Causal inference in paired two-arm experimental studies under non-compliance with application to prognosis of myocardial infarction

Francesco Bartolucci* Alessio Farcomeni†

Abstract

Motivated by a study about prompt coronary angiography in myocardial infarction, we propose a method to estimate the causal effect of a treatment in two-arm experimental studies with possible non-compliance in both treatment and control arms. The method is based on a causal model for repeated binary outcomes (before and after the treatment), which includes individual covariates and latent variables for the unobserved heterogeneity between subjects. Moreover, given the type of non-compliance, the model assumes the existence of three subpopulations of subjects: *compliers*, *never-takers*, and *always-takers*. The model is estimated by a two-step estimator: at the first step the probability that a subject belongs to one of the three subpopulations is estimated on the basis of the available covariates; at the second step the causal effects are estimated through a conditional logistic method, the implementation of which depends on the results from the first step. The estimator is approximately consistent and, under certain circumstances, exactly consistent. We provide evidence that the bias is negligible in relevant situations. Standard errors are computed on the basis of a sandwich formula. The application shows that prompt coronary angiography in patients with myocardial infarction may significantly decrease the risk of other events within the next two years, with a log-odds of about -2. Given that non-compliance is significant for patients being given the treatment because of high risk conditions, classical estimators fail to detect, or at least underestimate, this effect.

Key words: Conditional logistic regression; Counterfactuals; Finite mixture models; Latent variables; Potential outcomes.

*Department of Economics, Finance and Statistics, University of Perugia, 06123 Perugia, Italy, *email*: bart@stat.unipg.it

†Department of Public Health and Infectious Diseases, Sapienza - University of Rome, 00186 Roma, Italy, *email*: alessio.farcomeni@uniroma1.it

1 Introduction

It is well known that non-compliance may strongly complicate the estimation of the causal effect of a treatment in two-arm experimental studies, in particular when measured and/or unmeasured factors affect both the decision to comply and the reaction to the treatment. Different approaches have been proposed for causal inference in these circumstances. One of the most relevant approaches was proposed in [1] and relies on a potential outcome framework [2–5] that uses the indicator variable for the assigned treatment as an instrumental variable. Other approaches are strongly related to this one [6–10] and differentiate each other in terms of strength of the parametric assumptions and method of inference. It also worth mentioning approaches based on marginal structural models and inverse probability estimators for these models [11, 12], and approaches based on directed acyclic graphs (DAGs) [13, 14].

In this paper, we focus on two-arm experimental studies with all-or-nothing compliance and on the relevant case in which repeated binary outcomes, before and after the treatment, are available. All-or-nothing compliance means that the treatment may be either taken or not taken entirely, ruling out partial compliance; for approaches specifically tailored to partial compliance see [15] and [16]. In principle, most of the approaches mentioned above may be adopted in this context by including the pre-treatment outcome among the pre-treatment covariates. Among these approaches, we refer in particular to that proposed in [7] for binary outcomes: this is based on certain assumptions, which are related to those formulated in [1]. Some of these assumptions are parametric and concern the distribution of the potential outcomes given the individual covariates and the compliance status and the distribution of the compliance status given the individual covariates. Bayesian inference is used for this model so as to obtain an estimate of certain measures of causal effect of the received treatment. However, this approach, as well as similar approaches mentioned above, does not exploit the special nature of the pre-treatment outcome, which allows us to reduce the amount of parametric assumptions as detailed below.

One of the first attempts to formulate a causal framework which is specially tailored to two-arm experimental studies with repeated binary outcomes is in [17]. This approach is based on a DAG model with latent variables, the parameters of which have a causal interpretation.

As shown in [17], the same model may be formulated on the basis of potential outcomes. In particular, due to the existence of the pre-treatment outcome, the model does not require to formulate any assumption about the dependence of the post-treatment outcome on the individual covariates and even unobserved covariates may be considered. This is because a modified version of the conditional logistic estimator [18–21] may be used in order to estimate the causal effect. This estimator is much simpler than alternative estimators for causal effects, but in the formulation of [17] it may be applied when non-compliance is only in the treatment arm and therefore, using the terminology of [1], there are only *compliers* (who always comply with the treatment) and *never-takers* (who never take the treatment regardless of the assigned arm). There might also exist *defiers*, that is, subjects that systematically take the treatment if assigned to the control arm and vice-versa; however, we rule out their presence. This also assumed in [1] and the related papers mentioned above as a consequence of the assumption of *monotonicity* of the treatment.

In this article, we extend the approach of [17] by considering cases in which non-compliance may be also observed in the control arm. Therefore, there are three subpopulations: *compliers*, *never-takers*, and *always-takers* (who always take the treatment regardless of the assigned arm). In particular, we extend the causal model of [17] and, following the same inferential approach, we develop a conditional likelihood estimator of the causal effects. The latter may be simply applied. It is worth noting that these causal effects are measured on the logit scale, given that we are dealing with binary outcomes; the same scale is used in relevant methods for causal inference (e.g., [22–25]). Moreover, the adopted estimator is based on two steps. At the first step we estimate the probability that a subject is a complier, a never-taker, or an always-taker on the basis of observable covariates for this subject. At the second step, the conditional likelihood of a logistic model, based on a suitable design matrix which is set up by using the results from the first step, is maximized by a simple Newton-Raphson algorithm. Given the two-step formulation of the estimator, we use a sandwich formula [26] for deriving standard errors. These may be used to test the significance of the causal parameters. The properties of the proposed estimator are illustrated also considering a set of simulations. It turns out that it is approximately consistent, in a sense that will be clear in the following, but the point of convergence is typically very close

to the true parameter value, and it coincides with this point under certain conditions.

The approach here proposed is motivated by an original application about the effectiveness of coronary angiography (CA) in patients with non-ST elevation acute coronary syndrome. We are interested in evaluating whether a prompt CA (within 48h from hospital admission) should be recommended in light of a lower risk of recurrent cardiovascular events after leaving the hospital. A prompt CA, together with ECG and other exams performed on patients with coronary syndrome, may be helpful in better calibrating an in-hospital treatment. Even if the current guidelines of the European cardiologic society recommend CA within 48h of hospitalization [27], in some hospitals patients are submitted to CA only after a few days, or even not at all. In the cardiology literature, a definite recommendation has not yet emerged, with some studies reporting equivalence of CA performed before or after 48h of hospitalization [28–30], and other studies reporting superiority of prompt CA [31–33]. In our data, the medium/long term effects of coronary angiography within 48h from hospital admission have been estimated using a control given by the usual clinical practice in the hospital, which may or may not include the coronary angiography; when included, the designed study planned to schedule it only after at least 48h from hospitalization. Then, subjects assigned to the treatment group are expected to undergo CA within 48h from hospitalization, whereas patients assigned to the control group may or may not undergo CA. When a patient in the control group is submitted to CA, the analysis is expected to be executed after 48h from the hospitalization. Patients were randomized immediately at hospitalization. In practice, a significant fraction of controls received CA within 48h from hospitalization, possibly due to the need of information in order to promptly proceed with a treatment. Furthermore, a significant fraction of patients in the active group (treatment arm) did receive CA, but after 48h from hospitalization, possibly due to a busy hospital schedule which did not allow prompt CA performance. We consequently have a significant non-compliance in both arms, leading to the presence of never-takers and always-takers in addition to compliers. Note that non-compliance in this example is more likely a choice of the doctor, rather than of the patient. Given that unfortunately only informations about the patient are available, non-compliance is even harder to deal with. We focus on a relevant group of patients, those arriving at the hospital with myocardial infarction.

It is important to underline here that the type of subpopulation (never-takers, compliers, always-takers) is not known for all patients. More precisely, if a subject is randomized to the treatment but actually receives the control, we know that he/she is a never-taker; and similarly for the reverse mismatch. On the other hand, when the randomized and actually observed group match, there is uncertainty. A subject randomized to the treatment who receives the treatment may either be a complier or an always-taker who would have received the treatment regardless of randomization. Similarly for subjects randomized to and receiving the control. This point raises the need of specific inferential strategies, like the one here proposed.

The paper is organized as follows. In Section 2 we briefly describe the data from the study motivating this paper. In Section 3 we introduce the causal model for repeated binary response variables. The proposed two-step estimator is described in Section 4 and its properties are studied in Section 5. Application of our estimator to the dataset deriving from the cardiology study outlined above is described in Section 6. Final conclusions are reported in Section 7.

We implemented the estimator in an `R` function that we make available to the reader upon request.

2 Description of the Prompt Coronary Angiography data

The multicenter trial we consider is based on the inclusion of patients arriving at the hospital with last episode of *angina pectoris* within the last 24 hours. Patients were included in the study if they were diagnosed a myocardial infarction at hospitalization, and this could be believed to be their first episode of infarction. Patients with persistent ST elevation or who could not undergo CA were excluded from the study.

The binary response of interest is the recurrence within 2 years after leaving the hospital of any among: (*i*) another episode of myocardial infarction, (*ii*) an episode of *angina pectoris* of duration 20 minutes or longer, (*iii*) other significant cardiovascular events, or (*iv*) death which could be related to the current episode. The recorded data concern the presence or absence of episodes of *angina pectoris* or other cardiovascular events within the last month before hospitalization, and other covariates. The first can be considered as a pre-treatment

copy of the outcome. Among the covariates there are: gender, age, smoke, statin use, history of CHD in the family, hypertension, and glicemic index (GI) at hospitalization. We are interested in evaluating the causal effect of a prompt CA since our population of patients with myocardial infarction (IMA) at hospitalization could probably be better treated after CA, and this could prevent further events.

Overall, we have data on $n = 1,560$ subjects; their characteristics are summarized as follows: there are 63% males, 46% smokers, 75% have a history of CHD in the family, 31% have hypertension, and 81% use statines regularly. GI has a strongly skewed distribution, with median equal to 118 and MAD equal to 34; moreover, the mean age is 67.5 with a standard deviation of 10.8.

