fourth, when X follows a uniform on the unit interval, then the sign of β_2 does have an impact, a result of asymmetry around zero.

The above considerations are useful as well to get some intuition as to what an unmeasured or unknown confounder X brings to the model. In such a case, one would be fitting the marginal model, even though ideally the model including X should be fitted, but unfortunately that is impossible. The general finding is that the treatment effect will be attenuated for symmetric

unmeasured X's, with additional implications in the asymmetric case. The algebra shows that the precise nature of the impact depends on the distribution of X. For a general treatment of unmeasured confounding, see Vander Weele and Arah (2011).

The above discussion provides us with the rationale for preferring the covariate-adjusted estimand over the unadjusted one: the former provides an assessment of treatment effect that does not depend on the distribution of the covariate in a particular population (as long as the logistic model is correctly specified), whereas the latter will need to be recomputed each time a population with somewhat different covariate distribution is considered. However under some circumstances, an unadjusted analysis can be preferred by the study team. What we emphasize, however, is that choosing an estimand always needs to be well-motivated.

In this paper, we will examine the impact of adjusting for a continuous covariate in the analysis of the binary outcomes with logistic regression model for the estimation of odds ratio, focusing on evaluation of bias, power, and type I error through simulations. When evaluating bias we assume that the estimand of interest is the covariate-adjusted treatment effect and we expect to see some “bias” under unadjusted analyses. Therefore, we conducted extensive simulations to quantify the difference between the two estimators under various conditions. Simulation settings are described in Section 2, and simulation results are presented in Section 3. In Section 4, application to clinical trial data is illustrated. Section 5 concludes with a discussion.

2. Simulation settings

Simulation studies were conducted using SAS® statistical software (SAS 2008) for a clinical trial with two treatment groups and equal allocation, one baseline continuous covariate, and a

binary outcome. In the simulated trial, we assumed either (a) no treatment effect on outcome to evaluate the type I error, or (b) a certain level of treatment effect to evaluate power. We focused on the sample sizes of 50 and 300 per treatment group to mimic phase 2 and phase 3 trial settings, respectively. For each simulation setting, 10,000 data sets were generated. The simulation involved the following steps:

- 1) Simulate a continuous covariate, X , from a normal distribution, $X \sim N(30, 15^2)$.
- 2) Assign X value to one of the two treatment groups and ensure an equal sample size across treatment groups (N).
- 3) Simulate a response, Y (0, 1), based on the probability P with the following underlying assumed relationship between P , X , and treatment assignment, T :

$$P(Y = 1|X, T) = 1/[1 + \exp(-\beta_0 - \beta_1 T - \beta_2 X)]$$

Where β_1 is the treatment effect, β_2 is the covariate effect, $T = 0$ for assignment to comparator and $T = 1$ for assignment to active treatment.

- 4) Repeat step 1-3 $2N$ times to simulate a trial with a sample size of N per treatment group.
- 5) Fit a logistic regression model to the simulated data with or without adjusting for the continuous covariate, capturing the treatment effect estimates, standard errors, and p values associated with treatment effect.
- 6) Repeat step 1-5 10,000 times.

The performance of the covariate adjusted and unadjusted analyses was evaluated based on bias ($\hat{\beta}_1 - \beta_1$) in scenarios when there was no difference between treatments, and bias and relative bias ($\frac{\hat{\beta}_1 - \beta_1}{\beta_1} \times 100$) in scenarios where treatments differed. Analyses were also compared based on 95% confidence interval (CI) coverage (using normal theory approximation), standard errors (SE) (average of SEs from the 10,000 simulations), mean squared error (MSE), type I error rate for scenarios with no difference between treatments, and power for scenarios where treatments differed. $\hat{\beta}_1$ is the estimate of log odds ratio for unadjusted or adjusted analysis. β_1 is the true log odds ratio.

3. Simulation Results

Table 1 presents simulation results from 10,000 data sets with no treatment effect (i.e. $\beta_1=0$), with or without a covariate effect (β_2) for different sample sizes. In all cases except when $N=50$ for each treatment group, both the covariate adjusted and unadjusted analyses provided essentially unbiased treatment effect estimates and preserved the type I error close to the nominal level. Both the adjusted and unadjusted analyses were associated with moderate bias when $N=50$. When there was no covariate effect, both the adjusted and unadjusted analyses produced almost identical treatment effect estimate, SE, MSE, 95% CI coverage, and type I error rate. When there was a covariate effect, the adjusted analysis was associated with greater SE and MSE. However, other parameters were similar to those of the unadjusted analysis.

