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## **Methodological obstacles in causal inference: confounding, missing data, and measurement error**

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### **Citation**

Penning de Vries, B. B. L. (2022, January 25). *Methodological obstacles in causal inference: confounding, missing data, and measurement error*. Retrieved from <https://hdl.handle.net/1887/3250835>

Version: Publisher's Version

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**Note:** To cite this publication please use the final published version (if applicable).

IDENTIFICATION OF CAUSAL EFFECTS IN CASE-CONTROL  
STUDIES

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*BMC Medical Research Methodology* [Accepted for publication]

## **Abstract**

Case-control designs are an important tool in contrasting the effects of well-defined treatments. In this paper, we reconsider classical concepts, assumptions and principles and explore when the results of case-control studies can be endowed a causal interpretation. Our focus is on identification of target causal quantities, or estimands. We cover various estimands relating to intention-to-treat or per-protocol effects for popular sampling schemes (case-base, survivor, and risk-set sampling), each with and without matching. Our approach may inform future research on different estimands, other variations of the case-control design or settings with additional complexities.

## 10.1 Introduction

In causal inference, it is important that the causal question of interest is unambiguously articulated (Hernán and Robins, 2020). The causal question should dictate, and therefore be at the start of, investigation. When the target causal quantity, the estimand, is made explicit, one can start to question how it relates to the available data distribution and, as such, form a basis for estimation with finite samples from this distribution.

The counterfactual framework offers a language rich enough to articulate a wide variety of causal claims that can be expressed as what-if statements (Hernán and Robins, 2020). Another, albeit closely related, approach to causal inference is target trial emulation, an explicit effort to mitigate departures from a study (the ‘target trial’) that, if carried out, would enable one to readily answer the causal what-if question of interest (Hernán and Robins, 2016). While it may be too impractical or unethical to implement, making explicit what a target trial looks like has particular value in communicating the inferential goal and offers a reference against which to compare studies that have been or are to be conducted.

The counterfactual framework and emulation approach have become increasingly popular in observational cohort studies. Case-control studies, however, have not yet enjoyed this trend. A notable exception is given by Dickerman et al. (2020), who recently outlined an application of trial emulation with case-control designs to statin use and colorectal cancer.

In this paper, we give an overview of how observational data obtained with case-control designs can be used to identify a number of causal estimands and, in doing so, recast historical case-control concepts, assumptions and principles in a modern and formal framework.

## 10.2 Preliminaries

### *10.2.1 Identification versus estimation*

An estimand is said to be identifiable if the distribution of the available data is compatible with exactly one value of the estimand, or therefore, if the estimand can be expressed as a function of the available data distribution. Identification forms a basis for estimation with finite samples from this distribution (Petersen and Van der Laan, 2014). Once the estimand has been made explicit and an identifiability expression established, estimation is a purely statistical task. While the expression will often naturally translate into a plug-in estimator, there is, however, generally more than one way to translate an identifiability

result into an estimator and different estimators may have important differences in their statistical properties. Here, our focus is on identification, so that the purely statistical issues of the next step in causal inference, estimation, can be momentarily put aside.

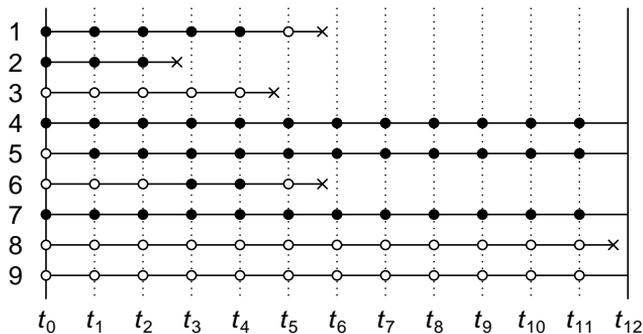
10.2.2 Case-control study nested in cohort study

To facilitate understanding, it is useful to consider every case-control study as being “nested” within a cohort study. A case-control study is effectively a cohort study with missingness governed by the control sampling scheme. Therefore, when the observed data distribution of a case-control study is compatible with exactly one value of a given estimand, then so is the available or observed data distribution of the underlying cohort study. In other words, identifiability of an estimand with a case-control study implies identifiability of the estimand with the cohort study within which it is nested. The converse is not evident and in fact may not be true. In this paper, the focus is on sets of conditions or assumptions that are sufficient for identifiability in case-control studies.

10.2.3 Set-up of underlying cohort study

Consider a time-varying exposure  $A_k$  that can take one of two levels, 0 or 1, at  $K$  successive time points  $t_k$  ( $k = 0, 1, \dots, K - 1$ ), where  $t_0$  denotes baseline (cohort

**Figure 10.1:** Illustration of possible courses of follow-up of an individual for a study with baseline  $t_0$  and administrative study end  $t_{12}$ .



Solid bullets indicate ‘exposed’; empty bullets indicate ‘not exposed’. The incident event of interest is represented by a cross.

entry or time zero). Study participants are followed over time until they sustain the event of interest or the administrative study end  $t_K$ , whichever comes first. We denote by  $T$  the time elapsed from baseline until the event of interest and let  $Y_k = I(T < t_k)$  indicate whether the event has occurred by  $t_k$ . The lengths between the time points are typically fixed at a constant (e.g., of one day, week, or month). Figure 10.1 depicts twelve equally spaced time points over, say, twelve months with several possible courses of follow-up of an individual. As the figure illustrates, individuals can switch between exposure levels during follow-up, as in any truly observational study. Apart from exposure and outcome data, we also consider a (vector of) covariate(s)  $L_k$ , which describes time-fixed individual characteristics or time-varying characteristics typically relating to a time window just before exposure or non-exposure at  $t_k$ ,  $k = 0, 1, \dots, K - 1$ .

#### 10.2.4 Causal contrasts

Although there are many possible contrasts, particularly with time-varying exposures, for simplicity we consider only two pairs of mutually exclusive interventions: (1) setting baseline exposure  $A_0$  to 1 versus 0; and (2) setting all of  $A_0, A_1, \dots, A_{K-1}$  to 1 ('always exposed') versus all to 0 ('never exposed'). For  $a = 0, 1$ , we let counterfactual outcome  $Y_k(a)$  indicate whether the event has occurred by  $t_k$  under the baseline-only intervention that sets  $A_0$  to  $a$ . By convention, we write  $\bar{1} = (1, 1, \dots, 1)$  and  $\bar{0} = (0, 0, \dots, 0)$ , and let  $Y_k(\bar{1})$  and  $Y_k(\bar{0})$  indicate whether the event has occurred by  $t_k$  under the intervention that sets  $(A_0, A_1, \dots, A_{K-1})$  all to 1 and all to 0, respectively. Further details about the notation and set-up are given in Supplementary Appendix S10.1.

#### 10.2.5 Case-control sampling

The fact that each time-specific exposure variable can take only one value per time point means that at most one counterfactual outcome can be observed per individual. This type of missingness is common to all studies. Relative to the cohort studies within which they are nested, case-control studies have additional missingness, which is governed by the control sampling scheme. In this paper, we focus on three well-known sampling schemes: case-base sampling, survivor sampling, and risk-set sampling. The next sections give an overview of conditions under which intention-to-treat and always-versus-never-exposed per-protocol effects can be identified with the data that are observed under these sampling schemes.

### 10.3 Case-control studies without matching

Table 10.1 summarises a number of identification results for case-control studies without matching. More formal statements and proofs are given in Supplementary Appendix S10.2. In all case-control studies that we consider in this section, cases are compared with controls with regard to their exposure status via an odds ratio, even when an effect measure other than the odds ratio is targeted. An individual qualifies as a case if and only if they sustain the event of interest by the administrative study end (i.e.,  $Y_K = 1$ ) and adhered to one of the protocols of interest until the time of the incident event. In Figure 10.1, the individual represented by row 1 is therefore regarded as a case (an exposed case in particular) in our investigation of intention-to-treat effects but not in that of per-protocol effects. Whether an individual (also) serves as a control depends on the control sampling scheme.

#### 10.3.1 Case-base sampling

The first result in Table 10.1 describes how to identify the intention-to-treat effect as quantified by the marginal risk ratio

$$\frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}$$

under case-base sampling. (For identification of a conditional risk ratio, see Theorem 10.2 of Supplementary Appendix S10.2.) Case-base sampling, also known as case-cohort sampling, means that no individual who is at risk at baseline of sustaining the event of interest is precluded from selection as a control. Selection as a control,  $S$ , is further assumed independent of baseline covariate  $L_0$  and exposure  $A_0$ . Selecting controls from survivors only (e.g., rows 4, 5, 7 and 9 in Figure 10.1) violates this assumption when survival depends on  $L_0$  or  $A_0$ .