Randomization was performed with a proportion of 1:2, and in fact 66% of the patients were assigned to the prompt CA group. Only 52% of the patients were actually submitted to prompt CA, anyway. In order to clarify the issue of compliance, we introduce two distinct binary variables, Z and X, which denote the assigned treatment ($Z = 1$ for assigned to prompt CA and $Z = 0$ otherwise) and the taken treatment ($X = 1$ for actually submitted to prompt CA and $X = 0$ otherwise), respectively. There was non-compliance in both groups, with more than 1/3 of the subjects assigned to each group ending up taking the other treatment. More precisely, 370 subjects assigned to the prompt CA did undergo CA later than 48h after hospitalization, and 170 patients assigned to the control group had prompt CA. Two patients experienced recurrence within 48h from hospitalization and before receiving CA. In order to evaluate the sensitivity of estimates to these peculiar patients, we have repeated the analysis excluding those two patients, obtaining essentially the same results.

Given that after model selection we conclude that GI and use of statines are predictive of compliance (see Section 6), we study these two variables a bit more in depth here. In Table 1 we report the proportion of patients belonging to the groups of "assigned and received control" (that includes compliers and never-takers), surely always-takers (assigned to control and received treatment), surely never-takers (assigned to treatment and received control), and "assigned and received treatment" (that includes compliers and always-takers), given the level of GI and the use or not of statines. The level of GI is discretized on the basis of the quartiles of its empirical

distribution. It is important to underline that in Table 1 the first and last groups are made of both compliers and subjects who were by chance assigned to the treatment they would have taken anyway. That is, in the first group we have both compliers assigned to the control and never-takers randomized to the control; in the last group we have both compliers assigned to the treatment and always-takers who were also randomized to the treatment.

		GI quartile				Use of statines	
Arm	Group	1st	2nd	3rd	4th	No	Yes
Control ($Z = 0$)	Compliers + never-takers ($X = 0$)	0.634	0.702	0.674	0.638	0.606	0.676
	Always-takers ($X = 0$)	0.366	0.298	0.326	0.362	0.394	0.324
Treatment ($Z = 1$)	Never-takers ($X = 0$)	0.336	0.335	0.389	0.430	0.443	0.352
	Compliers + always-takers ($X = 1$)	0.664	0.665	0.611	0.570	0.557	0.648

Table 1: *Conditional proportion of the group of "assigned and received control", never-takers, always-takers, and "assigned and received treatment", given GI and the use or not of statines.*

From the results in Table 1 we observe that the proportion of never-takers steadily increases with GI, whereas the proportion of always-takers is larger for the first and last quartiles. On the other hand, the use of statines seems to increase the compliance in both directions, with a decrease of 7% of always-takers and 9% of never-takers.

3 The causal model

Let Y_1 and Y_2 denote the binary outcomes of interest, let $\boldsymbol{V}$ be a vector of observable covariates, let Z be a binary variable equal to 1 when a subject is assigned to the treatment and to 0 when he/she is assigned to the control, and let X be the corresponding binary variable for the treatment actually received. In the present framework, $\boldsymbol{V}$ and Y_1 are pre-treatment variables, whereas Y_2 is a post-treatment variable. Moreover, non-compliance of the subjects involved in the experimental study implies that X may differ from Z, since we consider experimental studies in which subjects randomized to both arms can access the treatment and therefore any configuration of (Z, X) may be observed. Consequently, we assume the existence of three subpopulations of subjects enrolled in the study: *compliers*, *never-takers*, and *always-takers*. As already mentioned, we assume there are no defiers, and this is a modeling assumption. It can be easily justified for the data at hand given that the decision to undergo CA is not a choice of

the patient.

In the following, we introduce a latent variable model for the analysis of data deriving from the experimental study described above. This model extends that proposed in [17] to deal with two-arm experimental studies of the same type in which, however, non-compliance may be only observed in the treatment arm. We then derive results about the proposed model which are useful for making inference on its parameters.

3.1 Model assumptions

We assume that the behavior of a subject depends on the observable covariates $\boldsymbol{V}$, a latent variable U representing the effect of unobservable covariates on both response variables, and a latent variable C representing the attitude to comply with the assigned treatment. The latent variable U is a scalar but can be seen as the sum of many unobserved covariates, provided that this sum does not change between the two occasions of observation (before and after treatment). The latent variable C is discrete with three possible values: 0 for never-takers, 1 for compliers, and 2 for always-takers. The model is based on assumptions A1-A5 that are reported below. In formulating these assumptions we use the symbol $W_1 \perp\!\!\!\perp W_2|W_3$ to denote conditional independence between the random variables W_1 and W_2 given W_3; this notation naturally extends to random vectors. Moreover, with reference to the variables in our study, we also let $p_1(y|u,\boldsymbol{v}) = \text{pr}(Y_1 = y|U = u, \boldsymbol{V} = \boldsymbol{v})$ and $p_2(y|u,\boldsymbol{v},c,x) = \text{pr}(Y_2 = y|U = u, \boldsymbol{V} = \boldsymbol{v}, C = c, X = x)$, and by $1\{\cdot\}$ we denote the indicator function.

In the following, we describe the model assumptions introducing the variables of interest in the following order: U, $\boldsymbol{V}$, Y_1, C, Z, X, Y_2.

A1: $C \perp\!\!\!\perp (U, Y_1)|\boldsymbol{V}$;

A2: $Z \perp\!\!\!\perp (U, \boldsymbol{V}, Y_1, C)$;

A3: $X \perp\!\!\!\perp (U, \boldsymbol{V}, Y_1)|(C, Z)$ and, with probability 1, $X = Z$ when $C = 1$ (compliers), $X = 0$ when $C = 0$ (never-takers), and $X = 1$ when $C = 2$ (always-takers);

A4: $Y_2 \perp\!\!\!\perp (Y_1, Z)|(U, \boldsymbol{V}, C, X)$;

A5: for all u, $\boldsymbol{v}$, c, and x, we have

$$\text{logit}[p_2(1|u,\boldsymbol{v},c,x)] - \text{logit}[p_1(1|u,\boldsymbol{v})] = \boldsymbol{t}(c,x)'\boldsymbol{\beta}, \tag{1}$$

where

$$\boldsymbol{t}(c,x) = \begin{pmatrix} 1\{c=0\}(1-x) \\ 1\{c=1\}(1-x) \\ 1\{c=1\}x \\ 1\{c=2\}x \end{pmatrix} \quad \text{and} \quad \boldsymbol{\beta} = \begin{pmatrix} \beta_0 \\ \beta_1 \\ \beta_2 \\ \beta_3 \end{pmatrix}.$$

According to assumption A1 the tendency to comply depends only on $(U, \boldsymbol{V})$, whereas assumption A2 is typically satisfied in randomized experiments of our interest and, in any case, it may be relaxed by requiring that Z is conditionally independent of U given $(\boldsymbol{V}, Y_1)$; this is shown in [17]. Assumption A3 is rather obvious considering that C represents the tendency of a subject to comply with the assigned treatment. Assumption A4 implies that there is no direct effect of Y_1 on Y_2, since the distribution of the latter depends only on $(U, \boldsymbol{V}, C, X)$; it also implies an assumption known as *exclusion restriction* [1], according to which Z affects Y_2 only through X. Finally, assumption A5 states that the distribution of Y_2 depends on a vector of causal parameters $\boldsymbol{\beta}$, the elements of which are interpretable as follows:

- β_0: effect of control on never-takers;
- β_1: effect of control on compliers;
- β_2: effect of treatment on compliers;
- β_3: effect of treatment on always-takers.

The most interesting quantity to estimate is the *causal effect* of the treatment over the control in the subpopulation of compliers, the definition of which is related to that of the *local average treatment effect* given in [1]. In the present context, this effect may be defined as

$$\delta = \text{logit}[p_2(1|u,\boldsymbol{v},1,1)] - \text{logit}[p_2(1|u,\boldsymbol{v},1,0)] = \beta_2 - \beta_1$$

and corresponds to the increase of the logit of the probability of success when x goes from 0 to 1, all the other factors remaining unchanged.

The above assumptions imply the dependence structure between the observable and unobservable variables may be represented by the DAG in Figure 1. These assumptions lead to a causal model in the sense of [13] since all the observable and unobservable factors affecting the response variables of interest are included. Moreover, using the same approach adopted in [17], the model may be also formulated in terms of potential outcomes, enforcing in this way its causal interpretation.

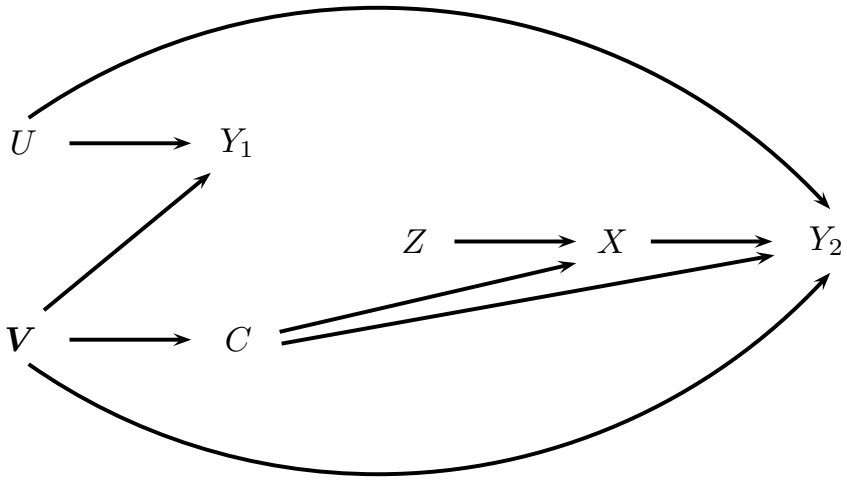

Figure 1: *DAG for the proposed causal model.* $\boldsymbol{V}$ *and* U *represent observable and unobservable covariates affecting the response variables* Y_1 *and* Y_2*.* C *is a variable recording the compliance status and* Z *and* X *are binary variables for the assigned and received treatment.*

Finally, it may be of interest to compare the model here formulated with that introduced in [7], which is the most similar among the models considered in Section 1. As already mentioned, the approach in [7] could also be used to analyze data having the structure here described treating the pre-treatment outcome Y_1 as a pre-treatment covariate on the same footing of the covariates in $\boldsymbol{V}$. However, this approach is based on formulating a parametric assumption for the potential outcome corresponding to the post-treatment outcome given the pre-treatment covariates, received treatment, and compliance status. Here we avoid this full parametric formulation treating Y_1 in a different way. In particular, in (1) we formulate a parametric assumption only on the difference between the logit for the conditional probability that Y_2 is equal to 1 and that

for the conditional probability that Y_1 is equal to 1, given C, U, $\boldsymbol{V}$, and X. How these logits depend on U and $\boldsymbol{V}$ is completely arbitrary. In this regard note that more complex formulations than that in (1) may be assumed for the difference between the two logits by allowing, for instance, this difference to also depend on the covariates. However, we prefer to rely on the simplest formulation which also results in the most meaningful model.