Table 2 shows simulation results from 10,000 data sets with a certain level of treatment effect ($\beta_1=0.7$), with or without a covariate effect for different sample sizes. When there was no

covariate effect, both the adjusted and unadjusted analyses produced almost identical treatment effect estimates, SE, MSE, 95% CI coverage, and power, with essentially unbiased estimates (except for when $N=50$ both analyses were associated with moderate relative bias around 8%). When there was a covariate effect, adjusted analysis still produced essentially unbiased estimates (except for when $N=50$ with moderate relative bias around 9%), and close to nominal CI coverage. However, the unadjusted analysis was associated with biased treatment effect estimates (relative bias ranging from 20-24%) which were smaller than the true value, and resulted in smaller than nominal CI coverage. SEs from the unadjusted analysis were smaller than those from adjusted analysis. Despite smaller standard errors, unadjusted analyses resulted in reduced power (by up to 12% compared to covariate-adjusted) due to negatively biased estimates of treatment effect. MSEs were similar from both analyses.

Simulation results for scenarios with different levels of treatment effect (β_1 assuming values from 0.3 to 1.0) are presented in Table 3 and 4. Table 3 shows results for positive covariate effect (i.e. with the same sign as treatment effect), whereas Table 4 – for scenarios with negative covariate effect. In the presence of a covariate effect (regardless of the sign), an unadjusted analysis was associated with biased estimates and poor 95% CI coverage: the larger the treatment effect, the greater the bias and smaller than nominal coverage level. However, the relative biases were relatively stable with the same covariate effect regardless of the level of the treatment effect and sample size. The SEs were consistently smaller with the unadjusted analysis compared to the adjusted analysis. The adjusted analysis produced unbiased estimates when the sample size was large ($N=300$), and moderately biased estimates when the sample size was small (relative bias about 10%, $N=50$). The 95% CI coverage was at nominal level with the adjusted analysis

regardless of the sample size and treatment effect. The adjusted analysis was associated with significantly increased power compared to the unadjusted analysis (up to 29% absolute difference). MSEs were larger with the adjusted analysis when the sample size was small (N=50 per arm) and smaller when the sample size was large (N=300 per arm) compared to the unadjusted analysis.

Simulation results summarizing the performance of unadjusted vs adjusted analyses for scenarios with different levels of covariate effect are displayed in Table 5. The unadjusted analysis was associated with biased estimates and poor 95% CI coverage: the larger the covariate effect, the greater the bias, relative bias, and smaller than nominal level of the CI coverage. The adjusted analysis produced unbiased estimates when the sample size was large, and moderately biased estimates when the sample size was small, greater power, but larger SE compared with unadjusted analysis. In general, the adjusted analysis was associated with larger MSEs when the sample size was small and smaller MSEs when the sample size was large.

Power comparisons for scenarios with a certain (positive) level of covariate effect and different levels of treatment effect and sample size are shown in Figure 1. Significantly increased power was associated with the adjusted analysis compared to the unadjusted analysis.

We also conducted additional simulations generating data with two covariates: one that is prognostic and one that is not using the following formula:

$$P(Y = 1|X, T, Z) = 1/[1 + \exp(-\beta_0 - \beta_1 T - \beta_2 X - \beta_3 Z)]$$

where X, Y, T, and P were the same as described before, Z was a non-prognostic covariate with a normal distribution, $Z \sim N(20, 10^2)$. Then, we compared a model that adjusts for only the

prognostic covariate with a model that adjusts for only the non-prognostic covariate (Table 6).

The difference between the analysis of adjusting for the prognostic covariate and the unadjusted analysis was consistent with previous results. Adjusting for the non-prognostic covariate yielded almost identical results as the unadjusted analysis.

4. Clinical Trial Examples

Covariate adjusted and unadjusted analyses were applied to data from five diabetes clinical trials in which an experimental drug (treatment) was compared with different active controls over 52 weeks. The analyses were focused on percentage of patients whose 52- week endpoint HbA1c was less than 7.0%. Data from all those who withdrew were removed from the analysis. Results of treatment comparisons for different analyses are presented in Table 7 and Figure 2. Covariate adjusted analysis produced larger treatment effects compared to unadjusted analysis with larger standard errors and smaller p-values in all studies except for study 4, where adjusted and unadjusted analyses produced comparable treatment effects and standard errors. The reason for that is that the treatment group had slightly lower baseline HbA1c values (compared to the control group) in study 4 and slightly higher values in all other studies. The differences (treatment-comparator) in baseline HbA1c were 0.03%, 0.09%, 0.05%, -0.05%, 0.12% for study 1 to 5, respectively.