To account for baseline confounding, inverse probability weights could be derived from control data according to

$$W = \frac{A_0}{\Pr(A_0 = 1|L_0, S = 1)} + \frac{1 - A_0}{1 - \Pr(A_0 = 1|L_0, S = 1)}. \quad (10.1)$$

We then compute the odds of baseline exposure among cases and among controls in the pseudopopulation that is obtained by weighting everyone by subject-specific values of  $W$ . The ratio of these odds coincides with the target risk ratio under the three key identifiability conditions of consistency, baseline conditional exchangeability and positivity (Hernán and Robins, 2020).

The identification result for case-base sampling suggests a plug-in estimator: replace all functionals of the theoretical data distribution with sample analogues. For example, to obtain the weight for an individual with baseline covariate level  $l_0$ , replace the theoretical propensity score  $\Pr(A_0 = 1|L_0 = l_0, S = 1)$  with an estimate  $\widehat{\Pr}(A_0 = 1|L_0 = l_0, S = 1)$  derived from a fitted model (e.g., a logistic regression model) that imposes parametric constraints on the distribution of  $A_0$  given  $L_0$  among the controls.

### 10.3.2 Survivor sampling

With survivor (cumulative incidence or exclusive) sampling, a subject is eligible for selection as a control only if they reach the administrative study end event-free. To identify the conditional odds ratio of baseline exposure versus baseline non-exposure given  $L_0$ ,

$$\frac{\text{Odds}(Y_K(1) = 1|L_0)}{\text{Odds}(Y_K(0) = 1|L_0)},$$

selection as a control,  $S$ , is assumed independent of baseline exposure  $A_0$  given  $L_0$  and survival until the end of study (i.e.,  $Y_K = 0$ ).

The directed acyclic graph (DAG) of Figure 10.2 is compatible with both survivor sampling and case-base sampling. For those well versed in DAGs, it is tempting to conclude from it that restricting the analysis to those included in the study, i.e., conditioning on study inclusion, would result in bias (or departure from identification), by way of collider stratification. Although conditioning on study inclusion may indeed induce an association between baseline exposure and unmeasured cause  $U$  of  $Y_K$  (within levels of  $L_0$ ), it is important to recognise it need not result in bias (Westreich, 2012; Hughes et al., 2019).

In fact, as is shown in Supplementary Appendix S10.2, Theorem 10.3, the above odds ratio is identified by the ratio of the baseline exposure odds given  $L_0$  among the cases versus controls, provided the key identifiability conditions of consistency, baseline conditional exchangeability, and positivity are met.

All estimands in Table 10.1 describe a marginal effect, except for the odds ratio, which is conditional on baseline covariates  $L_0$ . The corresponding marginal odds ratio

$$\frac{\text{Odds}(Y_K(1) = 1)}{\text{Odds}(Y_K(0) = 1)}$$

is not identifiable from the available data distribution under the stated assumptions (see remark to Theorem 10.3, Supplementary Appendix S10.2).

**Table 10.1:** Overview of (non-parametric) identification results for case-control studies without matching.

| Sampling scheme | Estimand  | Assumptions   | Identification strategy  |
|-----------------|---|---|--|
| Case-base       | Risk ratio for intention-to-treat effect<br>$\frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}$                         | <ul style="list-style-type: none"> <li>Control selection <math>S</math> independent of baseline covariates <math>L_0</math> and exposure <math>A_0</math></li> <li>Consistency</li> <li>Baseline exchangeability given <math>L_0</math></li> <li>Positivity (Theorem 10.1)</li> </ul>   | <ol style="list-style-type: none"> <li>Derive time-fixed IP weights <math>W</math> from control data</li> <li>Compute the baseline exposure odds among cases, weighted by <math>W</math></li> <li>Compute the baseline exposure odds among controls, weighted by <math>W</math></li> </ol> |
| Survivor        | Odds ratio for intention-to-treat effect<br>$\frac{\text{Odds}(Y_K(1) = 1 L_0)}{\text{Odds}(Y_K(0) = 1 L_0)}$ | <ul style="list-style-type: none"> <li>Control selection <math>S</math> independent of baseline exposure <math>A_0</math> given baseline covariates <math>L_0</math> and survival until <math>t_K</math> (<math>Y_K = 0</math>)</li> <li>Consistency</li> <li>Baseline exchangeability given <math>L_0</math></li> <li>Positivity (Theorem 10.3)</li> </ul> | <ol style="list-style-type: none"> <li>Derive the conditional baseline exposure odds given <math>L_0</math> among cases</li> <li>Derive the conditional baseline exposure odds given <math>L_0</math> among controls</li> <li>Take the ratio of the results of steps 1 and 2</li> </ol>    |

Table 10.1 continued.

| Sampling scheme | Estimand  | Assumptions  | Identification strategy   |
|-----------------|---|--|---|
| Risk-set        | <p>Hazard ratio for intention-to-treat effect</p> $\frac{\Pr(Y_{k+1}(1) = 1   Y_k(1) = 0)}{\Pr(Y_{k+1}(0) = 1   Y_k(0) = 0)}$ | <ul style="list-style-type: none"> <li>Control selection <math>S_k</math> independent of baseline covariates <math>L_0</math> and exposure <math>A_0</math> given eligibility at <math>t_k</math> (<math>Y_k = 0</math>) with constant sampling probability among those eligible<sup>†</sup></li> <li>Consistency</li> <li>Baseline exchangeability given number of times selected as a control</li> <li>Positivity</li> <li>Constant counterfactual hazards (Theorem 10.4)</li> </ul> | <ol style="list-style-type: none"> <li>Derive time-fixed IP weights <math>W</math> from control data</li> <li>Compute baseline exposure odds among cases, weighted by <math>W</math></li> <li>Compute baseline exposure odds among controls, weighted by <math>W</math> times <math>\sum_{k=0}^{K-1} S_k</math>, the number of times selected as a control</li> <li>Take the ratio of the results of steps 2 and 3</li> </ol> |

Table 10.1 continued.

| Sampling scheme | Estimand  | Assumptions   | Identification strategy   |
|-----------------|---|---|---|
|                 | Hazard ratio for per-protocol effect  | <ul style="list-style-type: none"> <li>Control selection <math>S_k</math> independent of covariate and exposure history up to <math>t_k</math> given eligibility at <math>t_k</math> (<math>Y_k = 0</math>) with constant sampling probability among those eligible<sup>†</sup></li> <li>Consistency</li> <li>Sequential conditional exchangeability</li> <li>Positivity</li> <li>Constant counterfactual hazards (Theorem 10.6)</li> </ul> | <ol style="list-style-type: none"> <li>Derive time-varying IP weights <math>W_k</math> from control data</li> <li>Censor from time of protocol deviation</li> <li>Compute (baseline) exposure odds among cases, weighted by those weights <math>W_k</math> such that <math>Y_k = 0</math> and <math>Y_{k+1} = 1</math></li> <li>Compute (baseline) exposure odds among all controls, weighted by <math>\sum_{k=0}^{K-1} W_k S_k</math>, the weighted number of times selected as a control</li> <li>Take the ratio of the results of steps 3 and 4</li> </ol> |
|                 | $\frac{\Pr(Y_{k+1}(\bar{1}) = 1   Y_k(\bar{1}) = 0)}{\Pr(Y_{k+1}(\bar{0}) = 1   Y_k(\bar{0}) = 0)}$ |   |   |

However, approximate identifiability can be achieved by invoking the rare event assumption (or rare disease assumption), in which case the marginal odds ratio approximates the marginal risk ratio.

### 10.3.3 Risk-set sampling for intention-to-treat effect

With risk-set (or incidence density) sampling, for all time windows  $[t_k, t_{k+1})$ ,  $k = 0, \dots, K - 1$ , every subject who is event-free at  $t_k$  is eligible for selection as a control for the period  $[t_k, t_{k+1})$ . This means that study participants may be selected as a control more than once.

Consider the intention-to-treat effect quantified by the marginal (discrete-time) hazard ratio (or rate ratio)

$$\frac{\Pr(Y_{k+1}(1) = 1 | Y_k(1) = 0)}{\Pr(Y_{k+1}(0) = 1 | Y_k(0) = 0)}.$$

(For identification of a conditional hazard ratio, see Theorem 10.5, Supplementary Appendix S10.2.) For identification of the above marginal hazard ratio under risk-set sampling, it is assumed that selection as a control between  $t_k$  and  $t_{k+1}$ ,  $S_k$ , is independent of the baseline covariates and exposure given eligibility at  $t_k$  (i.e.,  $Y_k = 0$ ). It is also assumed that the sampling probability among those eligible,  $\Pr(S_k = 1 | Y_k = 0)$ , is constant across time windows  $k = 0, \dots, K - 1$ . To this end, it suffices that the marginal hazard  $\Pr(Y_{k+1} = 1 | Y_k = 0)$  remains constant across time windows and that every  $k$ th sampling fraction  $\Pr(S_k = 1)$  is equal, up to a proportionality constant, to the probability  $\Pr(Y_{k+1} = 1, Y_k = 0)$  of an incident case in the  $k$ th window (see remark to Theorem 10.4, Supplementary Appendix S10.2). For practical purposes, this suggests sampling a fixed number of controls for every case from among the set of eligible individuals. To illustrate, consider Figure 10.1 and note first of all that the individual represented by row 1 trivially qualifies as a case, because the individual survived until the event occurred. Because the event was sustained between  $t_5$  and  $t_6$ , the proposed sampling suggests selecting a fixed number of controls from among those who are eligible at  $t_5$ . Thus, rows (and only rows) 4 through 9 as well as row 1 itself in Figure 10.1 qualify for selection as a control for this case. Even though the individual of row 1 is a case, the individual may also be selected as a control when the individuals of row 2, 3 and 6 (but not 8) sustain the event.