3.2 Preliminary results for inference

Assumptions A1-A5 imply that the probability function of the conditional distribution of (Y_1, Z, X, Y_2) given $(U, \boldsymbol{V}, C)$ is equal to

$$p(y_1, z, x, y_2|u, \boldsymbol{v}, c) = p_1(y_1|u, \boldsymbol{v})q(z)f(x|c, z)p_2(y_2|u, \boldsymbol{v}, c, x),$$

where $q(z) = \text{pr}(Z = z)$ and $f(x|c, z) = \text{pr}(X = x|C = c, Z = z)$. After some algebra, for the conditional distribution of (Y_1, Z, X, Y_2) given $(U, \boldsymbol{V})$ we have

$$p(y_1, z, x, y_2|u, \boldsymbol{v}) = \frac{e^{(y_1+y_2)\lambda(u,\boldsymbol{v})}}{1 + e^{\lambda(u,\boldsymbol{v})}} q(z) \sum_{c=0}^{2} f(x|c, z) \frac{e^{y_2 \boldsymbol{t}(c,x)'\boldsymbol{\beta}}}{1 + e^{\lambda(u,\boldsymbol{v}) + \boldsymbol{t}(c,x)'\boldsymbol{\beta}}} \pi(c|\boldsymbol{v}),$$

where $\lambda(u, \boldsymbol{v}) = \text{logit}[p_1(1|u, \boldsymbol{v})]$ and $\pi(c|\boldsymbol{v}) = \text{pr}(C = c|\boldsymbol{V} = \boldsymbol{v})$.

This probability function considerably simplifies when $x \neq z$. In fact, for $z = 1$ and $x = 0$, $f(x|c, z)$ is equal to 1 when $c = 0$ (never-takers) and to 0 otherwise. Similarly, for $z = 0$ and $x = 1$, $f(x|c, z)$ is equal to 1 when $c = 2$ (always-takers) and to 0 otherwise. We then have

$$p(y_1, z, x, y_2|u, \boldsymbol{v}) = \frac{e^{(y_1+y_2)\lambda(u,\boldsymbol{v})}}{1 + e^{\lambda(u,\boldsymbol{v})}} q(z) \frac{e^{y_2 \boldsymbol{t}(c,x)'\boldsymbol{\beta}}}{1 + e^{\lambda(u,\boldsymbol{v}) + \boldsymbol{t}(c,x)'\boldsymbol{\beta}}} \pi(c|\boldsymbol{v}),$$

with

$$c = \begin{cases} 0 & \text{if } z = 1, x = 0, \\ 2 & \text{if } z = 0, x = 1. \end{cases} \tag{2}$$

Consequently, (Y_1, Y_2) is conditionally independent of U given $(\boldsymbol{V}, Z, X, Y_+)$ and $Z \neq X$. In fact the probability function of the corresponding distribution, which is denoted by $r(y_1, y_2|u, \boldsymbol{v}, z, x, y_+)$,

is such that

$$r(y_1, y_2|u, \boldsymbol{v}, z, x, 1) = \frac{p(y_1, y_2|u, \boldsymbol{v}, z, x)}{p(0, 1|u, \boldsymbol{v}, z, x) + p(1, 0|u, \boldsymbol{v}, z, x)} = \frac{e^{y_2 \boldsymbol{t}(c,x)'\boldsymbol{\beta}}}{1 + e^{\boldsymbol{t}(c,x)'\boldsymbol{\beta}}},$$

with c defined as in (2). It important to note that this expression depends neither on u nor on $\boldsymbol{v}$ and, in fact, it may be equivalently denoted by $r(y_1, y_2|z, x, 1)$ that, more explicitly, may be written as

$$r(y_1, y_2|z, x, 1) = \begin{cases} \dfrac{e^{y_2\beta_0}}{1 + e^{\beta_0}} & \text{if } z = 1, x = 0, \\ \dfrac{e^{y_2\beta_3}}{1 + e^{\beta_3}} & \text{if } z = 0, x = 1. \end{cases} \tag{3}$$

Obviously, $r(y_1, y_2|u, \boldsymbol{v}, z, x, y_+) = 1$ for $y_+ = 0, 1$, and then it is independent of u and $\boldsymbol{v}$ also in these cases.

When $x = z$, the conditional probability $p(y_1, z, x, y_2|u, \boldsymbol{v})$ has the following expression:

$$p(y_1, z, x, y_2|u, \boldsymbol{v}) = \frac{e^{(y_1+y_2)\lambda(u,\boldsymbol{v})}}{1 + e^{\lambda(u,\boldsymbol{v})}} q(z) \sum_{c=z}^{z+1} \frac{e^{y_2 \boldsymbol{t}(c,x)'\boldsymbol{\beta}}}{1 + e^{\lambda(u,\boldsymbol{v}) + \boldsymbol{t}(c,x)'\boldsymbol{\beta}}} \pi(c|\boldsymbol{v}),$$

where sum $\sum_{c=z}^{z+1}$ is extended to $c = 0, 1$ for $x = z = 0$ and to $c = 1, 2$ for $x = z = 1$. This is the expression of a mixture distribution between the conditional distribution of Y_2 for the subpopulation of never-takers and that of compliers (when $z = x = 0$) or for the subpopulation of compliers and that of always-takers (when $z = x = 1$). However, along the same lines as in [17], it may proved that $r(y_1, y_2|u, \boldsymbol{v}, z, x, 1)$ is approximately equal to

$$r^*(y_1, y_2|\boldsymbol{v}, z, x, 1) = \begin{cases} \displaystyle\sum_{c=0}^{1} \frac{e^{y_2\beta_c}}{1 + e^{\beta_c}} \pi^*_{01}(c|\boldsymbol{v}) & \text{if } z = x = 0, \\ \displaystyle\sum_{c=1}^{2} \frac{e^{y_2\beta_{c+1}}}{1 + e^{\beta_{c+1}}} \pi^*_{12}(c|\boldsymbol{v}) & \text{if } z = x = 1, \end{cases} \tag{4}$$

where

$$\pi^*_{01}(c|\boldsymbol{v}) = \frac{\pi(c|\boldsymbol{v})}{\pi(0|\boldsymbol{v}) + \pi(1|\boldsymbol{v})}, \quad c = 0, 1,$$

and

$$\pi^*_{12}(c|\boldsymbol{v}) = \frac{\pi(c|\boldsymbol{v})}{\pi(1|\boldsymbol{v}) + \pi(2|\boldsymbol{v})}, \quad c = 1, 2.$$

The first is the probability of being a never-taker or a complier given that the subject is in one of these subpopulation and his/her covariates; a similar interpretation holds for the probabilities of the second type. Regarding the quality of the approximation above, we have to clarify that $r(y_1, y_2|u, \boldsymbol{v}, z, x, 1) = r^*(y_1, y_2|\boldsymbol{v}, z, x, 1)$ for $\beta_0 = \beta_1$ and $\beta_2 = \beta_3$, case in which expression (4) simplifies, becoming also independent of $\boldsymbol{v}$. Moreover, the quality of the approximation worsens as the distance between β_0 and β_1 and that between β_2 and β_3 increase.

4 Pseudo conditional likelihood inference

For a sample of n subjects included in the two-arm experimental study, let y_{i1} denote the observed value of Y_1 for subject i, $i = 1, \ldots, n$, let y_{i2} denote the value of Y_2 for the same subject, and let $\boldsymbol{v}_i$, z_i, and x_i denote the corresponding values of $\boldsymbol{V}$, Z, and X, respectively. In the following, we introduce an approach for estimating the causal parameter vector $\boldsymbol{\beta}$ which closely follows that proposed in [17]. The approach relies on the maximization of a likelihood based on the probability function $r(y_1, y_2|z, x, 1)$, for the cases in which (Y_1, Y_2) is conditionally independent of U given (V, Z, X, Y_+), and on its approximated version, denoted by $r^*(y_1, y_2|\boldsymbol{v}, z, x, 1)$, otherwise. The expressions of these conditional probabilities are given in (3) and (4). It results a pseudo conditional likelihood estimator, in the sense of [26], whose main advantage is the simplicity of use; see also [34] for a related approach applied in a different field. Note that this approach requires the preliminary estimation of the probability that every subject belongs to one of the three subpopulations (compliers, never-takers, and always-takers). Overall, the approach is based on two steps that are detailed in the following.