5. Discussion

The simulation results demonstrated that, when the sample size was large and regardless of positive or negative covariate effect, the covariate adjusted analysis produced unbiased, larger treatment effect estimates, larger standard error, and increased power compared with the

unadjusted analysis without inflation of type I error in the analysis of binary data. The unadjusted analysis was associated with biased estimates: the larger the treatment effect, the larger the bias; the larger the covariate effect, the larger the bias. When there was no covariate effect, the adjusted analysis produced almost identical estimates of treatment effect, standard errors, mean squared error, and power as the unadjusted analysis. Therefore, according to International Conference on Harmonization guidelines (Lewis 1999), the covariate adjustment analysis can be pre-specified in the statistical analysis plan, though we may not be quite sure about the level of the covariate effect on the outcome at the design stage. Even if there is no covariate effect, adjusting for the covariate will not have much detrimental effect on estimating treatment effect. However, if there is a covariate effect (regardless of whether it is positive or negative), the benefit of adjusting the covariate is obvious.

Analysis results for binary data with a small sample size should be interpreted with caution. The simulations results demonstrated that even the covariate adjusted analysis could be associated with moderately biased estimates.

The unadjusted analysis is a marginal or population averaged analysis without consideration of heterogeneity among patients, whereas the adjusted analysis is a population-averaged analysis that is conditional on specific subject characteristics (and in this sense is a step towards subject-specific analysis). The adjusted analysis is recommended due to the more individualized, unbiased treatment effect estimates corrected for covariate imbalance, resulting in gain in power, and reduction in effective sample size (Pocock 2002).

Simulations are always limited to the cases considered in the study. We only considered the case of adjusting for one continuous, normally-distributed variable. When adjusting for more than one covariate, the same conclusion for treatment estimates, SE, and power would be expected. A loss of efficiency may occur if adjustment is made for a large number of uncorrelated covariates. To determine how many of such unnecessary covariates can be included in a logistic regression model before performance begins to suffer could be a future research topic.

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Appendix: The marginal probability of response for the unadjusted analysis

1): Using probit link and X with standard normal distribution:

$$\begin{aligned}
 & \int \Phi(\beta_0 + \beta_1 T + \beta_2 x) \frac{1}{\sqrt{2\pi}} \exp\left(-\frac{x^2}{2}\right) dx \\
 &= \frac{1}{2\pi} \int_{x=-\infty}^{+\infty} dx \int_{t=-\infty}^{t=\eta+\beta_2 x} \exp\left(-\frac{t^2 + x^2}{2}\right) dt, \quad \text{where } \eta = \beta_0 + \beta_1 T \\
 &= \frac{1}{2\pi} \int_{s=-\infty}^0 ds \int_{x=-\infty}^{+\infty} \exp\left(-\frac{(s + \eta + \beta_2 x)^2 + x^2}{2}\right) dx, \quad \text{where } t - \eta - \beta_2 x = s \\
 &= \frac{1}{2\pi} \int_{s=-\infty}^0 ds \int_{x=-\infty}^{+\infty} \exp\left[-\frac{(s + \eta)^2}{2(\beta_2^2 + 1)}\right] \exp\left\{-\frac{1}{2}\left[x\sqrt{\beta_2^2 + 1} + \frac{(s + \eta)\beta_2}{\sqrt{\beta_2^2 + 1}}\right]^2\right\} dx, \\
 &= \frac{1}{\sqrt{2\pi}} \int_{s=-\infty}^0 \exp\left[-\frac{(s + \eta)^2}{2(\beta_2^2 + 1)}\right] ds \frac{1}{\sqrt{2\pi}} \int_{x=-\infty}^{+\infty} \exp\left\{-\frac{1}{2}\left[x\sqrt{\beta_2^2 + 1} + \frac{(s + \eta)\beta_2}{\sqrt{\beta_2^2 + 1}}\right]^2\right\} dx
 \end{aligned}$$

while,

$$(s + \eta)^2 + 2(s + \eta)\beta_2 x + (\beta_2^2 + 1)x^2 = \left[x\sqrt{\beta_2^2 + 1} + \frac{(s + \eta)\beta_2}{\sqrt{\beta_2^2 + 1}}\right]^2 + \frac{(s + \eta)^2}{\beta_2^2 + 1}$$

Then

$$\frac{1}{\sqrt{2\pi}} \int_{x=-\infty}^{+\infty} \exp \left\{ -\frac{1}{2} \left[x \sqrt{\beta_2^2 + 1} + \frac{(s + \eta)\beta_2}{\sqrt{\beta_2^2 + 1}} \right]^2 \right\} dx = \frac{1}{\sqrt{\beta_2^2 + 1}}$$