Once cases and controls are selected, we can start to derive inverse probability weights  $W$  according to equation (10.1). We then compute the odds of baseline exposure among cases in the pseudopopulation that is obtained by weighting everyone by  $W$  and the odds of baseline exposure among controls weighted by  $W$

multiplied by the number of times the individual was selected as a control. The ratio of these odds coincides with the target hazard ratio under the three key identifiability conditions of consistency, baseline conditional exchangeability and positivity together with the assumption that the hazards in the numerator and denominator of the causal hazard ratio are constant across the time windows.

#### 10.3.4 Risk-set sampling for per-protocol effect

For the per-protocol effect quantified by the (discrete-time) hazard ratio (or rate ratio)

$$\frac{\Pr(Y_{k+1}(\bar{1}) = 1 | Y_k(\bar{1}) = 0)}{\Pr(Y_{j+1}(\bar{0}) = 1 | Y_k(\bar{0}) = 0)},$$

eligibility again requires that the respective subject is event-free at  $t_k$  (i.e.,  $Y_k = 0$ ). Selection as a control between  $t_k$  and  $t_{k+1}$ ,  $S_k$ , is further assumed independent of covariate and exposure history up to  $t_k$  given eligibility at  $t_k$  (but see Supplementary Appendix S10.2 for a slightly weaker assumption). As for the intention-to-treat effect, it is also assumed that the probability to be selected as a control  $S_k$  given eligibility is constant across time windows. This assumption is guaranteed to hold if the marginal hazard  $\Pr(Y_{k+1} = 1 | Y_k = 0)$  remains constant across time windows and that every  $k$ th sampling fraction  $\Pr(S_k = 1)$  is equal, up to a proportionality constant, to the probability of an incident case in the  $k$ th window. Figure 10.1 shows five incident events yet only three qualify as a case (rows 2, 3 and 8) when it concerns per-protocol effects. When the first case emerges (row 2), all rows meet the eligibility criterion for selection as a control. When the second emerges, the individual of row 2, who fails to survive event-free until  $t_4$ , is precluded as a control. When the case of row 8 emerges, only the individuals of rows 4, 5, 7 and 9 are eligible as controls.

Once cases and controls are selected, we can start to derive time-varying inverse probability weights according to

$$W_k = \prod_{j=0}^k \left[ \frac{A_j}{\Pr(A_j = 1 | L_0, \dots, L_j, A_0, \dots, A_{j-1}, Y_j = 0, S_j = 1)} + \frac{1 - A_j}{1 - \Pr(A_j = 1 | L_0, \dots, L_j, A_0, \dots, A_{j-1}, Y_j = 0, S_j = 1)} \right].$$

It is important to note that the weights are derived from control information but are nonetheless used to weight both cases and controls (Robins, 1999).

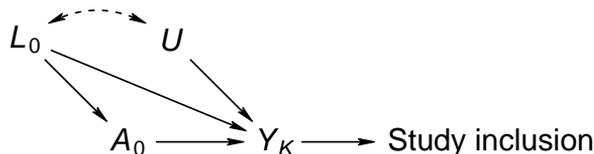
The denominators of the weights describe the propensity to switch exposure level. However, once the weights are derived, every subject is censored from the time that they fail to adhere to one of the protocols of interest for all downstream analysis. The uncensored exposure levels are therefore constant over time. We then compute the baseline exposure odds among cases, weighted by the weights  $W_k$  corresponding to the interval  $[t_k, t_{k+1})$  of the incident event (i.e.,  $Y_k = 0, Y_{k+1} = 1$ ), as well as the baseline exposure odds among controls, weighted by  $\sum_{k=0}^{K-1} W_k S_k$ , the weighted number of times selected as control. The ratio of these odds equals the target hazard ratio under the three key identifiability conditions of consistency, sequential conditional exchangeability, and positivity together with the assumption that hazards in the numerator and denominator of the causal hazard ratio for the per-protocol effect are constant across the time windows.

## 10.4 Case-control studies with matching

Table 10.2 gives an overview of identification results for case-control studies with exact pair matching. Formal statements and proofs are given in Supplementary Appendix S10.3, which also includes a generalisation of the results of Table 10.2 to exact 1-to- $M$  matching. While the focus in this section is on exact covariate matching, for partial matching we refer the reader to Supplementary Appendix S10.4, where we consider parametric identification by way of conditional logistic regression.

Pair matching involves assigning a single control exposure level, which we denote by  $A'$ , to every case. As for case-control studies without matching, in a case-control studies with matching an individual qualifies as a case if and only if they sustain the event of interest by the administrative study end (i.e.,  $Y_K = 1$ )

**Figure 10.2:** Directed acyclic graph for a setting where inclusion (as case or control) into the case-control study with case-base or survivor sampling is determined by the outcome variable  $Y_K$ .  $U$  represents an unknown or unobserved cause of  $Y_K$ . The dashed double-headed arrow represents an unmeasured or observed common cause.



and adhered to one of the protocols of interest until the time of the incident event. How a matched control exposure is assigned is encoded in the sampling scheme and the assumptions of Table 10.2. For example, for identification of the causal marginal risk ratio under case-base sampling,  $A'$  is sampled from all study participants whose baseline covariate value matches that of the case, independently of the participants' baseline exposure value and whether they survive until the end of study. The matching is exact in the sense that the control exposure information is derived from an individual who has the same value for the baseline covariate as the case.

The identification strategy is the same for all results listed in Table 10.2. Only the case-control pairs  $(A_0, A')$  with discordant exposure values (i.e.,  $(1, 0)$  or  $(0, 1)$ ) are used. Under the stated sampling schemes and assumptions, the respective estimands are identified by the ratio of discordant pairs.

## 10.5 Discussion

This paper gives a formal account of how and when causal effects can be identified in case-control studies and, as such, underpins the case-control application of Dickerman et al. (2020). Like Dickerman et al., we believe that case-control studies should generally be regarded as being nested within cohort studies. This view emphasises that the threats to the validity of cohort studies should also be considered in case-control studies. For example, in case-control applications with risk-set sampling, researchers often consider the covariate and exposure status only at, or just before, the time of the event (for cases) or the time of sampling (for controls). However, where a cohort study would require information on baseline levels or the complete treatment and covariate history of participants, one should suspect that this holds for the nested case-control study too. To gain clarity, we encourage researchers to move away from using person-years, -weeks, or -days (rather than individuals) as the default units of inference (Hernán, 2015), and to realise that inadequately addressed deviations from a target trial may lead to bias (or departure from identifiability), regardless of whether the study that attempts to emulate it is a case-control or a cohort study (Dickerman et al., 2020).

What is meant by a cohort study differs between authors and contexts (Vandenbroucke and Pearce, 2012). The term 'cohort' may refer to either a 'dynamic population', or a 'fixed cohort', whose "membership is defined in a permanent fashion" and "determined by a single defining event and so becomes permanent" (Rothman et al., 2008). While it may sometimes be of interest to

**Table 10.2:** Overview of (non-parametric) identification results for case-control studies without matching.

| Sampling scheme | Estimand   | Assumptions   | Identification strategy   |
|-----------------|--|---|---|
| Case-base       | Risk ratio for<br>intention-to-treat effect<br>$\frac{\Pr(Y_K(1) = 1)}{\Pr(\bar{Y}_K(0) = 1)}$ | <ul style="list-style-type: none"> <li>• Matched control exposure <math>A'</math> sampled from the baseline exposure levels of all subjects with same baseline covariate level <math>L_0</math> as case, independently of the subjects' baseline exposure or survival status</li> <li>• Consistency</li> <li>• Baseline conditional exchangeability</li> <li>• Positivity</li> <li>• <math>\Pr(Y_K = 1 L_0 = l, A_0 = 1) / \Pr(Y_K = 1 L_0 = l, A_0 = 0)</math> constant across levels <math>l</math></li> </ul> (Theorem 10.7) | <ol style="list-style-type: none"> <li>1. Compute the frequency of discordant case-control pairs with <math>A_0 = 1</math> and <math>A' = 0</math></li> <li>2. Compute the frequency of discordant case-control pairs with <math>A_0 = 0</math> and <math>A' = 1</math></li> <li>3. Take the ratio of the results of steps 1 and 2</li> </ol> |