At the *first step* we estimate the probabilities that a subject is a never-taker ($c = 0$), a complier ($c = 1$), or an always-taker ($c = 2$). In this regard, we assume the following multinomial

logit model with compliers as reference category:

$$\log \frac{\pi(0|\boldsymbol{v})}{\pi(1|\boldsymbol{v})} = \boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_0, \tag{5}$$

$$\log \frac{\pi(2|\boldsymbol{v})}{\pi(1|\boldsymbol{v})} = \boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_2. \tag{6}$$

This implies that

$$\pi(0|\boldsymbol{v}) = \frac{\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_0]}{1+\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_0]+\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_2]}, \tag{7}$$

$$\pi(1|\boldsymbol{v}) = \frac{1}{1+\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_0]+\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_2]}, \tag{8}$$

$$\pi(2|\boldsymbol{v}) = \frac{\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_2]}{1+\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_0]+\exp[\boldsymbol{g}(\boldsymbol{v})'\boldsymbol{\alpha}_2]}. \tag{9}$$

Similar assumptions about the distribution of the indicator variable for the compliance status are formulated in [7].

Given that the assignment is randomized, the parameter vectors $\boldsymbol{\alpha}_0$ and $\boldsymbol{\alpha}_2$ are estimated by maximizing the log-likelihood

$$\begin{aligned}
\ell_1(\boldsymbol{\alpha}_0,\boldsymbol{\alpha}_2) &= \sum_i \ell_{1i}(\boldsymbol{\alpha}_0,\boldsymbol{\alpha}_2), \\
\ell_{1i}(\boldsymbol{\alpha}_0,\boldsymbol{\alpha}_2) &= (1-z_i)(1-x_i)\log[\pi(0|\boldsymbol{v}_i)+\pi(1|\boldsymbol{v}_i)] + \sum_i (1-z_i)x_i \log \pi(2|\boldsymbol{v}_i) \\
&\quad + \sum_i z_i(1-x_i)\log \pi(0|\boldsymbol{v}_i) + \sum_i z_i x_i \log[\pi(1|\boldsymbol{v}_i)+\pi(2|\boldsymbol{v}_i)].
\end{aligned}$$

For this aim, a simple Newton-Raphson algorithm may be used, which is based on the first and second derivatives of this function. In particular, the first derivative of this function may be found as follows. First of all we write

$$\begin{aligned}
\ell_{1i}(\boldsymbol{\alpha}_0,\boldsymbol{\alpha}_2) &= (1-z_i)(1-x_i)\log\frac{\pi(0|\boldsymbol{v}_i)+\pi(1|\boldsymbol{v}_i)}{\pi(1|\boldsymbol{v}_i)} + (1-z_i)x_i\log\frac{\pi(2|\boldsymbol{v}_i)}{\pi(1|\boldsymbol{v}_i)} \\
&\quad + z_i(1-x_i)\log\frac{\pi(0|\boldsymbol{v}_i)}{\pi(1|\boldsymbol{v}_i)} + z_i x_i \log\frac{\pi(1|\boldsymbol{v}_i)+\pi(2|\boldsymbol{v}_i)}{\pi(1|\boldsymbol{v}_i)} + n\log\pi(1|\boldsymbol{v}_i).
\end{aligned}$$

Then, based on assumptions (5) and (6), we have

$$\begin{aligned}\ell_{1i}(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2) &= (1-z_i)(1-x_i)\log\{1+\exp[\boldsymbol{g}(\boldsymbol{v}_i)'\boldsymbol{\alpha}_0]\} + (1-z_i)x_i\boldsymbol{g}(\boldsymbol{v}_i)'\boldsymbol{\alpha}_2 \\ &\quad + z_i(1-x_i)\boldsymbol{g}(\boldsymbol{v}_i)'\boldsymbol{\alpha}_0 + z_i x_i \log\{1+\exp[\boldsymbol{g}(\boldsymbol{v}_i)'\boldsymbol{\alpha}_2]\} \\ &\quad - \log\{1+\exp[\boldsymbol{g}(\boldsymbol{v}_i)'\boldsymbol{\alpha}_0] + \exp[\boldsymbol{g}(\boldsymbol{v}_i)'\boldsymbol{\alpha}_2]\},\end{aligned}$$

so that

$$\begin{aligned}\frac{\partial \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0} &= \sum_i \frac{\partial \ell_{1i}(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0}, \\ \frac{\partial \ell_{1i}(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0} &= [(1-z_i)(1-x_i)\pi^*(0|\boldsymbol{v}_i) + z_i(1-x_i) - \pi(0|\boldsymbol{v}_i)]\,\boldsymbol{g}(\boldsymbol{v}_i),\end{aligned}$$

and

$$\begin{aligned}\frac{\partial \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_2} &= \sum_i \frac{\partial \ell_{1i}(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_2}, \\ \frac{\partial \ell_{1i}(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_2} &= [z_i x_i \pi^*(2|\boldsymbol{v}_i) + (1-z_i)x_i - \pi(2|\boldsymbol{v}_i)]\,\boldsymbol{g}(\boldsymbol{v}_i).\end{aligned}$$

Moreover, regarding the second derivative, we have

$$\begin{aligned}\frac{\partial^2 \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0 \partial \boldsymbol{\alpha}_0'} &= \sum_i \{(1-z_i)(1-x_i)\pi^*_{01}(0|\boldsymbol{v}_i)[1-\pi^*_{01}(0|\boldsymbol{v}_i)] - \pi(0|\boldsymbol{v}_i)[1-\pi(0|\boldsymbol{v}_i)]\}\,\boldsymbol{g}(\boldsymbol{v}_i)\boldsymbol{g}(\boldsymbol{v}_i)', \\ \frac{\partial^2 \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0 \partial \boldsymbol{\alpha}_2'} &= \sum_i \pi(0|\boldsymbol{v}_i)\pi(2|\boldsymbol{v}_i)\boldsymbol{g}(\boldsymbol{v}_i)\boldsymbol{g}(\boldsymbol{v}_i)', \\ \frac{\partial^2 \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0 \partial \boldsymbol{\alpha}_0'} &= \sum_i \{z_i x_i \pi^*_{12}(2|\boldsymbol{v}_i)[1-\pi^*_{12}(2|\boldsymbol{v}_i)] - \pi_{12}(2|\boldsymbol{v}_i)[1-\pi_{12}(2|\boldsymbol{v}_i)]\}\,\boldsymbol{g}(\boldsymbol{v}_i)\boldsymbol{g}(\boldsymbol{v}_i)'.\end{aligned}$$

The estimated parameter vectors, obtained by maximizing $\ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)$, are denoted by $\hat{\boldsymbol{\alpha}}_0$ and $\hat{\boldsymbol{\alpha}}_2$ and the corresponding probabilities are denoted by $\hat{\pi}(0|\boldsymbol{v})$, $\hat{\pi}(1|\boldsymbol{v})$, and $\hat{\pi}(2|\boldsymbol{v})$, which are obtained by (7), (8), and (9), respectively. Finally, by inversion of minus the Hessian matrix, which is based on the second derivatives above, it is also possible to obtain the standard errors for the parameter estimates $\hat{\boldsymbol{\alpha}}_0$ and $\hat{\boldsymbol{\alpha}}_2$ in the usual way.

At the *second step*, we maximize the following weighted conditional log-likelihood:

$$\begin{aligned}
\ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2) &= \sum_i d_i \ell_{2i}(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2), \\
\ell_{2i}(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2) &= (1-z_i)(1-x_i) \sum_{c=0}^{1} \hat{\pi}^*_{01}(c|\boldsymbol{v}_i) \frac{\exp(y_{i2}\beta_c)}{1+\exp(\beta_c)} + (1-z_i)x_i \frac{\exp(y_{i2}\beta_3)}{1+\exp(\beta_3)} \\
&+ z_i(1-x_i) \frac{\exp(y_{i2}\beta_0)}{1+\exp(\beta_0)} + z_i x_i \sum_{c=1}^{2} \hat{\pi}^*_{12}(c|\boldsymbol{v}_i) \frac{\exp(y_{i2}\beta_{c+1})}{1+\exp(\beta_{c+1})},
\end{aligned}$$

where $d_i = 1\{y_{i1} + y_{i2} = 1\}$, so that only discordant configurations are considered, and we recall that β_0 is the effect of control on never-takers, β_1 is the effect of control on compliers, β_2 is the effect of treatment on compliers, and β_3 is the effect of treatment on always-takers.

In order to compute the first and second derivatives of $\ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)$ with respect to $\boldsymbol{\beta}$, it is convenient to express i-th component of this function as

$$\ell^*_{2i}(\boldsymbol{\eta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2) = y_{i2} \log(\hat{\boldsymbol{w}}_i'\boldsymbol{\eta}) + (1-y_{i2}) \log(1 - \hat{\boldsymbol{w}}_i'\boldsymbol{\eta}),$$

where $\boldsymbol{\eta} = (\eta_0, \eta_1, \eta_2, \eta_3)'$, with

$$\eta_h = \frac{\exp(\beta_h)}{1+\exp(\beta_h)}, \quad h = 0, \ldots, 3,$$

and the vector of $\hat{\boldsymbol{w}}_i$ is defined as follows depending on z_i, x_i, and the estimates from the first step:

$$\hat{\boldsymbol{w}}_i = \begin{cases} (\hat{\pi}^*_{01}(0|\boldsymbol{v}_i), \hat{\pi}^*_{01}(1|\boldsymbol{v}_i), 0, 0)', & \text{if } z_i = x_i = 0, \\ (0,0,0,1)', & \text{if } z_i = 0, x_i = 1, \\ (1,0,0,0)', & \text{if } z_i = 1, x_i = 0, \\ (0, 0, \hat{\pi}^*_{12}(1|\boldsymbol{v}_i), \hat{\pi}^*_{12}(2|\boldsymbol{v}_i))', & \text{if } z_i = x_i = 1. \end{cases}$$