And

$$\begin{aligned} & \frac{1}{\sqrt{2\pi}} \int_{s=-\infty}^0 \exp \left[-\frac{(s + \eta)^2}{2(\beta_2^2 + 1)} \right] ds \\ &= \sqrt{\beta_2^2 + 1} \frac{1}{\sqrt{2\pi}} \int_{v=-\infty}^{v=-\frac{\eta}{\sqrt{\beta_2^2 + 1}}} \exp \left(-\frac{v^2}{2} \right) dv \\ &= \sqrt{\beta_2^2 + 1} \Phi \left(\frac{\eta}{\sqrt{\beta_2^2 + 1}} \right) \end{aligned}$$

Where,

$$v = \frac{s + \eta}{\sqrt{\beta_2^2 + 1}}, \quad ds = \sqrt{\beta_2^2 + 1} dv$$

Hence,

$$\int \Phi(\beta_0 + \beta_1 T + \beta_2 x) \frac{1}{\sqrt{2\pi}} \exp \left(-\frac{x^2}{2} \right) dx$$

$$= \Phi\left(\frac{\beta_0 + \beta_1 T}{\sqrt{\beta_2^2 + 1}}\right) \text{ (known results)}$$

2): Using logit link and X with bridge distribution (Wang and Louis 2003, 2004)

$$\int \frac{\exp(\beta_0 + \beta_1 T + \beta_2 x)}{1 + \exp(\beta_0 + \beta_1 T + \beta_2 x)} f(\beta_2 x) d(\beta_2 x)$$

$$= \frac{\exp \phi(\beta_0 + \beta_1 T)}{1 + \exp \phi(\beta_0 + \beta_1 T)}$$

Where,

$$f(\beta_2 x) = \frac{1}{2\pi} \cdot \frac{1}{2\pi \cosh(\phi \beta_2 x) + \cos(\phi \pi)}$$

$$\phi = \frac{1}{\sqrt{1 + \frac{3}{\pi^2} \beta_2^2}}$$

Again the sign of β_2 is not important.

3): Using logit link and X with uniform $[-\frac{k}{2}, \frac{k}{2}]$:

$$\int \frac{\exp(\beta_0 + \beta_1 T + \beta_2 x)}{1 + \exp(\beta_0 + \beta_1 T + \beta_2 x)} f(x) dx$$

$$= \frac{1}{k} \int_{-k/2}^{k/2} \frac{\exp(\beta_0 + \beta_1 T + \beta_2 x)}{1 + \exp(\beta_0 + \beta_1 T + \beta_2 x)} dx$$

$$= \frac{1}{k} \cdot \frac{1}{\beta_2} \ln \left[\frac{1 + \exp\left(\beta_0 + \beta_1 T + \beta_2 \frac{k}{2}\right)}{1 + \exp\left(\beta_0 + \beta_1 T - \beta_2 \frac{k}{2}\right)} \right]$$

This one is also symmetric in β_2 .

Replace β_2 by $-\beta_2$,

$$\begin{aligned} & \frac{1}{k} \cdot \frac{1}{-\beta_2} \ln \left[\frac{1 + \exp\left(\beta_0 + \beta_1 T - \beta_2 \frac{k}{2}\right)}{1 + \exp\left(\beta_0 + \beta_1 T + \beta_2 \frac{k}{2}\right)} \right] \\ &= \frac{1}{k} \cdot \frac{1}{-\beta_2} \left\{ -\ln \left[\frac{1 + \exp\left(\beta_0 + \beta_1 T + \beta_2 \frac{k}{2}\right)}{1 + \exp\left(\beta_0 + \beta_1 T - \beta_2 \frac{k}{2}\right)} \right] \right\} \end{aligned}$$

=original expression

4): Using logit link and X with uniform [0, 1]:

$$\begin{aligned} & \int \frac{\exp(\beta_0 + \beta_1 T + \beta_2 x)}{1 + \exp(\beta_0 + \beta_1 T + \beta_2 x)} f(x) dx \\ &= \int_0^1 \frac{\exp(\beta_0 + \beta_1 T + \beta_2 x)}{1 + \exp(\beta_0 + \beta_1 T + \beta_2 x)} dx \\ &= \frac{1}{\beta_2} \ln[1 + \exp(\beta_0 + \beta_1 T + \beta_2 x)] \Big|_0^1 \end{aligned}$$

$$= \frac{1}{\beta_2} \ln \left[\frac{1 + \exp(\beta_0 + \beta_1 T + \beta_2)}{1 + \exp(\beta_0 + \beta_1 T)} \right]$$

Table 1: Summary of analysis results from 10,000 simulations with $\beta_0=-2$, $\beta_1=0$, and with/without a covariate effect (Type I error rate comparison) with incidence rate of 75%/12% for each arm.