Table 10.2 continued.

| Sampling scheme | Estimand  | Assumptions   | Identification strategy                                  |
|-----------------|---|---|--|
| Survivor        | <p>Odds ratio for intention-to-treat effect</p> $\frac{\text{Odds}(Y_K(1) = 1 L_0)}{\text{Odds}(Y_K(0) = 1 L_0)}$ | <ul style="list-style-type: none"> <li>• Matched control exposure <math>A'</math> sampled from all the baseline exposure levels of all survivors (<math>Y_K = 0</math>) with same value for <math>L_0</math> as case, independently of the subjects' baseline exposure</li> <li>• Consistency</li> <li>• Baseline conditional exchangeability</li> <li>• Positivity</li> <li>• <math>\text{Odds}(Y_K = 1 L_0, A_0 = 1)/\text{Odds}(Y_K = 1 L_0, A_0 = 0)</math> constant across levels <math>l</math> (Theorem 10.8)</li> </ul> | (Same as identification strategy for case-base sampling) |

Table 10.2 continued.

| Sampling scheme | Estimand  | Assumptions   | Identification strategy                                  |
|-----------------|---|---|--|
| Risk-set        | Hazard ratio for intention-to-treat effect<br>$\frac{\Pr(Y_{k+1}(1) = 1   L_0, Y_k(1) = 0)}{\Pr(Y_{k+1}(0) = 1   L_0, Y_k(0) = 0)}$ | <ul style="list-style-type: none"> <li>• For a case with incident event in <math>[t_k, t_{k+1})</math> (i.e., <math>Y_k = 0, Y_{k+1} = 1</math>), matched control exposure <math>A'</math> sampled from the baseline exposure levels of all subjects that are event-free at <math>t_k</math> (<math>Y_k = 0</math>) and have the same value for <math>L_0</math> as case. Sampling among these individuals is independent of baseline exposure or survival status</li> <li>• Consistency</li> <li>• Baseline conditional exchangeability</li> <li>• Positivity</li> <li>• <math>\Pr(Y_{k+1} = 1   L_0 = l, A_0 = 1, Y_k = 0) / \Pr(Y_{k+1} = 1   L_0 = l, A_0 = 0, Y_k = 0)</math> constant across levels <math>k, l</math> (Theorem 10.9)</li> </ul> | (Same as identification strategy for case-base sampling) |

Table 10.2 continued.

| Sampling scheme | Estimand  | Assumptions   | Identification strategy                                  |
|-----------------|---|---|--|
| Risk-set        | Hazard ratio for per-protocol effect <sup>†</sup> | <ul style="list-style-type: none"> <li>For a case with incident event in <math>[t + k, t_{k+1})</math> (i.e., <math>Y_k = 0, Y_{k+1} = 1</math>), matched control exposure <math>A'</math> sampled from the baseline exposure levels <math>A_0</math> of all individuals who adhered to one of the protocols until <math>t_k</math> (i.e., <math>A_0 = \dots = A_k</math>) and have covariate history up to <math>t_k</math>. Sampling among these individuals is independent of baseline exposure or survival status</li> <li>Consistency</li> <li>Positivity</li> <li><math>\Pr(Y_{k+1} = 1   L_0, \dots, L_k, A_0 = \dots = A_k = 1, Y_k = 0) / \Pr(Y_{k+1} = 1   L_0, \dots, L_k, A_0 = \dots = A_k = 0, Y_k = 0)</math> constant across levels <math>k</math> and independent of <math>L_0, \dots, L_k</math> (Theorem 10.10)</li> </ul> | (Same as identification strategy for case-base sampling) |

$$\begin{aligned}
 \dagger \frac{\Pr(Y_{k+1}(\bar{1}) = 1 | L_0, \dots, L_k, A_0 = \dots = A_k = 1, Y_k(\bar{1}) = 0)}{\Pr(Y_{k+1}(\bar{0}) = 1 | L_0, \dots, L_k, A_0 = \dots = A_k = 0, Y_k(\bar{0}) = 0)}
 \end{aligned}$$

ask what would have happened with a dynamic cohort (e.g., the residents of a country) had it been subjected to one treatment protocol versus another, the results in this paper relate to fixed cohorts.

Like the cohort studies within which they are (at least conceptually) nested, case-control studies require an explicit definition of time zero, the time at which a choice is to be made between treatment strategies or protocols of interest (Dickerman et al., 2020). Given a fixed cohort, time zero is generally determined by the defining event of the cohort (e.g., first diagnosis of a particular disease or having survived one year since diagnosis). This event may occur at different calendar times for different individuals. However, while a fixed cohort may be ‘open’ to new members relative to calendar time, it is always ‘closed’ along the time axis on which all subject-specific time zeros take a common point.

In this paper, time was regarded as discrete. Since we considered arbitrary intervals between time points and because, in real-world studies, time is never measured in a truly continuous fashion, this does not represent an important limitation for practical purposes. It is however important to note that the intervals between interventions and outcome assessments (in a target trial) are an intrinsic part of the estimand that lies at the start of investigation. Careful consideration of time intervals in the design of the conceptual target trial and of the actual cohort or case-control study is therefore warranted.

We emphasize that identification and estimation are distinct steps in causal inference. Although our focus was on the former, identifiability expressions often naturally translate into estimators. The task of finding the estimator with the most appealing statistical properties is not necessarily straightforward, however, and is beyond the scope of this paper.

We specifically studied two causal contrasts (i.e., pairs of interventions), one corresponding to intention-to-treat effects and the other to always-versus-never per-protocol effects of a time-varying exposure. There are of course many more causal contrasts, treatment regimes and estimands conceivable that could be of interest. We argue that also for these estimands, researchers should seek to establish identifiability before they select an estimator.

The conditions under which identifiability is to be sought for practical purposes may well include more constraints or obstacles to causal inference, such as additional missingness (e.g., outcome censoring) and measurement error, than we have considered here. While some of our results assume that hazards or hazard ratios remain constant over time, in many cases these are likely time-varying (Lefebvre et al., 2006; Guess, 2006). There are also more case-control designs (e.g., the case-crossover design) to consider. These additional complexities and designs are beyond the scope of this paper and represent an interesting direction

for future research.

The case-control family of study designs is an important yet often misunderstood tool for identifying causal relations (Knol et al., 2008; Pearce, 2016; Mansournia et al., 2018; Labrecque et al., 2021). Although there is much to be learned, we believe that the modern arsenal for causal inference, which includes counterfactual thinking, is well-suited to make transparent for these classical epidemiological study designs what assumptions are sufficient or necessary to endow the study results with a causal interpretation and, in turn, help resolve or prevent misunderstanding.

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**Supplementary Material**

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**S10.1 Notation and set-up**

We will suppose that the interest lies with the effect of a time-varying exposure that can take one of two levels at any given time on a failure time outcome. In particular, we consider a strictly increasing sequence  $(t_0, t_1, \dots, t_K)$  of  $K + 1$  time points (with  $t_{K+1} = -t_{-1} = +\infty$  for notational convenience). For  $k = 0, 1, \dots, K - 1$ , let  $A_k$  denote the level of time-varying exposure of interest at  $t_k$ . We denote the history of any stochastic sequence  $(X_0, X_1, \dots, X_{K-1})$  up to and including  $t_k$  by  $\bar{X}_k = (X_0, X_1, \dots, X_k)$  for  $k = 0, 1, \dots, K - 1$  (and let  $\bar{X} = \bar{X}_{K-1}$

and  $\bar{X}_{-1} = 0$  for notational convenience). For example,  $\bar{A} = (A_0, A_1, \dots, A_{K-1})$ . Denote by  $T(\bar{a})$  the counterfactual time elapsed until the event of interest since  $t_0$  that would have been realised had  $\bar{A}$  been set to  $\bar{a}$ , and let  $Y_k(\bar{a}) = I(T(\bar{a}) < t_k)$  for  $k = 0, 1, \dots, K$ , where  $I$  represents the indicator function. By convention, we stipulate that for all  $k$ ,  $Y_k(\bar{a})$  is invariant to the  $k$ th through  $K - 1$ th elements of  $\bar{a}$  (i.e., current survival status is not affected by future exposures). With slight abuse of notation, for  $k = 0, 1, \dots, K$ , we let  $Y_k(a_0)$  denote the outcome that would have been realised had (only)  $A_0$  been set to  $a_0$ .