Then we have the following first derivative:

$$\begin{aligned}
\frac{\partial \ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta}} &= \sum_i d_i \frac{\partial \ell_{2i}(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta}}, \\
\frac{\partial \ell_{2i}(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta}} &= \operatorname{diag}(\boldsymbol{a}) \frac{\partial \ell^*_{2i}(\boldsymbol{\eta}|\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\eta}},
\end{aligned}$$

$$\frac{\partial \ell_{2i}^*(\boldsymbol{\eta}|\boldsymbol{\alpha}_0,\boldsymbol{\alpha}_2)}{\partial \boldsymbol{\eta}} = \left(\frac{y_{i2}}{\hat{\boldsymbol{w}}_i'\boldsymbol{\eta}} - \frac{1-y_{i2}}{1-\hat{\boldsymbol{w}}_i'\boldsymbol{\eta}}\right),$$

where $\boldsymbol{a} = \text{diag}(\boldsymbol{\eta})(\mathbf{1}-\boldsymbol{\eta})$, with $\mathbf{1}$ denoting a column vector of ones of suitable dimension. Similarly, with

$$\frac{\partial^2 \ell_2^*(\boldsymbol{\eta}|\hat{\boldsymbol{\alpha}}_0,\hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\eta}\partial \boldsymbol{\eta}'} = -\sum_i d_i \left[\frac{y_{i2}}{(\hat{\boldsymbol{w}}_i'\boldsymbol{\eta})^2} + \frac{1-y_{i2}}{(1-\hat{\boldsymbol{w}}_i'\boldsymbol{\eta})^2}\right] \hat{\boldsymbol{w}}_i\hat{\boldsymbol{w}}_i',$$

we have that

$$\frac{\partial^2 \ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0,\hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta}\partial \boldsymbol{\beta}'} = \text{diag}(\boldsymbol{a})\frac{\partial^2 \ell_2^*(\boldsymbol{\eta}|\hat{\boldsymbol{\alpha}}_0,\hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\eta}\partial \boldsymbol{\eta}'}\text{diag}(\boldsymbol{a}) + \text{diag}(\boldsymbol{b})\text{diag}\left[\frac{\partial \ell_2^*(\boldsymbol{\eta}|\hat{\boldsymbol{\alpha}}_0,\hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\eta}}\right],$$

where $\boldsymbol{b} = \text{diag}(\boldsymbol{a})(\mathbf{1}-2\boldsymbol{\eta})$.

In order to obtain the standard errors for the parameter estimates, we first use a sandwich formula [26] for estimating the variance-covariance matrix of the overall estimator $\hat{\boldsymbol{\theta}} = (\hat{\boldsymbol{\alpha}}_0', \hat{\boldsymbol{\alpha}}_2', \hat{\boldsymbol{\beta}})'$. In particular, we have

$$\hat{\boldsymbol{\Sigma}} = \hat{\boldsymbol{H}}^{-1}\hat{\boldsymbol{K}}\hat{\boldsymbol{H}}^{-1}, \tag{10}$$

where the matrices $\hat{\boldsymbol{H}}$ and $\hat{\boldsymbol{K}}$ are defined in Appendix. Then, the standard errors for $\hat{\boldsymbol{\beta}}$ are computed by the square root of the diagonal elements of the submatrix of $\hat{\boldsymbol{\Sigma}}$ corresponding to this vector. We can then obtain the standard error for the estimate of the causal effect on the compliers, that is, $\hat{\delta} = \hat{\beta}_2 - \hat{\beta}_1$, by a standard rule based on the same submatrix of $\hat{\boldsymbol{\Sigma}}$. This standard error is denoted by $\text{se}(\hat{\delta})$ and may be used to test the null hypothesis of null causal effect on the compliers ($H_0 : \delta = 0$) through the Wald test statistic $\hat{\delta}/\text{se}(\hat{\delta})$.

As mentioned above, one of the main advantages of the proposed approach is the simplicity of implementation. In particular, we implemented both estimation steps, to maximize $\ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)$ and to maximize $\ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)$, in a single `R` function that is available to the reader upon request. Both steps follow a Newton-Raphon scheme based on the first and second derivatives of the functions to be maximized; the computation of these derivatives is implemented in a very few lines of commands using the matrix notation when possible. Moreover, we noticed that the implemented `R` function is very fast to converge since the functions to be maximized have

regular shapes and then a reduced number of iterations is required. Overall, the only part of the code that needs some effort concerns the computation of the matrices to be used in the sandwich formula (10) for the standard errors.

5 Properties of the proposed estimator

The proposed estimator is based on an approximation of the conditional probability of the response variables Y_1 and Y_2, given their sum Y_+, that has been defined at the end of Section 3.2. Along the same lines as in [17] and employing standard results about likelihood inference estimators based on misspecified models [26], it can be shown that, under certain regularity conditions, $\hat{\boldsymbol{\beta}} \xrightarrow{p} \boldsymbol{\beta}_*$ as $n \to \infty$, where $\boldsymbol{\beta}_*$ is a suitable point of the parameter space. Now let $\bar{\boldsymbol{\beta}} = (\bar{\beta}_0, \bar{\beta}_1, \bar{\beta}_2, \bar{\beta}_3)'$ denote the true parameter vector. Then, $\boldsymbol{\beta}_* = \bar{\boldsymbol{\beta}}$ when $\bar{\beta}_0 = \bar{\beta}_1$ (the control has the same effect on never-takers and compliers) and $\bar{\beta}_2 = \bar{\beta}_3$ (the treatment has the same effect on compliers and always-takers) and then in this case the estimator is consistent; this also happens if the model for the compliance, based on $\boldsymbol{g}(\boldsymbol{v})$, is misspecified. On the other hand, $\boldsymbol{\beta}_*$ is not ensured to be equal to $\bar{\boldsymbol{\beta}}$ when $\bar{\beta}_0 \neq \bar{\beta}_1$ and/or $\bar{\beta}_2 \neq \bar{\beta}_3$, but $\boldsymbol{\beta}_*$ is expected to be close to $\bar{\boldsymbol{\beta}}$ if $\bar{\beta}_0$ is close to $\bar{\beta}_1$ and $\bar{\beta}_2$ is close to $\bar{\beta}_3$. In this sense the estimator is approximately consistent.

For what concerns the asymptotic distribution of $\hat{\boldsymbol{\theta}}$, which includes $\hat{\boldsymbol{\alpha}}_0$ and $\hat{\boldsymbol{\alpha}}_2$ further to $\hat{\boldsymbol{\theta}}$, using again some standard results [26] we have that

$$\sqrt{n}(\hat{\boldsymbol{\theta}} - \boldsymbol{\theta}_*) \xrightarrow{d} N(\mathbf{0}, \boldsymbol{\Omega}(\boldsymbol{\theta}_*)),$$

as $n \to \infty$, where $\boldsymbol{\theta}_* = (\boldsymbol{\alpha}'_{0*}, \boldsymbol{\alpha}'_{2*}, \boldsymbol{\beta}'_*)'$ is the point of convergence of $\hat{\boldsymbol{\theta}}$ and $\boldsymbol{\Omega}(\boldsymbol{\theta}_*)$ is the limit in probability of the matrix $\hat{\boldsymbol{\Sigma}}/n$. This result, which holds provided that the matrix $\boldsymbol{\Omega}(\boldsymbol{\theta}_*)$ is of full rank, is the basis of the proposed sandwich formula (10) to compute standard errors for $\hat{\boldsymbol{\beta}}$ and $\hat{\delta}$.

In order to illustrate the performance of the proposed estimator, even coherently with the above asymptotic properties, we implemented a simulation study based on a *benchmark design*,

under which the estimator is consistent, and two alternative designs. Under the benchmark design, we assume the existent of only one observable covariate V. Both U and V are assumed to have a standard normal distribution and are independent. Moreover, Y_1, Z, and Y_2 have Bernoulli distributions with parameters chosen as follows:

$$\begin{aligned} p_1(1|u,v) &= \text{expit}\{(u+v)/\sqrt{1+\rho} - 1\}, \\ q(1) &= 0.5, \\ p_2(1|u,v,c,x) &= \text{expit}\{(u+v)/\sqrt{1+\rho} - 1 + \boldsymbol{t}(c,x)'\bar{\boldsymbol{\beta}}\}, \end{aligned}$$

where expit$(\cdot)$ is the inverse of the logit$(\cdot)$ function. Moreover, C has a multinomial distribution with parameters such that:

$$\log \frac{\pi(0|v)}{\pi(1|v)} = -v - 1, \tag{11}$$

$$\log \frac{\pi(2|v)}{\pi(1|v)} = v - 1; \tag{12}$$

see also equations (7), (8), and (9). Finally, we considered two different values for the sample size $n = 1000, 2000$ and two different sets of values for true parameter vector $\bar{\boldsymbol{\beta}}$, that is, $(1,1,1,1)'$ and $(0.5, 0.5, 1.5, 1.5)'$. In the first case we have $\bar{\delta} = 0$ for the causal effect and in the second case we have $\bar{\delta} = 1$. For each of the resulting four scenarios, obtained combining the values of n with those of $\boldsymbol{\beta}$, we generated 1,000 samples from the assumed model and for every sample we computed the following estimators:

- COV: proposed pseudo conditional likelihood estimator of $\boldsymbol{\beta}$ and δ based on a model that at the first step uses the available covariate V to predict the compliance status, and then $\boldsymbol{g}(v) = (1, v)'$;
- NULL: as above but without the use of the covariate V to predict the compliance status, so that $g(v) = 1$;
- ITT: *intention to treat* estimator of δ based on the conditional logistic regression of Y_2 on $(1, Z)$ given $Y_+ = 1$;

- TR: *treatment received* estimator of δ based on the conditional logistic regression of Y_2 on $(1, X)$ given $Y_+ = 1$.

The results of the simulation described above under the benchmark design are reported in Tables 2 and 3; the first table concerns the estimators COV and NULL of $\boldsymbol{\beta}$, whereas the second concerns the estimators of δ based on all the four approaches, including ITT and TR. These results are reported in term of bias, standard deviation (s.d.), mean of the standard errors computed for every sample (mean s.e.) and, limited to Table 3, the rejection rate of the hypothesis $H_0 : \delta = 0$ based on the Walt test statistic (rej.rate).