N	β_2	Unadjusted Logistic						Adjusted Logistic					
		$\hat{\beta}_1$	Bias	SE	MSE	Cov (%)	Rej. rate (%)	$\hat{\beta}_1$	Bias	SE	MSE	Cov (%)	Rej. rate (%)
50	0	0.06	0.06	0.66	0.44	96	3.5	0.06	0.06	0.67	0.45	97	3.5
100	0	0.00	0.00	0.45	0.20	96	4.3	0.00	0.00	0.45	0.21	95	4.6
150	0	0.00	0.00	0.36	0.13	96	4.4	0.00	0.00	0.37	0.13	96	4.5
200	0	0.00	0.00	0.31	0.10	95	5.0	0.00	0.00	0.31	0.10	95	4.8
250	0	0.00	0.00	0.28	0.08	95	4.7	0.00	0.00	0.28	0.08	95	4.7
300	0	0.00	0.00	0.25	0.06	95	4.9	0.00	0.00	0.25	0.06	95	4.9
50	0.12	-	-	-	-	-	-	-	-	-	-	-	-
		-0.12	0.12	0.71	0.52	97	3.4	0.09	0.09	0.88	0.78	96	4.1
100	0.12	0.00	0.00	0.48	0.23	96	4.1	0.00	0.00	0.58	0.34	95	4.8
150	0.12	0.00	0.00	0.39	0.15	95	4.8	0.00	0.00	0.46	0.22	95	5.3
200	0.12	0.00	0.00	0.33	0.11	95	5.0	0.00	0.00	0.40	0.16	95	5.1
250	0.12	-	-	-	-	-	-	-	-	-	-	-	-
		0.00	0.00	0.30	0.09	95	5.3	0.01	0.01	0.35	0.13	95	5.1
300	0.12	0.00	0.00	0.27	0.07	95	4.5	0.00	0.00	0.32	0.10	95	4.7

Cov: coverage of 95% CI; Rej. rate: rejection rate; β_0 : intercept; β_1 : treatment effect; β_2 :

covariate effect.

Table 2: Summary of analysis results from 10,000 simulations with $\beta_0 = -2$, $\beta_1 = 0.7$, and with/without a covariate effect with incidence rate of 75%/12% for one arm, and 84%/21% for the other arm.

N	β_2	Unadjusted Logistic							Adjusted Logistic						
		$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Power (%)	$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Power (%)
50	0	0.75	0.05	7.6	0.59	0.35	96	22.6	0.76	0.06	8.8	0.60	0.36	96	22.8
100	0	0.72	0.02	3.2	0.40	0.16	95	43.1	0.73	0.03	3.8	0.41	0.17	95	43.3
150	0	0.72	0.02	2.5	0.33	0.11	95	59.9	0.72	0.02	2.8	0.33	0.11	95	59.9
200	0	0.71	0.01	2.0	0.28	0.08	95	72.7	0.72	0.02	2.2	0.28	0.08	95	72.6
250	0	0.71	0.01	0.8	0.25	0.06	95	80.7	0.71	0.01	1.0	0.25	0.06	95	80.9
300	0	0.71	0.01	1.0	0.23	0.05	95	88.5	0.71	0.01	1.2	0.23	0.05	95	88.4
50	0.12	0.56	-0.14	-20.0	0.52	0.29	94	16.6	0.76	0.06	8.9	0.62	0.39	95	21.8
100	0.12	0.55	-0.15	-22.1	0.36	0.16	92	32.2	0.73	0.03	4.4	0.42	0.18	95	40.3
150	0.12	0.54	-0.16	-22.8	0.29	0.11	91	45.4	0.72	0.02	2.9	0.34	0.12	95	56.3
200	0.12	0.53	-0.17	-23.8	0.25	0.09	89	55.1	0.71	0.01	1.1	0.29	0.09	95	67.2
250	0.12	0.53	-0.17	-24.1	0.23	0.08	88	65.5	0.71	0.01	0.9	0.26	0.07	95	77.3
300	0.12	0.53	-0.17	-24.0	0.21	0.07	87	73.7	0.71	0.01	0.8	0.24	0.06	95	84.7

Rel Bias: relative Bias; Cov: coverage of 95% CI; β_0 : intercept; β_1 : treatment effect; β_2 : covariate effect.

Table 3: Summary of analysis results from 10,000 simulations with $\beta_0 = -4$, $\beta_2 = 0.2$ (a positive covariate effect) and different levels of treatment effect with incidence rate of 72% for one arm, and 76% to 82% for the other arm..