### *Consistency*

For theorems about per-protocol effects, we assume consistency of the form: for  $k = 1, \dots, K$  and all  $\bar{a}$ ,  $Y_k(\bar{a}) = Y_k$  if  $a_l = A_l$  for all  $l = 0, \dots, k - 1$  such that  $Y_l = 0$ . For theorems about intention-to-treat effects, a weaker condition is sufficient and assumed: for  $k = 1, \dots, K$  and  $a = 0, 1$ ,  $Y_k(a) = Y_k$  if  $a = A_0$ . The assumption may be further relaxed for theorems in which the estimand does not involve  $Y_k(a)$ ,  $k < K$ : for  $a = 0, 1$ ,  $Y_K(a) = Y_K$  if  $a = A_0$ .

### *Conditional exchangeability*

We also consider a sequence of variables  $\bar{L} = (L_0, L_1, \dots, L_{K-1})$  that satisfies one of the following conditions:

$$\forall k, \forall \bar{a} : (Y_{k+1}(\bar{a}), \dots, Y_K(\bar{a})) \perp\!\!\!\perp A_k | Y_k(\bar{a}) = 0, \bar{L}_k, \bar{A}_{k-1} = \bar{a}_{k-1},$$

(sequential conditional exchangeability, SCE)

where  $\bar{a}_{k-1}$  is understood to represent the  $(k - 1)$ th through  $(K - 1)$ th elements of  $\bar{a}$ , or

$$\forall a_0 : (Y_1(a_0), \dots, Y_K(a_0)) \perp\!\!\!\perp A_0 | L_0,$$

(baseline conditional exchangeability, BCE)

although sometimes a weaker form of BCE suffices:  $\forall a_0 : Y_K(a_0) \perp\!\!\!\perp A_0 | L_0$ .

### *Positivity*

For the theorems that follow, we assume positivity to preclude division by zero and undefined conditional probabilities, so that the weights that we will encounter are finite and strictly greater than 1. The assumption can sometimes be relaxed if we are willing to interpolate or extrapolate under (parametric) modelling assumptions.

## S10.2 Identification results for non-matching strategies

### *Intention-to-treat effect*

For simplicity, it is assumed below that the covariates are discrete. The results can however be extended to more general distributions.

**Theorem 10.1** (Case-base sampling for marginal intention-to-treat effect).  
*Suppose BCE holds as well as*

$$\Pr(S = 1|L_0, A_0) = \Pr(S = 1) = \delta \tag{S1}$$

for some  $\delta \in (0, 1]$ . Then,

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)W|S = 1]}{\mathbb{E}[I(A_0 = 0)W|S = 1]}} = \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)},$$

where

$$W = \frac{1}{\Pr(A_0 = a|L_0, S = 1)} \Big|_{a=A_0},$$

*Proof.* First, observe that  $\Pr(A_0 = a|L_0, S = 1) = \Pr(A_0 = a|L_0)$  for  $a = 0, 1$ , because

$$\begin{aligned} \Pr(A_0 = a|L_0, S = 1) &= \frac{\Pr(S = 1|L_0, A_0 = a) \Pr(A_0 = a|L_0)}{\Pr(S = 1|L_0)} \\ &= \frac{\delta}{\delta} \Pr(A_0 = a|L_0) && \text{(by S1)} \\ &= \Pr(A_0 = a|L_0) \end{aligned}$$

Hence,

$$W = \frac{1}{\Pr(A_0 = a|L_0)} \Big|_{a=A_0}.$$

Now, consider the numerator of the left-hand side of the main equation in Theorem 10.1 and note that, because of the above, we have

$$\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]} = \frac{\sum_{y=0}^1 \mathbb{E}[I(A_0 = 1)WY_K|Y_K = y] \Pr(Y_K = y)}{\sum_{y=0}^1 \mathbb{E}[I(A_0 = 0)WY_K|Y_K = y] \Pr(Y_K = y)}$$

$$\begin{aligned}
&= \frac{\mathbb{E}[I(A_0 = 1)WY_K]}{\mathbb{E}[I(A_0 = 0)WY_K]} \\
&= \frac{\mathbb{E}[WY_K|A_0 = 1] \Pr(A_0 = 1)}{\mathbb{E}[WY_K|A_0 = 0] \Pr(A_0 = 0)},
\end{aligned}$$

where

$$\begin{aligned}
\mathbb{E}[WY_K|A_0 = a] &= \mathbb{E}\{\mathbb{E}[WY_K|L_0, A_0 = a]|A_0 = a\} \\
&= \sum_l \frac{\Pr(Y_K = 1|L_0 = l, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \\
&= \sum_l \frac{\Pr(Y_K(a) = 1|L_0 = l, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \\
&\hspace{15em} \text{(by consistency)} \\
&= \sum_l \frac{\Pr(Y_K(a) = 1|L_0 = l) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \\
&\hspace{15em} \text{(by baseline conditional exchangeability)} \\
&= \sum_l \frac{\Pr(Y_K(a) = 1|L_0 = l) \Pr(A_0 = a|L_0 = l) \Pr(L_0 = l)}{\Pr(A_0 = a|L_0 = l) \Pr(A_0 = a)} \\
&= \frac{1}{\Pr(A_0 = a)} \sum_l \Pr(Y_K(a) = 1, L_0 = l) \\
&= \frac{\Pr(Y_K(a) = 1)}{\Pr(A_0 = a)},
\end{aligned}$$

so that

$$\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]} = \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}.$$

Next, consider the denominator of the left-hand side of the main equation in Theorem 10.1 and observe that

$$\frac{\mathbb{E}[I(A_0 = 1)W|S = 1]}{\mathbb{E}[I(A_0 = 0)W|S = 1]} = \frac{\mathbb{E}[I(A_0 = 1)WS]}{\mathbb{E}[I(A_0 = 0)WS]} = \frac{\mathbb{E}[WS|A_0 = 1] \Pr(A_0 = 1)}{\mathbb{E}[WS|A_0 = 0] \Pr(A_0 = 0)},$$

where

$$\begin{aligned}
\mathbb{E}[WS|A_0 = a] &= \mathbb{E}\{\mathbb{E}[WS|L_0, A_0 = a]|A_0 = a\} \\
&= \sum_l \frac{\Pr(S = 1|L_0, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)}
\end{aligned}$$

$$\begin{aligned}
 &= \sum_l \frac{\delta \Pr(L_0 = l | A_0 = a)}{\Pr(A_0 = a | L_0 = l)} && \text{(by S1)} \\
 &= \frac{\delta}{\Pr(A_0 = a)} \sum_l \Pr(L_0 = l) \\
 &= \frac{\delta}{\Pr(A_0 = a)},
 \end{aligned}$$

so that

$$\frac{\mathbb{E}[I(A_0 = 1)W | S = 1]}{\mathbb{E}[I(A_0 = 0)W | S = 1]} = 1.$$

It follows that

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)W | Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W | Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)W | S = 1]}{\mathbb{E}[I(A_0 = 0)W | S = 1]}} = \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}.$$

□

**Theorem 10.2** (Case-base sampling for conditional intention-to-treat effect). *Suppose BCE hold as well as S1, or the weaker version  $\Pr(S = 1 | L_0, A_0) = \Pr(S = 1 | L_0) = \delta_{L_0} \in (0, 1]$ . Then,*

$$\frac{\frac{\mathbb{E}[I(A_0 = 1) | L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0) | L_0, Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1) | L_0, S = 1]}{\mathbb{E}[I(A_0 = 0) | L_0, S = 1]}} = \frac{\Pr(Y_K(1) = 1 | L_0)}{\Pr(Y_K(0) = 1 | L_0)}.$$

*Proof.* We have

$$\begin{aligned}
 &\frac{\mathbb{E}[I(A_0 = 1) | L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0) | L_0, Y_K = 1]} \\
 &= \frac{\sum_{y=0}^1 \mathbb{E}[I(A_0 = 1)Y_K | L_0, Y_K = y] \Pr(Y_K = y | L_0)}{\sum_{y=0}^1 \mathbb{E}[I(A_0 = 0)Y_K | L_0, Y_K = y] \Pr(Y_K = y | L_0)} \\
 &= \frac{\mathbb{E}[I(A_0 = 1)Y_K | L_0]}{\mathbb{E}[I(A_0 = 0)Y_K | L_0]} \\
 &= \frac{\mathbb{E}[Y_K | L_0, A_0 = 1] \Pr(A_0 = 1 | L_0)}{\mathbb{E}[Y_K | L_0, A_0 = 0] \Pr(A_0 = 0 | L_0)}
 \end{aligned}$$

$$\begin{aligned}
 &= \frac{\mathbb{E}[Y_K(1)|L_0, A_0 = 1] \Pr(A_0 = 1|L_0)}{\mathbb{E}[Y_K(0)|L_0, A_0 = 0] \Pr(A_0 = 0|L_0)} && \text{(by consistency)} \\
 &= \frac{\mathbb{E}[Y_K(1)|L_0] \Pr(A_0 = 1|L_0)}{\mathbb{E}[Y_K(0)|L_0] \Pr(A_0 = 0|L_0)}. && \text{(by baseline conditional exchangeability)}
 \end{aligned}$$