$\bar{\beta}_0$	$\bar{\beta}_1$	$\bar{\beta}_2$	$\bar{\beta}_3$	$\bar{\delta}$	n	method		$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$
1.0	1.0	1.0	1.0	0.0	1000	COV	bias	0.0414	0.0242	0.0235	0.0286
							s.d.	0.3441	0.3084	0.3236	0.3057
							mean s.e.	0.3282	0.3083	0.3191	0.2980
						NULL	bias	0.0488	0.0315	0.0278	0.0322
							s.d.	0.3728	0.3867	0.3531	0.3376
							se	0.3548	0.3680	0.3483	0.3245
1.0	1.0	1.0	1.0	0.0	2000	COV	bias	0.0056	0.0040	0.0125	0.0135
							s.d.	0.2235	0.2103	0.2254	0.2054
							mean s.e.	0.2269	0.2134	0.2203	0.2083
						NULL	bias	0.0077	0.0079	0.0135	0.0151
							s.d.	0.2415	0.2475	0.2357	0.2212
							mean s.e.	0.2449	0.2489	0.2379	0.2265
0.5	0.5	1.5	1.5	1.0	1000	COV	bias	0.0289	0.0181	0.0375	0.0294
							s.d.	0.3162	0.2864	0.3629	0.3504
							mean s.e.	0.3187	0.2894	0.3554	0.3350
						NULL	bias	0.0247	0.0291	0.0454	0.0372
							s.d.	0.3452	0.3451	0.4130	0.3776
							mean s.e.	0.3445	0.3468	0.4033	0.3641
0.5	0.5	1.5	1.5	1.0	2000	COV	bias	-0.0034	0.0151	0.0278	0.0148
							s.d.	0.2279	0.2055	0.2376	0.2362
							mean s.e.	0.2223	0.2027	0.2426	0.2326
						NULL	bias	-0.0028	0.0190	0.0341	0.0168
							s.d.	0.2442	0.2406	0.2648	0.2575
							mean s.e.	0.2400	0.2408	0.2702	0.2526

Table 2: *Performance of the proposed estimators COV and NULL of $\boldsymbol{\beta}$ under the benchmark design.*

From the results in Table 2 we conclude that the proposed estimator has a negligible bias regardless if the covariate V is used or not to predict the compliance status. Moreover, this bias tends to reduce as the sample size increases. Concerning the variability, we note that the

$\bar{\beta}_0$	$\bar{\beta}_1$	$\bar{\beta}_2$	$\bar{\beta}_3$	$\bar{\delta}$	n	method	bias	s.d.	mean s.e.	rej.rate
1.0	1.0	1.0	1.0	0.0	1000	COV	-0.0007	0.4466	0.4458	0.0350
						NULL	-0.0037	0.5195	0.5120	0.0290
						ITT	-0.0004	0.2345	0.2339	0.0480
						TR	-0.0070	0.2344	0.2341	0.0600
1.0	1.0	1.0	1.0	0.0	2000	COV	0.0085	0.3004	0.3073	0.0440
						NULL	0.0056	0.3356	0.3454	0.0310
						ITT	0.0036	0.1584	0.1643	0.0440
						TR	0.0089	0.1586	0.1644	0.0460
0.5	0.5	1.5	1.5	1.0	1000	COV	0.0195	0.4594	0.4618	0.6290
						NULL	0.0163	0.5362	0.5385	0.4855
						ITT	-0.5009	0.2372	0.2373	0.5520
						TR	-0.0096	0.2379	0.2420	0.9830
0.5	0.5	1.5	1.5	1.0	2000	COV	0.0127	0.3194	0.3169	0.9130
						NULL	0.0151	0.3649	0.3634	0.8140
						ITT	-0.4945	0.1666	0.1671	0.8560
						TR	0.0053	0.1699	0.1705	1.0000

Table 3: *Performance of the proposed estimators COV and NULL of δ and the estimators ITT and TR under the benchmark design.*

estimator based on the use of covariate V to predict the compliance status tends to have a smaller standard deviation with respect to the NULL estimator. Moreover, the standard deviation is roughly proportional to $1/\sqrt{n}$ and the mean of the standard errors is always very close to this deviation. All these results are in agreement with the asymptotic properties illustrated the beginning of this section. In particular, under the benchmark design we have $\bar{\beta}_0 = \bar{\beta}_1$ and $\bar{\beta}_1 = \bar{\beta}_2$ and then the estimator proposed is consistent. The same conclusions about the performance of the estimators COV and NULL of $\boldsymbol{\beta}$ may be drawn on the basis of Table 3 with reference to the estimation of δ. In particular, we note that the Wald test for the hypothesis $H_0 : \delta = 0$ has the expected behavior. It also interesting to observe that, while the estimator TR of δ has always a negligible bias, the estimator ITT is strongly unbiased when $\bar{\boldsymbol{\beta}} = (0.5, 0.5, 1.5, 1.5)'$ and then $\bar{\delta} = 1$.

Then we considered an *alternative design* for the simulation study in which $\bar{\beta}_0 \neq \bar{\beta}_1$ and $\bar{\beta}_1 \neq \bar{\beta}_2$, so that it is possible to evaluate the quality of the approximation on which the proposed approach is based. This alternative design is equal to the benchmark design, with the exception that $\bar{\boldsymbol{\beta}}$ is equal to $(0, 1, 1, 2)'$ or $(-0.5, 0.5, 1.5, 2.5)'$. In the first case we still have $\bar{\delta} = 0$ and in the second case we have $\bar{\delta} = 1$. The simulation results are reported in Tables 4

and 5, which have the same structure as Tables 2 and 3 above.

$\bar{\beta}_0$	$\bar{\beta}_1$	$\bar{\beta}_2$	$\bar{\beta}_3$	$\bar{\delta}$	n	method		$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$
0.0	1.0	1.0	2.0	0.0	1000	COV	bias	0.0297	0.0799	0.0692	0.0429
							s.d.	0.3159	0.3465	0.2897	0.4045
							mean s.e.	0.3209	0.3471	0.2851	0.4050
						NULL	bias	0.0021	0.2305	0.0686	0.0562
							s.d.	0.3490	0.4907	0.3039	0.4315
							mean s.e.	0.3523	0.4976	0.2979	0.4279
0.0	1.0	1.0	2.0	0.0	2000	COV	bias	0.0255	0.0485	0.0492	0.0269
							s.d.	0.2284	0.2414	0.1983	0.3022
							mean s.e.	0.2248	0.2379	0.1981	0.2812
						NULL	bias	0.0025	0.1730	0.0509	0.0340
							s.d.	0.2491	0.3300	0.2090	0.3203
							mean s.e.	0.2459	0.3171	0.2063	0.2971
-0.5	0.5	1.5	2.5	1.0	1000	COV	bias	0.0046	0.0371	0.0725	0.0857
							s.d.	0.3575	0.3084	0.3259	0.5238
							mean s.e.	0.3538	0.3042	0.3106	0.5056
						NULL	bias	-0.0216	0.1514	0.0645	0.1006
							s.d.	0.3917	0.3873	0.3408	0.5400
							mean s.e.	0.3841	0.3877	0.3269	0.5313
-0.5	0.5	1.5	2.5	1.0	2000	COV	bias	0.0198	0.0320	0.0381	0.0442
							s.d.	0.2543	0.2163	0.2074	0.3705
							mean s.e.	0.2451	0.2120	0.2131	0.3415
						NULL	bias	-0.0091	0.1482	0.0276	0.0589
							s.d.	0.2741	0.2797	0.2166	0.3917
							mean s.e.	0.2653	0.2682	0.2226	0.3594

Table 4: *Performance of the proposed estimators COV and NULL of $\boldsymbol{\beta}$ under the alternative design 1.*

It is worth noting that the bias of the proposed estimator is very low in all cases considered in Tables 4 and 5, at least when the covariate V is used to predict the compliance status. Moreover, in terms of variability, the estimator behaves as expected and the mean of the standard error computed for every sample is close to the standard deviation. Consequently, the rejection rate of the test for $H_0 : \delta = 0$ is very close to the nominal level when this hypothesis is true and it is much higher otherwise. On the other hand, under this first alternative design, the estimation of δ is strongly biased when it is based on the estimators ITT and TR, with the first estimator that tends to underestimate the causal effect (when $\bar{\delta} = 1$) and the second that tends to overestimate this effect (also when $\bar{\delta} = 0$). This bias has obviously consequences on the rejection rate of the Wald test for H_0.

Finally, we considered an alternative simulation design which is very similar the above one,

$\bar{\beta}_0$	$\bar{\beta}_1$	$\bar{\beta}_2$	$\bar{\beta}_3$	$\bar{\delta}$	n	method	bias	s.d.	mean s.e.	rej.rate
0.0	1.0	1.0	2.0	0.0	1000	COV	-0.0107	0.4547	0.4514	0.0312
						NULL	-0.1619	0.5759	0.5876	0.0171
						ITT	-0.0022	0.2334	0.2369	0.0400
						TR	0.9244	0.2569	0.2430	0.9680
0.0	1.0	1.0	2.0	0.0	2000	COV	0.0006	0.3170	0.3103	0.0450
						NULL	-0.1221	0.3966	0.3801	0.0380
						ITT	0.0066	0.1686	0.1667	0.0580
						TR	0.9245	0.1683	0.1709	1.0000
-0.5	0.5	1.5	2.5	1.0	1000	COV	0.0354	0.4370	0.4368	0.6771
						NULL	-0.0870	0.5006	0.5108	0.4601
						ITT	-0.4813	0.2308	0.2378	0.6000
						TR	0.8805	0.2641	0.2625	1.0000
-0.5	0.5	1.5	2.5	1.0	2000	COV	0.0060	0.2999	0.3011	0.9240
						NULL	-0.1207	0.3577	0.3495	0.7140
						ITT	-0.5007	0.1697	0.1673	0.8450
						TR	0.8654	0.1887	0.1843	1.0000

Table 5: *Performance of the proposed estimators COV and NULL of δ and the estimators ITT and TR under the alternative design 1.*

with the only difference that the unobservable variable U is assumed to also affect the compliance status. In particular, instead of (11) and (12) we assumed that

$$\begin{aligned} \log \frac{\pi(0|u,v)}{\pi(1|u,v)} &= -(0.5u+v)/\sqrt{1.5} - 1, \\ \log \frac{\pi(2|u,v)}{\pi(1|u,v)} &= (0.5u+v)/\sqrt{1.5} - 1. \end{aligned}$$

The simulations results are reported in Tables 6 and 7, which have the usual structure.