N	β_1	Unadjusted Logistic							Adjusted Logistic						
		$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Pow er (%)	$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Pow er (%)
50	0.3	0.16	-0.14	-46	0.47	0.24	94	5.5	0.33	0.03	11	0.68	0.47	96	6.9
	0.4	0.22	-0.18	-45	0.47	0.25	92	6.6	0.44	0.04	10	0.69	0.47	96	8.1
	0.5	0.26	-0.24	-47	0.47	0.28	91	8.2	0.54	0.04	7	0.69	0.48	95	11.0
	0.6	0.33	-0.27	-45	0.48	0.30	90	9.6	0.66	0.06	10	0.70	0.49	95	14.4
	0.7	0.38	-0.32	-45	0.48	0.33	90	11.3	0.77	0.07	9	0.71	0.50	96	16.9
	0.8	0.45	-0.35	-44	0.49	0.36	88	13.7	0.88	0.08	10	0.71	0.52	96	20.5
	0.9	0.52	-0.38	-42	0.49	0.39	86	16.6	1.00	0.10	11	0.72	0.53	95	26.2
	1.0	0.57	-0.43	-43	0.50	0.44	84	19.2	1.10	0.10	10	0.73	0.55	96	30.8
300	0.3	0.16	-0.14	-47	0.19	0.05	88	13.2	0.30	0.00	1	0.26	0.07	95	21.4
	0.4	0.21	-0.19	-48	0.19	0.07	82	20.0	0.40	0.00	1	0.26	0.07	95	33.1
	0.5	0.22	-	-47	0.19	0.07	76	28.9	0.50	0.00	2	0.26	0.07	95	48.5

	5	7	0.2 3		9	9			1	1		6	7		
	0. 6	0.3 2	- 0.2 8	-47	0.1 9	0.1 1	69	38.4	0.6 1	0.0 1	1	0.2 7	0.0 7	95	62.4
	0. 7	0.3 8	- 0.3 2	-46	0.1 9	0.1 4	60	49.6	0.7 1	0.0 1	1	0.2 7	0.0 7	95	75.3
	0. 8	0.4 4	- 0.3 6	-45	0.1 9	0.1 7	53	61.6	0.8 1	0.0 1	2	0.2 7	0.0 7	95	86.0
	0. 9	0.4 9	- 0.4 1	-45	0.2 0	0.2 1	45	70.9	0.9 1	0.0 1	1	0.2 7	0.0 8	95	92.8
	1. 0	0.5 5	- 0.4 5	-45	0.2 0	0.2 4	37	79.9	1.0 1	0.0 1	1	0.2 8	0.0 8	95	96.4

Rel Bias: relative Bias; Cov: coverage of 95% CI; β_0 : intercept; β_1 : treatment effect; β_2 : covariate effect.

Table 4: Summary of analysis results from 10,000 simulations with $\beta_0 = 4$, $\beta_2 = -0.2$ (a negative covariate effect) and different levels of treatment effect with incidence rate of 27% for one arm and 30% to 38% for the other arm..

N	β_1	Unadjusted Logistic							Adjusted Logistic						
		$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Pow er (%)	$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Pow er (%)
50	0.3	0.16	-0.14	-48	0.45	0.22	93	5.8	0.33	0.03	9	0.67	0.45	96	7.0
	0.4	0.21	-0.19	-47	0.45	0.23	92	7.0	0.45	0.05	12	0.67	0.45	96	8.9
	0.5	0.26	-0.24	-48	0.45	0.26	91	8.1	0.55	0.05	9	0.67	0.45	96	11.5
	0.6	0.31	-0.29	-49	0.44	0.28	89	9.9	0.65	0.05	8	0.67	0.45	95	14.6
	0.7	0.35	-0.35	-49	0.44	0.31	87	11.9	0.76	0.06	9	0.67	0.45	96	18.5
	0.8	0.41	-0.39	-49	0.44	0.35	85	14.0	0.86	0.06	7	0.67	0.45	96	22.8
	0.9	0.46	-0.44	-49	0.44	0.39	82	16.6	0.98	0.08	9	0.67	0.46	96	28.6
	1.0	0.51	-0.49	-49	0.44	0.43	78	20.1	1.09	0.09	9	0.68	0.47	95	35.1
300	0.3	0.15	-0.15	-49	0.18	0.05	87	13.7	0.30	0.00	1	0.26	0.07	95	22.2
	0.4	0.20	-0.20	-49	0.18	0.07	80	20.4	0.41	0.01	2	0.26	0.07	95	35.3
	0.5	0.25	-0.25	-50	0.18	0.07	72	28.7	0.51	0.01	1	0.26	0.07	95	50.6