Also,

$$\begin{aligned}
 \frac{\mathbb{E}[I(A_0 = 1)|L_0, S = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, S = 1]} &= \frac{\mathbb{E}[I(A_0 = 1)S|L_0]}{\mathbb{E}[I(A_0 = 0)S|L_0]} \\
 &= \frac{\mathbb{E}[S|L_0, A_0 = 1] \Pr(A_0 = 1|L_0)}{\mathbb{E}[S|L_0, A_0 = 0] \Pr(A_0 = 0|L_0)} \\
 &= \frac{\delta_{L_0} \Pr(A_0 = 1|L_0)}{\delta_{L_0} \Pr(A_0 = 0|L_0)} \\
 &\text{(under the assumption that } \Pr(S = 1|L_0, A_0) = \Pr(S = 1|L_0) = \delta_{L_0} \in (0, 1]) \\
 &= \frac{\Pr(A_0 = 1|L_0)}{\Pr(A_0 = 0|L_0)}.
 \end{aligned}$$

It immediately follows that

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)|L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)|L_0, S = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, S = 1]}} = \frac{\Pr(Y_K(1) = 1|L_0)}{\Pr(Y_K(0) = 1|L_0)}.$$

□

**Corollary 10.1.** *If in addition to the conditions of Theorem 10.2,*

$$\frac{\Pr(Y_K = 1|L_0 = l, A_0 = 1)}{\Pr(Y_K = 1|L_0 = l, A_0 = 0)} = \theta \quad \text{(homogeneity condition H1)}$$

for all  $l$  and some constant  $\theta$ , then

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)|L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)|L_0, S = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, S = 1]}} = \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)},$$

because of the collapsibility of the risk ratio.

**Theorem 10.3** (Survivor sampling for conditional intention-to-treat effect).  
 Suppose BCE holds as well as

$$\Pr(S = 1|L_0, A_0, Y_K) = \Pr(S = 1|L_0, Y_K) = \delta_{L_0} \times (1 - Y_K) \quad (\text{S2})$$

for some  $\delta_{L_0} \in (0, 1]$ . Then,

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)|L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)|L_0, S = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, S = 1]}} = \frac{\text{Odds}(Y_K(1) = 1|L_0)}{\text{Odds}(Y_K(0) = 1|L_0)}.$$

*Proof.* First, consider the numerator of the left-hand side of the equation in Theorem 10.3 and observe

$$\begin{aligned} \frac{\mathbb{E}[I(A_0 = 1)|L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, Y_K = 1]} &= \frac{\Pr(Y_K = 1|L_0, A_0 = 1)}{\Pr(Y_K = 1|L_0, A_0 = 0)} \text{Odds}(A_0 = 1|L_0) \\ &= \frac{\Pr(Y_K(1) = 1|L_0, A_0 = 1)}{\Pr(Y_K(1) = 1|L_0, A_0 = 0)} \text{Odds}(A_0 = 1|L_0) \\ &\quad \text{(by consistency)} \\ &= \frac{\Pr(Y_K(1) = 1|L_0)}{\Pr(Y_K(1) = 1|L_0)} \text{Odds}(A_0 = 1|L_0). \\ &\quad \text{(by baseline conditional exchangeability)} \end{aligned}$$

Next, consider the denominator and observe that

$$\begin{aligned} \frac{\mathbb{E}[I(A_0 = 1)|L_0, S = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, S = 1]} &= \frac{\mathbb{E}[I(A_0 = 1)S|L_0]}{\mathbb{E}[I(A_0 = 0)S|L_0]} \\ &= \frac{\mathbb{E}[S|L_0, A_0 = 1]}{\mathbb{E}[S|L_0, A_0 = 0]} \text{Odds}(A_0 = 1|L_0) \\ &= \frac{\delta_{L_0} \Pr(Y_K = 0|L_0, A_0 = 1)}{\delta_{L_0} \Pr(Y_K = 0|L_0, A_0 = 0)} \text{Odds}(A_0 = 1|L_0) \quad \text{(by S2)} \\ &= \frac{\Pr(Y_K(1) = 0|L_0, A_0 = 1)}{\Pr(Y_K(0) = 0|L_0, A_0 = 0)} \text{Odds}(A_0 = 1|L_0) \\ &\quad \text{(by consistency)} \\ &= \frac{\Pr(Y_K(1) = 0|L_0)}{\Pr(Y_K(0) = 0|L_0)} \text{Odds}(A_0 = 1|L_0). \\ &\quad \text{(by baseline conditional exchangeability)} \end{aligned}$$

It follows that

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)|L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)|L_0, S = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, S = 1]}} = \frac{\text{Odds}(Y_K(1) = 1|L_0)}{\text{Odds}(Y_K(0) = 1|L_0)}.$$

□

**Remark to Theorem 10.3.** Under BCE, the stronger version of  $S2$ ,

$$\Pr(S = 1|L_0, A_0, Y_K) = \Pr(S = 1|Y_K) = \delta \times (1 - Y_K) \quad (S2^*)$$

for some  $\delta \in (0, 1]$  and with

$$W = \frac{1}{\Pr(A_0 = a|L_0)} \Bigg|_{a=A_0},$$

we have

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)W|S = 1]}{\mathbb{E}[I(A_0 = 0)W|S = 1]}} = \frac{\text{Odds}(Y_K(1) = 1)}{\text{Odds}(Y_K(0) = 1)} \quad (10.2)$$

(see proof below). However, from

$$\begin{aligned} \Pr(A_0 = a|L_0, S = 1) &= \frac{\Pr(S = 1|L_0, A_0 = a) \Pr(A_0 = a|L_0)}{\Pr(S = 1|L_0)} \\ &= \frac{\delta \Pr(Y_K = 0|L_0, A_0 = a) \Pr(A_0 = a|L_0)}{\delta \Pr(Y_K = 0|L_0)} \quad (\text{by } S2^*) \\ &= \Pr(A_0 = a|L_0, Y_K = 0), \end{aligned}$$

it follows that the weights  $W$  above are not identified by

$$\frac{1}{\Pr(A_0 = a|L_0, S = 1)} \Bigg|_{a=A_0}$$

when  $Y_K \not\perp A_0|L_0$ . (However,  $\Pr(A_0 = a|L_0, S = 1)$  approximates  $\Pr(A_0 = a|L_0)$  under a rare event assumption.) In fact, the target marginal odds ratio is not identifiable, under BCE and  $S2^*$  with unknown  $\delta$ , from the available data distribution, which is formed by the distribution of  $(L_0, A_0, Y_K, S)|(Y_K = 1 \vee S = 1)$ . A proof is given below.

*Proof of (10.2) under stated conditions.* As shown in the proof to Theorem 10.1,

$$\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]} = \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}.$$

Now,

$$\frac{\mathbb{E}[I(A_0 = 1)W|S = 1]}{\mathbb{E}[I(A_0 = 0)W|S = 1]} = \frac{\mathbb{E}[I(A_0 = 1)WS]}{\mathbb{E}[I(A_0 = 0)WS]} = \frac{\mathbb{E}[WS|A_0 = 1] \Pr(A_0 = 1)}{\mathbb{E}[WS|A_0 = 0] \Pr(A_0 = 0)},$$

where

$$\begin{aligned} \mathbb{E}[WS|A_0 = a] &= \mathbb{E}\{\mathbb{E}[WS|L_0, A_0 = a]|A_0 = a\} \\ &= \sum_l \frac{\Pr(S = 1|L_0, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \\ &= \sum_l \frac{\delta \Pr(Y_K = 0|L_0 = l, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \quad (\text{by S2}^*) \\ &= \frac{\delta}{\Pr(A_0 = a)} \sum_l \Pr(Y_K = 0|L_0 = l, A_0 = a) \Pr(L_0 = l) \\ &= \frac{\delta}{\Pr(A_0 = a)} \sum_l \Pr(Y_K(a) = 0|L_0 = l, A_0 = a) \Pr(L_0 = l) \\ &\hspace{15em} (\text{by consistency}) \\ &= \frac{\delta}{\Pr(A_0 = a)} \sum_l \Pr(Y_K(a) = 0, L_0 = l) \\ &\hspace{15em} (\text{by baseline conditional exchangeability}) \\ &= \frac{\delta \Pr(Y_K(a) = 0)}{\Pr(A_0 = a)}, \end{aligned}$$

so that

$$\frac{\mathbb{E}[I(A_0 = 1)W|S = 1]}{\mathbb{E}[I(A_0 = 0)W|S = 1]} = \frac{\Pr(Y_K(1) = 0)}{\Pr(Y_K(0) = 0)}$$

and, in turn,

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)W|S = 1]}{\mathbb{E}[I(A_0 = 0)W|S = 1]}} = \frac{\text{Odds}(Y_K(1) = 1)}{\text{Odds}(Y_K(0) = 1)}.$$