Comparing the results in Table 6 with those in Table 4, we observe that the effect of the unobservable variable on the compliance status generally increases the bias of the proposed estimator under both COV and NULL schemes. However, it is interesting to note that this bias remains rather low, especially under the COV scheme. This is confirmed by the results in Table 7 which is referred to the estimation of δ and shows a behavior of the COV estimator which is generally much better than that of the ITT and TR estimators of this causal effect.

In conclusion, the proposed estimator confirms the expected characteristics when $\bar{\beta}_0 = \bar{\beta}_1$ and $\bar{\beta}_2 = \bar{\beta}_3$, case in which it is consistent regardless of how the model for the compliance is specified. Moreover, at least under the model assumed in the simulation, the impact on the bias

$\bar{\beta}_0$	$\bar{\beta}_1$	$\bar{\beta}_2$	$\bar{\beta}_3$	$\bar{\delta}$	n	method		$\hat{\beta}_0$	$\hat{\beta}_1$	$\hat{\beta}_2$	$\hat{\beta}_3$
0.0	1.0	1.0	2.0	0.0	1000	COV	bias	0.0413	0.1298	0.0483	0.0471
							s.d.	0.3707	0.4048	0.2860	0.4459
							mean s.e.	0.3528	0.3844	0.2853	0.4259
						NULL	bias	-0.0064	0.3009	0.0364	0.0685
							s.d.	0.4013	0.6050	0.2885	0.4572
							mean s.e.	0.3799	0.6155	0.2928	0.4424
0.0	1.0	1.0	2.0	0.0	2000	COV	bias	0.0339	0.1197	0.0504	0.0110
							s.d.	0.2431	0.2633	0.2027	0.2983
							mean s.e.	0.2442	0.2613	0.2006	0.2902
						NULL	bias	-0.0049	0.2547	0.0357	0.0336
							s.d.	0.2653	0.3459	0.2103	0.3095
							mean s.e.	0.2620	0.3386	0.2057	0.3011
-0.5	0.5	1.5	2.5	1.0	1000	COV	bias	0.0368	0.0925	0.0560	0.0948
							s.d.	0.3934	0.3457	0.3458	0.5319
							mean s.e.	0.3875	0.3330	0.3174	0.5286
						NULL	bias	-0.0133	0.2198	0.0393	0.1161
							s.d.	0.4207	0.4403	0.3421	0.5535
							mean s.e.	0.4136	0.4151	0.3254	0.5470
-0.5	0.5	1.5	2.5	1.0	2000	COV	bias	0.0152	0.0978	0.0305	0.0206
							s.d.	0.2765	0.2361	0.2139	0.3476
							mean s.e.	0.2688	0.2309	0.2164	0.3534
						NULL	bias	-0.0275	0.2121	0.0148	0.0419
							s.d.	0.2913	0.2862	0.2196	0.3641
							mean s.e.	0.2860	0.2811	0.2222	0.3656

Table 6: *Performance of the proposed estimators COV and NULL of $\boldsymbol{\beta}$ under the alternative design 2.*

of the distance between $\bar{\beta}_0$ and $\bar{\beta}_1$ and the distance between $\bar{\beta}_2$ and $\bar{\beta}_3$ is moderate, especially when the available covariate is used to predict the compliance status. Finally, even when the unobservable covariate is assumed to affect this status, and then one of the assumptions of the causal model introduced in Section 3.1 is violated, such an estimator seems to maintain its good performance.

Finally, we have to note that for a very limited number of simulated samples some elements of $\hat{\boldsymbol{\beta}}$ converged to a very low or high value; these samples have not been considered in the computation of the results in the Tables 2 to 7. This is due to the reduced information available in the sample about the behavior of a certain subpopulation of subjects, for instance that of always-takers. These cases happened only with $n = 1,000$ and never under the benchmark simulation design.

$\bar{\beta}_0$	$\bar{\beta}_1$	$\bar{\beta}_2$	$\bar{\beta}_3$	$\bar{\delta}$	n	method	bias	s.d.	mean s.e.	rej.rate
0.0	1.0	1.0	2.0	0.0	1000	COV	-0.0815	0.4940	0.4823	0.0290
						NULL	-0.2645	0.6780	0.6995	0.0120
						ITT	0.0000	0.2399	0.2396	0.0460
						TR	0.8650	0.2427	0.2445	0.9470
0.0	1.0	1.0	2.0	0.0	2000	COV	-0.0693	0.3319	0.3303	0.0410
						NULL	-0.2189	0.4014	0.3980	0.0420
						ITT	-0.0001	0.1669	0.1687	0.0460
						TR	0.8688	0.1757	0.1722	1.0000
-0.5	0.5	1.5	2.5	1.0	1000	COV	-0.0365	0.4826	0.4638	0.5784
						NULL	-0.1805	0.5522	0.5325	0.3890
						ITT	-0.4610	0.2490	0.2428	0.5960
						TR	0.8218	0.2629	0.2650	1.0000
-0.5	0.5	1.5	2.5	1.0	2000	COV	-0.0673	0.3162	0.3171	0.8350
						NULL	-0.1973	0.3593	0.3594	0.6250
						ITT	-0.4698	0.1650	0.1705	0.8830
						TR	0.8080	0.1848	0.1858	1.0000

Table 7: *Performance of the proposed estimators COV and NULL of δ and the estimators ITT and TR under the alternative design 2.*

6 Application to randomized study on coronary angiography after myocardial infarction

In this section we describe the application of the proposed estimator to the analysis of the data described in Section 2. We recall that the proposed approach is based on two steps: (*i*) estimation of the model for probability of being a never-taker, a complier, or an always-taker, and (*ii*) computation of the approximate conditional logistic estimator.

Regarding the first step, an important point is the selection of the covariates to explain the non-compliance. In particular, we performed model choice by minimizing the Bayesian Information Criterion (BIC, see [35]) and finally selected two predictors (GI discretized using the quartiles and use of statines); see also Section 2. The results from fitting this model are reported in Table 8 in terms of estimates of the parameters $\boldsymbol{\alpha}_0$ and $\boldsymbol{\alpha}_2$, which are involved in expressions (5) and (6), and corresponding t-statistics and p-values. For the categorical variable identifying the quartile of GI, we used the last quartile as reference category.

We observe a significant non-compliance. The probabilities of being an always-taker or a never-taker are related in both cases to GI and use of statines. There is a significant lower

Parameter estimates for probability of being a never-taker				
Estimator	Value	Std. Err.	t-statistic	p-value
$\hat{\alpha}_{00}$ (Intercept)	1.604	0.531	3.017	0.002
$\hat{\alpha}_{01}$ (1st quartile GI)	-0.757	0.384	-1.974	0.048
$\hat{\alpha}_{02}$ (2nd quartile GI)	-0.886	0.368	-2.406	0.016
$\hat{\alpha}_{03}$ (3rd quartile GI)	-0.437	0.388	-1.125	0.260
$\hat{\alpha}_{04}$ (use of statin)	-0.985	0.438	-2.247	0.025

Parameter estimates for probability of being an always-taker				
Estimator	Value	Std. Err.	t-statistic	p-value
$\hat{\alpha}_{20}$ (Intercept)	1.454	0.597	2.436	0.015
$\hat{\alpha}_{21}$ (1st quartile GI)	-0.565	0.444	-1.274	0.202
$\hat{\alpha}_{22}$ (2nd quartile GI)	-0.862	0.434	-1.987	0.046
$\hat{\alpha}_{23}$ (3rd quartile GI)	-0.459	0.449	-1.023	0.306
$\hat{\alpha}_{24}$ (use of statin)	-0.980	0.496	-1.977	0.048

Table 8: *Estimates of compliance probability parameters for the proposed model, computed on the prompt coronary angiography data; predictors are quartiles of glicemic index (GI) and use of statines.*

probability of being an always-taker in the second GI quartile with respect to the fourth, while the other two quartiles are not statistically different from the fourth. On the other hand, the probability of being a never-taker steadily increases with the GI category, with the third and fourth quartile not being significantly different. The estimated effects of GI for always-takers are explained considering that doctors may choose to assign to prompt CA even patients randomized to the control (therefore making them always-takers) when they have an abnormal GI (here, above the median or in the first quartile). Finally, the use of statines increases compliance in both directions. This effect can be related to the fact that patients using statines are better monitored and maybe already known to doctors, and therefore a higher adherence to the experimental settings is more likely for these patients.

Note that, even without covariates, by the proposed method we can obtain an approximately unbiased estimator of the causal effect (as seen by comparing $\hat{\delta}$ with $\hat{\delta}^{(1)}$ in Table 9), but the use of covariates allows to take into account part of the heterogeneity, therefore decreasing the standard error of this estimate.