	5	5	0.2		8	9			1	1		6	7		
	0.6	0.3	0.3		0.1	0.1			0.6	0.0		0.2	0.0		
		0	0	-50	8	2	60	39.1	0	0	1	6	7	95	65.8
	0.7	0.3	0.3		0.1	0.1			0.7	0.0		0.2	0.0		
		5	5	-50	8	5	50	50.6	1	1	2	6	7	95	79.8
	0.8	0.4	0.4		0.1	0.1			0.8	0.0		0.2	0.0		
		0	0	-50	8	9	37	61.2	1	1	1	6	7	95	88.7
	0.9	0.4	0.4		0.1	0.2			0.9	0.0		0.2	0.0		
		4	6	-51	8	4	27	71.0	1	1	1	6	7	95	94.7
	1.0	0.4	0.5		0.1	0.2			1.0	0.0		0.2	0.0		
		9	1	-51	8	9	18	81.1	1	1	1	6	7	95	98.2

Rel Bias: relative Bias; Cov: coverage of 95% CI; β_0 : intercept; β_1 : treatment effect; β_2 : covariate effect.

Table 5: Summary of analysis results from 10,000 simulations with $\beta_0 = -4$, $\beta_1 = 0.9$, and different levels of a covariate effect with incidence rate from 7% to 72% for one arm and 14% to 82% for the other arm.

N	β_2	Unadjusted Logistic							Adjusted Logistic						
		$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Pow er (%)	$\hat{\beta}_1$	Bi as	Rel.Bi as (%)	SE	MS E	Cov (%)	Pow er (%)
50	0.04	0.89	-0.01	-1	0.76	0.57	97	16.8	0.94	0.04	4	0.78	0.61	97	17.9
	0.08	0.75	-0.15	-17	0.46	0.23	93	35.4	0.94	0.04	5	0.53	0.28	95	42.7
	0.12	0.61	-0.29	-33	0.41	0.25	88	33.4	0.95	0.05	6	0.53	0.28	95	43.4
	0.16	0.54	-0.36	-40	0.44	0.32	86	21.7	0.97	0.07	7	0.61	0.38	96	34.3
	0.20	0.52	-0.38	-42	0.49	0.39	86	16.6	1.00	0.10	11	0.72	0.53	95	26.2
30	0.04	0.88	-0.02	-2	0.29	0.08	95	88.8	0.92	0.02	2	0.29	0.09	95	89.6
	0.08	0.73	-0.17	-19	0.18	0.06	83	97.7	0.91	0.01	1	0.21	0.04	95	99.3
	0.12	0.59	-0.31	-34	0.17	0.12	55	95.3	0.91	0.01	1	0.21	0.04	95	99.3
	0.16	0.52	-0.38	-42	0.18	0.17	42	84.8	0.91	0.01	1	0.24	0.06	95	97.5
	0.20	0.49	-0.41	-45	0.20	0.21	45	70.9	0.91	0.01	1	0.27	0.08	95	92.8

Rel Bias: relative Bias; Cov: coverage of 95% CI; β_0 : intercept; β_1 : treatment effect; β_2 : covariate effect.

Table 6: Summary of analysis results from 10,000 simulations with $\beta_0 = -4$, $\beta_2 = 0.2$, $\beta_3 = 0$ and different levels of treatment effect with incidence rate of 72% for one arm, and 76% to 82% for the other arm.

		Unadjusted Logistic							Adjusted Logistic (non-prognostic covariate)							Adjusted Logistic (prognostic covariate)						
N	$\hat{\beta}_1$	$\hat{\beta}_1$	Bias	Rel.Bias (%)	SE	MSE	Cov (%)	Power (%)	$\hat{\beta}_1$	Bias	Rel.Bias (%)	SE	MSE	Cov (%)	Power (%)	$\hat{\beta}_1$	Bias	Rel.Bias (%)	SE	MSE	Cov (%)	Power (%)
50	0.3	0.16	-0.1	-48	0.47	0.24	93	5.5	0.16	-0.1	-47	0.47	0.24	94	6.0	0.32	0.2	7	0.47	0.22	96	6.7
	0.4	0.22	-0.1	-45	0.47	0.25	93	6.7	0.22	-0.1	-44	0.48	0.26	93	7.1	0.46	0.2	14	0.48	0.23	95	9.1
	0.5	0.27	-0.1	-46	0.47	0.28	91	7.8	0.27	-0.1	-46	0.48	0.29	92	8.2	0.54	0.2	8	0.48	0.23	96	10.8
	0.6	0.33	-0.1	-45	0.48	0.33	90	9.5	0.33	-0.1	-45	0.49	0.34	91	9.9	0.66	0.2	11	0.49	0.24	96	13.8
	0.7	0.39	-0.1	-44	0.48	0.39	90	11.3	0.39	-0.1	-44	0.49	0.43	93	11.6	0.77	0.2	10	0.49	0.24	96	17.2
	0.8	0.44	-0.1	-45	0.49	0.47	87	13.0	0.44	-0.1	-44	0.49	0.47	88	13.4	0.8	0.2	9	0.49	0.25	96	20.7