□

*Proof of nonidentifiability of target marginal odds ratio under stated conditions.* Consider two distributions of  $(L_0, A_0, Y_K, S)$  satisfying S2\*, each characterised by the following conditionals:

$$\begin{aligned} Y_K &\sim \text{Bernoulli}(\alpha), \\ S|Y_K &\sim \text{Bernoulli}(\delta \times (1 - Y_K)), \\ L_0|Y_K, S &\sim L_0|Y_K \sim \text{Bernoulli}(5/10 - 2/10 \times Y_K), \\ A_0|L_0, Y_K, S &\sim A_0|L_0, Y_K \sim \text{Bernoulli}(3/10 + 2/10 \times L_0 + 3/10 \times Y_K). \end{aligned}$$

The parameter values of the distributions are given in the table below.

| Parameter | Distribution 1 | Distribution 2 |
|-----------|----------------|----------------|
| $\alpha$  | 1/10           | 2/10           |
| $\delta$  | 1/10           | 9/40           |

Now, for all  $l, a, y, s \in \{0, 1\}$ ,

$$\begin{aligned} &\Pr(L_0 = l, A_0 = a, Y_K = y, S = s | Y_K = 1 \vee S = 1) \\ &= \frac{\Pr(L_0 = l, A_0 = a, Y_K = y, S = s, Y_K = 1 \vee S = 1)}{\Pr(Y_K = 1 \wedge S = 0) + \Pr(Y_K = 0 \wedge S = 1) + \Pr(Y_K = 1 \wedge S = 1)} \\ &= \frac{I(y = 1 \vee s = 1) \Pr(L_0 = l, A_0 = a, Y_K = y, S = s)}{\Pr(Y_K = 1) + \delta \Pr(Y_K = 0)} \\ &= I(y = 1 \vee s = 1) \\ &\quad \times \frac{\Pr(L_0 = l, A_0 = a | Y_K = y) \Pr(S = s | Y_K = y) \Pr(Y_K = y)}{\alpha + \delta(1 - \alpha)} \\ &= \begin{cases} \Pr(L_0 = l, A_0 = a | Y_K = 0) \left(1 - \frac{\alpha}{\alpha + \delta(1 - \alpha)}\right) & \text{if } y = 0 \wedge s = 1, \\ \Pr(L_0 = l, A_0 = a | Y_K = 1) \frac{\alpha}{\alpha + \delta(1 - \alpha)} & \text{if } y = 1 \wedge s = 0, \\ 0 & \text{otherwise,} \end{cases} \end{aligned}$$

where

$$\frac{\alpha}{\alpha + \delta(1 - \alpha)} = 10/19$$

under Distribution 1 and under Distribution 2. Hence, Distribution 1 and 2 imply the same available data distribution.

However, as we now show, the distributions imply different target marginal odds ratios. Since

$$\Pr(Y_K(a) = 1) = \sum_{l=0}^1 \Pr(Y_K(a) = 1 | L_0 = l) \Pr(L_0 = l)$$

$$\begin{aligned}
 &= \sum_{l=0}^1 \Pr(Y_K(a) = 1 | L_0 = l, A_0 = a) \Pr(L_0 = l) \quad (\text{by BCE}) \\
 &= \sum_{l=0}^1 \Pr(Y_K = 1 | L_0 = l, A_0 = a) \Pr(L_0 = l) \quad (\text{by consistency}) \\
 &= \sum_{l=0}^1 \frac{\Pr(L_0 = l, A_0 = a | Y_K = 1) \Pr(Y_K = 1)}{\Pr(L_0 = l, A_0 = a)} \\
 &\quad \times \sum_{y=0}^1 \Pr(L_0 = l | Y_K = y) \Pr(Y_K = y) \\
 &= \sum_{l=0}^1 \left( 1 + \frac{\Pr(L_0 = l, A_0 = a | Y_K = 0) \Pr(Y_K = 0)}{\Pr(L_0 = l, A_0 = a | Y_K = 1) \Pr(Y_K = 1)} \right)^{-1} \\
 &\quad \times \sum_{y=0}^1 \Pr(L_0 = l | Y_K = y) \Pr(Y_K = y)
 \end{aligned}$$

for  $a = 0, 1$ , we have

$$\begin{aligned}
 \Pr(Y_K(1) = 1) &= \frac{5 + 2\alpha}{10 + (25/7)/\text{odds}(\alpha)} + \frac{5 - 2\alpha}{10 + (125/12)/\text{odds}(\alpha)} \quad \text{and} \\
 \Pr(Y_K(0) = 1) &= \frac{5 + 2\alpha}{10 + (25/2)/\text{odds}(\alpha)} + \frac{5 - 2\alpha}{10 + (125/3)/\text{odds}(\alpha)},
 \end{aligned}$$

so that

$$\frac{\text{Odds}(Y_K(1) = 1)}{\text{Odds}(Y_K(0) = 1)} = \begin{cases} \frac{587,791}{167,166} \approx 3.5 & \text{under Distribution 1,} \\ \frac{512,539}{148,789} \approx 3.4 & \text{under Distribution 2.} \end{cases}$$

Hence, we found an available data distribution that is compatible with more than one value of the target marginal odds ratio. This concludes the proof.  $\square$

**Theorem 10.4** (Risk-set sampling for marginal intention-to-treat effect).  
*Suppose BCE holds as well as*

$$\Pr(S_k = 1 | L_0, A_0, Y_k) = \Pr(S_k = 1 | Y_k) = \delta \times (1 - Y_k), \quad (\text{S3})$$

for some  $\delta \in (0, 1]$ . If

$$\Pr(Y_{k+1}(a) = 1 | Y_k(a) = 0) = \theta_a \quad (\text{H2})$$

for  $a = 0, 1$  and some constants  $\theta_0, \theta_1$ , then

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)W \sum_{k=0}^{K-1} S_k]}{\mathbb{E}[I(A_0 = 0)W \sum_{k=0}^{K-1} S_k]}} = \frac{\Pr(Y_{k+1}(1) = 1|Y_{k+1}(1) = 0)}{\Pr(Y_{k+1}(0) = 1|Y_{k+1}(0) = 0)},$$

where

$$W = \frac{1}{\Pr(A_0 = a|L_0, S_0 = 1)} \Big|_{a=A_0},$$

*Proof.* First, observe that  $\Pr(A_0 = a|L_0, S_0 = 1) = \Pr(A_0 = a|L_0)$  for  $a = 0, 1$ , because

$$\begin{aligned} \Pr(A_0 = a|L_0, S_0 = 1) &= \frac{\Pr(S_0 = 1|L_0, A_0 = a) \Pr(A_0 = a|L_0)}{\Pr(S_0 = 1|L_0)} \\ &= \frac{\delta}{\delta} \Pr(A_0 = a|L_0) && \text{(by S3)} \\ &= \Pr(A_0 = a|L_0) \end{aligned}$$

Hence,

$$W = \frac{1}{\Pr(A_0 = a|L_0)} \Big|_{a=A_0}.$$

For the numerator of the main result of Theorem 10.4, we thus have

$$\begin{aligned} \frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]} &= \frac{\mathbb{E}[I(A_0 = 1)WY_K]}{\mathbb{E}[I(A_0 = 0)WY_K]} \\ &= \frac{\mathbb{E}[WY_K|A_0 = 1] \Pr(A_0 = 1)}{\mathbb{E}[WY_K|A_0 = 0] \Pr(A_0 = 0)}, \end{aligned}$$

where

$$\begin{aligned} \mathbb{E}[WY_K|A_0 = a] &= \mathbb{E}\{\mathbb{E}[WY_K|L_0, A_0 = a]|A_0 = a\} \\ &= \sum_l \frac{\Pr(Y_K = 1|L_0 = l, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \\ &= \sum_l \frac{\Pr(Y_K(a) = 1|L_0 = l, A_0 = a) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \end{aligned}$$

(by consistency)

$$\begin{aligned}
 &= \sum_l \frac{\Pr(Y_K(a) = 1|L_0 = l) \Pr(L_0 = l|A_0 = a)}{\Pr(A_0 = a|L_0 = l)} \\
 &\quad \text{(by baseline conditional exchangeability)} \\
 &= \sum_l \frac{\Pr(Y_K(a) = 1|L_0 = l) \Pr(A_0 = a|L_0 = l) \Pr(L_0 = l)}{\Pr(A_0 = a|L_0 = l) \Pr(A_0 = a)} \\
 &= \frac{1}{\Pr(A_0 = a)} \sum_l \Pr(Y_K(a) = 1, L_0 = l) \\
 &= \frac{\Pr(Y_K(a) = 1)}{\Pr(A_0 = a)},
 \end{aligned}$$

so that

$$\begin{aligned}
 \frac{\mathbb{E}[I(A_0 = 1)W|Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W|Y_K = 1]} &= \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)} \\
 &= \frac{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(1) = 1, Y_k(1) = 0)}{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(0) = 1, Y_k(0) = 0)} \\
 &= \frac{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(1) = 1|Y_k(1) = 0) \Pr(Y_k(1) = 0)}{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(0) = 1|Y_k(0) = 0) \Pr(Y_k(0) = 0)} \\
 &= \frac{\sum_{k=0}^{K-1} \theta_1 \Pr(Y_k(1) = 0)}{\sum_{k=0}^{K-1} \theta_0 \Pr(Y_k(0) = 0)} \quad \text{(by H2)} \\
 &= \frac{\theta_1 \sum_{k=0}^{K-1} \Pr(Y_k(1) = 0)}{\theta_0 \sum_{k=0}^{K-1} \Pr(Y_k(0) = 0)}
 \end{aligned}$$