In Table 9 we report estimates of causal parameters, and compare them with four other estimators. The first (denoted by $\hat{\delta}^{(1)}$) is based on our proposed approach in which no covariates

Estimates of the causal parameters				
Estimator	Value	Std. Err.	t-statistic	p-value
$\hat{\beta}_0$	2.158	0.361	5.973	< 0.001
$\hat{\beta}_1$	1.948	0.677	2.878	0.004
$\hat{\beta}_2$	-0.072	0.370	-0.195	0.845
$\hat{\beta}_3$	2.252	0.455	4.945	< 0.001

Estimates of the causal effect for compliers				
Estimator	Value	Std. Err.	t-statistic	p-value
$\hat{\delta}$ (proposed method)	-2.020	0.769	-2.625	0.009
$\hat{\delta}^{(1)}$ (proposed method)	-1.938	0.929	-2.086	0.037
$\hat{\delta}^{(2)}$	-0.177	0.118	-1.500	0.133
$\hat{\delta}^{(3)}$	-0.513	0.119	-4.311	< 0.001
$\hat{\delta}^{(4)}$	-0.550	0.149	-3.691	< 0.001

Table 9: *Causal parameters for the proposed model estimated on the prompt coronary angiography data. Predictors are GI (discretized in quartiles) and use of statines. In the bottom panel, $\hat{\delta}$ is compared with the same estimate when covariates are not used ($\hat{\delta}^{(1)}$) and with competing estimators: $\hat{\delta}^{(2)}$, standard conditional estimator based on received treatment (X, TR); $\hat{\delta}^{(3)}$, standard conditional estimator based on assigned treatment (Z, ITT); $\hat{\delta}^{(4)}$, standard conditional estimator based on the assigned and complied treatment (Per Protocol analysis)*

are used to predict compliance. The other three estimators (denoted by $\hat{\delta}^{(2)}$, $\hat{\delta}^{(3)}$, and $\hat{\delta}^{(4)}$, respectively) are based on a conditional logistic regression on the received treatment (TR) and an Intention to Treat (ITT) and a Per Protocol analysis. The last two are based on the assigned treatment regardless of the actually received treatment and on patients actually receiving the assigned treatment, respectively. From the upper panel we can see that the control has approximately the same effect on never-takers and on compliers (with a log-odds of about 2). The treatment seems to have no effect on compliers, whereas on always-takers we again obtain a log-odds of about 2. Therefore, we can state that (*i*) lack of a prompt CA, regardless of whether it was assigned or as a result of non-compliance, may increase the risk of recurrence and (*ii*) if a patient who was assigned to the control group undergoes prompt CA, this is likely due to a possibly bad (even life threatening) condition, hence the high risk of recurrent events even under the treatment. A consequence is that bias with ITT and PP estimators arise mostly due to always takers. In fact, the effect of the control is approximately the same on never-takers and compliers ($\beta_0 \approx \beta_1$); on the other hand, there is a strong difference of the effect of treatment

as estimated on compliers and always-takers ($\beta_2 \neq \beta_3$).

Always-takers in this example can be expected to experience the event even after the treatment. Ignoring this fact will make the two groups artificially similar, as confirmed by the estimates $\hat{\delta}^{(2)}$, $\hat{\delta}^{(3)}$, and $\hat{\delta}^{(4)}$. In fact, our most important estimate is $\hat{\delta}$, which is approximately -2. When our final estimate is compared with $\hat{\delta}^{(2)}$, $\hat{\delta}^{(3)}$, and $\hat{\delta}^{(4)}$ we find that those are at most only half our causal estimate. The estimate of the causal parameter based on the received treatment ($\hat{\delta}^{(2)}$) is not even significant. Standard fits in this example may lead to grossly underestimate the effect of a prompt CA.

7 Discussion

An approach is introduced to estimate the causal effect of a treatment over control on the basis of a two-arm experimental study with possible non-compliance both in the control and treatment arm. The approach is applicable when the effect of the treatment is measured by a binary response variable observed before and after the treatment. It relies on a causal model formulated on the basis of latent variables for the effect of unobservable covariates at both occasions and to account for the difference between compliers and non-compliers in terms of reaction to control and treatment. The parameters of the model are estimated by a pseudo conditional likelihood approach based on an approximated version of the conditional probability of the two response variables given their sum and its application is based on two steps. Our estimator is generally approximately consistent and it is exactly consistent in certain cases. However, as we show by simulation, even when it is not exactly consistent its bias is typically negligible.

An important point is how the proposed approach compares with existing approaches for causal inference that may be adopted for two-arm experimental studies with non-compliance. In particular, many interesting approaches originates from the seminal paper [1], as the one proposed in [7] for the case of binary outcomes and considering pre-treatment covariates. However, there is no approach in the literature, to the best of our knowledge, that recognizes the nature of the pre-treatment copy of the outcome, and the latter is commonly used as any other covariate. In our approach we give a special role to Y_1 so that parametric assumptions are formulated

only on difference between the conditional logit for the distribution of post-treatment outcome and that for the distribution the pre-treatment outcome. In this way, unlike other approaches as that in [7], we do not need to specify the dependence of the distribution of the outcome of interest on the pre-treatment covariates and the effect of unobserved covariates may be also considered.

The proposed approach is applied to the analysis of data coming from a study on the effect of prompt coronary angiography in myocardial infarction. The application shows that prompt coronary angiography in patients with myocardial infarction may significantly decrease the risk of other events within the next two years, with a log-odds of about -2. On the other hand, estimates of this log-odds ratio obtained by the standard logistic approach are considerably closer to zero.

One of the basic assumptions on which the approach relies is that a subject is assigned to the control arm or to the treatment arm with a probability depending only on the observable covariates and not on the pre-treatment response variable. Indeed, we could relax this assumption, but we would have more complex expressions for the conditional probability of the response variables given their sum.

As a final comment we remark that we only considered the case of repeated response variables having a binary nature. However, the approach may be directly extended to the case of response variables having a different nature (e.g., counting), provided that the conditional distribution of these variables belongs to the natural exponential family and the causal effect is measured on a scale defined according to the canonical link function for the adopted distribution [36].

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Appendix: Matrices involved in the sandwich estimator for the variance of the estimator

We have that

$$\hat{\boldsymbol{H}} = \begin{pmatrix} \dfrac{\partial \ell_1(\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\alpha}_0 \partial \boldsymbol{\alpha}_0'} & \dfrac{\partial \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_0 \partial \boldsymbol{\alpha}_2'} & \boldsymbol{O} \\ \dfrac{\partial \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_2 \partial \boldsymbol{\alpha}_0'} & \dfrac{\partial \ell_1(\boldsymbol{\alpha}_0, \boldsymbol{\alpha}_2)}{\partial \boldsymbol{\alpha}_2 \partial \boldsymbol{\alpha}_2'} & \boldsymbol{O} \\ \dfrac{\partial \ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta} \partial \boldsymbol{\alpha}_0'} & \dfrac{\partial \ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta} \partial \boldsymbol{\alpha}_2'} & \dfrac{\partial \ell_2(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta} \partial \boldsymbol{\beta}'} \end{pmatrix}$$

and

$$\hat{\boldsymbol{K}} = \sum_i \begin{pmatrix} \dfrac{\partial \ell_{1i}(\hat{\boldsymbol{\alpha}}_0)}{\partial \boldsymbol{\alpha}_0} \\ \dfrac{\partial \ell_{1i}(\hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\alpha}_2} \\ \dfrac{\partial \ell_{2i}(\hat{\boldsymbol{\beta}}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta}} \end{pmatrix} \begin{pmatrix} \dfrac{\partial \ell_{1i}(\hat{\boldsymbol{\alpha}}_0)}{\partial \boldsymbol{\alpha}_0'} & \dfrac{\partial \ell_{1i}(\hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\alpha}_2'} & \dfrac{\partial \ell_{2i}(\hat{\boldsymbol{\beta}}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta}'} \end{pmatrix}.$$

In the above expressions, $\boldsymbol{O}$ denotes a matrix of zeros of suitable dimension. Moreover, all the derivatives have been defined, with the exception of the derivative of $\ell_2(\hat{\boldsymbol{\beta}}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)$ with respect to $\boldsymbol{\alpha}_0$ (or $\boldsymbol{\alpha}_2$) and $\boldsymbol{\beta}$. In particular, we have that:

$$\frac{\partial^2 \ell_2^*(\boldsymbol{\beta}|\hat{\boldsymbol{\alpha}}_0, \hat{\boldsymbol{\alpha}}_2)}{\partial \boldsymbol{\beta} \partial \boldsymbol{\alpha}_c'} = \operatorname{diag}(\hat{\boldsymbol{a}}) \sum_i d_i \left(\frac{y_{i2}}{\hat{\boldsymbol{w}}_i' \boldsymbol{\eta}} - \frac{1 - y_{i2}}{1 - \hat{\boldsymbol{w}}_i' \boldsymbol{\eta}} \right) \frac{\partial \hat{\boldsymbol{w}}_i}{\partial \boldsymbol{\alpha}_c'}, \quad c = 0, 2,$$

where

$$\frac{\partial \hat{\boldsymbol{w}}_i}{\partial \boldsymbol{\alpha}_0'} = \begin{cases} (\hat{\pi}_{01}^*(0|\boldsymbol{v}_i)\hat{\pi}_{01}^*(1|\boldsymbol{v}_i), -\hat{\pi}_{01}^*(0|\boldsymbol{v}_i)\hat{\pi}_{01}^*(1|\boldsymbol{v}_i), 0, 0)' \boldsymbol{g}(\boldsymbol{v}_i), & z_i = x_i = 0, \\ \boldsymbol{O}, & \text{otherwise,} \end{cases}$$

and

$$\frac{\partial \hat{\boldsymbol{w}}_i}{\partial \boldsymbol{\alpha}_0'} = \begin{cases} (0, 0, -\hat{\pi}_{12}^*(1|\boldsymbol{v}_i)\hat{\pi}_{01}^*(1|\boldsymbol{v}_i), \hat{\pi}_{12}^*(1|\boldsymbol{v}_i)\hat{\pi}_{12}^*(2|\boldsymbol{v}_i))' \boldsymbol{g}(\boldsymbol{v}_i), & z_i = x_i = 1, \\ \boldsymbol{O}, & \text{otherwise.} \end{cases}$$

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