		4	3		9				5	3		9				7	7		9			
	0		-		0				0	-		0				0	0		0			
	.9	0	0		.4	0.	8	15	.5	.4	-44	.5	0.	8	16	.9	0		.5	0.	9	25
		0	0	-45	9	1	6	.4	0	0		0	1	6	.1	8	8	9	0	6	6	.5
	1		-		0				0	-		0				1	0		0			
	.0	0	0		.5	0.	8	18	.5	.9	-41	.5	0.	8	19	.1	1		.5	0.	9	30
		0	0	-42	0	3	5	.9	9	1		1	3	5	.2	1	1	11	1	7	5	.9
3	0		-		0				0	-		0				0	0		0			
0	.3	0	0		.1	0.	8	13	.1	.3	-47	.1	0.	8	13	.3	0		.1	0.	9	21
		0	0	-48	9	6	8	.3	6	4		9	6	8	.3	0	0	1	9	4	5	.0
	0		-		0				0	-		0				0	0		0			
	.4	0	0		.1	0.	8	19	.2	.1	-48	.1	0.	8	19	.4	0		.1	0.	9	33
		0	0	-48	9	7	2	.6	1	9		9	7	2	.5	0	0	1	9	4	5	.4
	0		-		0				0	-		0				0	0		0			
	.5	0	0		.1	0.	7	28	.2	.2	-47	.1	0.	7	28	.5	0		.1	0.	9	47
		0	0	-47	9	9	6	.9	7	4		9	9	6	.8	0	0	1	9	4	5	.7
	0		-		0				0	-		0				0	0		0			
	.6	0	0		.1	0.	6	38	.3	.2	-47	.1	0.	6	38	.6	0		.1	0.	9	63
		0	0	-47	9	2	8	.4	2	8		9	2	8	.2	1	1	1	9	4	5	.8
	0		-		0				0	-		0				0	0		0			
	.7	0	0		.1	0.	6	50	.3	.3	-46	.1	0.	6	50	.7	0		.1	0.	9	76
		0	0	-46	9	4	1	.3	8	2		9	4	2	.1	1	1	2	9	4	5	.4
	0		-		0				0	-		0				0	0		0			
	.8	0	0		.1	0.	5	61	.4	.3	-46	.2	0.	5	60	.8	0		.2	0.	9	86
		0	0	-46	9	7	3	.0	3	7		0	7	3	.8	1	1	2	0	4	5	.1
	0	0	-	-46	0	0.	4	70	0	-	-46	0	0.	4	70	0	0	1	0	0.	9	92

	.9	.49	0.41		.20	.21	4	.3	.49	0.41		.20	.21	4	.3	.91	.01		.20	0.4	5	.6
	1.0	0.55	0.45		0.2	0.2	3.7	80.1	0.55	0.45		0.2	0.2	3.8	80.1	1.0	0.55		0.2	0.4	9.5	96.4

Rel Bias: relative Bias; Cov: coverage of 95% CI; β_0 : intercept; β_1 : treatment effect; β_2 :

prognostic covariate effect; β_3 : non-prognostic covariate effect.

Table 7. Analysis results from five diabetes clinical studies.

Study	Unadjusted Logistic					Adjusted Logistic				
	Coef	SE	LL	UL	p value	Coef	SE	LL	UL	p value
1	0.87	0.19	0.48	1.26	<0.001	1.13	0.22	0.68	1.58	<0.001
2	0.93	0.19	0.56	1.31	<0.001	1.22	0.21	0.8	1.65	<0.001
3	0.54	0.2	0.14	0.93	0.006	0.73	0.22	0.28	1.18	0.001
4	0.46	0.19	0.09	0.83	0.013	0.48	0.19	0.09	0.87	0.013
5	1.05	0.19	0.68	1.42	<0.001	1.4	0.21	0.98	1.83	<0.001

Coef: log odds ratio; LL: lower limit of 95% confidence interval; UL: upper limit of 95%

confidence interval.

(a)

(b)

Figure 1: Power comparison from 10,000 simulations with (a) $\beta_0=-4$, $\beta_2=0.2$, $N=300$ per arm, and different levels of treatment effect with incidence rate of 72% for one arm, and 76% to 82% for the other arm; (b) $\beta_0=-4$, $\beta_1=0.7$, $\beta_2=0.2$, and different sample sizes with incidence rate of 72% for one arm and 80% for the other arm.

Figure 2. Log odds ratio and 95% CI by study.