For the denominator, we have

$$\frac{\mathbb{E}[I(A_0 = 1)W \sum_{k=0}^{K-1} S_k]}{\mathbb{E}[I(A_0 = 0)W \sum_{k=0}^{K-1} S_k]} = \frac{\mathbb{E}[W \sum_{k=0}^{K-1} S_k | A_0 = 1] \Pr(A_0 = 1)}{\mathbb{E}[W \sum_{k=0}^{K-1} S_k | A_0 = 0] \Pr(A_0 = 0)},$$

where

$$\begin{aligned}
 &\mathbb{E}[W \sum_{k=0}^{K-1} S_k | A_0 = a] \\
 &= \sum_{k=0}^{K-1} \mathbb{E}\{\mathbb{E}[W S_k | L_0, A_0 = a] | A_0 = a\} \\
 &= \sum_{k=0}^{K-1} \sum_l \frac{\Pr(S_k = 1 | L_0, A_0 = a) \Pr(L_0 = l | A_0 = a)}{\Pr(A_0 = a | L_0 = l)} \\
 &= \sum_{k=0}^{K-1} \sum_l \frac{\delta \Pr(Y_k = 0 | L_0 = l, A_0 = a) \Pr(L_0 = l | A_0 = a)}{\Pr(A_0 = a | L_0 = l)} \quad \text{(by S3)}
 \end{aligned}$$

$$\begin{aligned}
 &= \sum_{k=0}^{K-1} \sum_l \frac{\delta \Pr(Y_k = 0 | L_0 = l, A_0 = a) \Pr(L_0 = l)}{\Pr(A_0 = a)} \\
 &= \sum_{k=0}^{K-1} \sum_l \frac{\delta \Pr(Y_k(a) = 0 | L_0 = l, A_0 = a) \Pr(L_0 = l)}{\Pr(A_0 = a)} \quad (\text{by consistency}) \\
 &= \sum_{k=0}^{K-1} \sum_l \frac{\delta \Pr(Y_k(a) = 0 | L_0 = l) \Pr(L_0 = l)}{\Pr(A_0 = a)} \\
 &\quad (\text{by baseline conditional exchangeability}) \\
 &= \frac{1}{\Pr(A_0 = a)} \sum_{k=0}^{K-1} \sum_l \delta \Pr(Y_k(a) = 0, L_0 = l) \\
 &= \frac{1}{\Pr(A_0 = a)} \sum_{k=0}^{K-1} \delta \Pr(Y_k(a) = 0),
 \end{aligned}$$

so that

$$\begin{aligned}
 \frac{\mathbb{E}[I(A_0 = 1)W \sum_{k=0}^{K-1} S_k]}{\mathbb{E}[I(A_0 = 0)W \sum_{k=0}^{K-1} S_k]} &= \frac{\sum_{k=0}^{K-1} \delta \Pr(Y_k(1) = 0)}{\sum_{k=0}^{K-1} \delta \Pr(Y_k(0) = 0)} \\
 &= \frac{\sum_{k=0}^{K-1} \Pr(Y_k(1) = 0)}{\sum_{k=0}^{K-1} \Pr(Y_k(0) = 0)}.
 \end{aligned}$$

It follows that

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)W | Y_K = 1]}{\mathbb{E}[I(A_0 = 0)W | Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1)W \sum_{k=0}^{K-1} S_k]}{\mathbb{E}[I(A_0 = 0)W \sum_{k=0}^{K-1} S_k]}} = \frac{\Pr(Y_{k+1}(1) = 1 | Y_k(1) = 0)}{\Pr(Y_{k+1}(0) = 1 | Y_k(0) = 0)}.$$

□

**Remark to Theorem 10.4.** *Condition S3 holds if, for some constant  $\delta_k^*$ ,*

$$\left. \begin{aligned}
 \Pr(S_k = 1) &= \delta_k^* \Pr(Y_{k+1} = 1, Y_k = 0), \\
 S_k \perp\!\!\!\perp (L_0, A_0, \bar{Y}_k) &| Y_k = 0, \\
 \Pr(S_k = 1 | Y_k = 1) &= 0.
 \end{aligned} \right\} \quad (\text{S3}^*)$$

*The first requirement of S3\* essentially means that the frequency of incident cases in the  $k$ th window is proportional to the frequency of controls selected in this window. Under S3\*, S3 is met with  $\delta = \delta_k^* \Pr(Y_{k+1} = 1 | Y_k = 0)$ , because*

$$\Pr(S_k = 1 | L_0, A_0, \bar{Y}_k) = \Pr(S_k = 1 | Y_k)$$

$$\begin{aligned}
 &= \Pr(S_k = 1|Y_k = 0) \times (1 - Y_k) \\
 &= \Pr(S_k = 1|Y_k = 0) \times (1 - Y_k) \\
 &= \frac{\Pr(S_k = 1)}{\Pr(Y_k = 0)} \times (1 - Y_k) \\
 &= \frac{\delta_k^* \Pr(Y_{k+1} = 1, Y_k = 0)}{\Pr(Y_k = 0)} \times (1 - Y_k) \\
 &= \delta_k^* \Pr(Y_{k+1} = 1|Y_k = 0) \times (1 - Y_k).
 \end{aligned}$$

Therefore, stipulating that  $\delta_k^*$  is  $k$ -invariant is to state that  $\Pr(Y_{k+1} = 1|Y_k = 0)$  is constant for  $k = 0, \dots, K - 1$ .

**Theorem 10.5** (Risk-set sampling for conditional intention-to-treat effect). *Suppose BCE holds as well as S3, or the weaker version  $\Pr(S_k = 1|L_0, A_0, Y_k) = \Pr(S_k = 1|L_0, Y_k) = \delta_{L_0} \times (1 - Y_k)$ ,  $\delta_{L_0} \in (0, 1]$ . If*

$$\Pr(Y_{k+1}(a) = 1|L_0 = l, Y_k(a) = 0) = \theta_a \quad (\text{H3})$$

for  $a = 0, 1$ , all  $l$  and some constants  $\theta_0, \theta_1$ , then

$$\frac{\frac{\mathbb{E}[I(A_0 = 1)|L_0, Y_K = 1]}{\mathbb{E}[I(A_0 = 0)|L_0, Y_K = 1]}}{\frac{\mathbb{E}[I(A_0 = 1) \sum_{k=0}^{K-1} S_k | L_0]}{\mathbb{E}[I(A_0 = 0) \sum_{k=0}^{K-1} S_k | L_0]}} = \frac{\Pr(Y_{k+1}(1) = 1|L_0, Y_k(1) = 0)}{\Pr(Y_{k+1}(0) = 1|L_0, Y_k(0) = 0)}.$$

The proof to Theorem 10.5 is similar to that of Theorem 10.4 and therefore omitted.

### *Per-protocol effect*

In this subsection, an individual qualifies as a case if and only if  $Y_K = 1$  and the subject adheres to the protocol that was assigned at baseline. For any study participant, let  $S_k$  denote selection as a control for the period  $[t_k, t_{k+1})$  and suppose  $S_k$  satisfies

$$\left. \begin{aligned}
 &S_k = 1 \Rightarrow Y_k = 0 \text{ with probability 1, and} \\
 &\Pr(S_k = 1|\bar{L}_k, \bar{A}_k, Y_k = 0) = \Pr(S_k = 1|\bar{A}_{k-1}, Y_k = 0) \text{ and} \\
 &\Pr(S_k = 1|\bar{A}_{k-1}, A_0 = \dots = A_{k-1}, Y_k = 0) = \delta,
 \end{aligned} \right\} \quad (\text{S4})$$

for some  $\delta \in (0, 1]$ .

**Remark to Theorem 10.6.** *Condition  $S_4$  holds if, for some constant  $\delta_k^*$ ,*

$$\left. \begin{aligned} \Pr(S_k = 1) &= \delta_k^* \Pr(Y_{k+1} = 1, Y_k = 0, \forall j < k : A_j = A_0) \text{ and} \\ S_k \perp\!\!\!\perp (\bar{L}_k, \bar{A}_k, \bar{Y}_k) | (Y_k = 0, \forall j < k : A_j = A_0) \text{ and} \\ S_k = 1 &\Rightarrow (Y_k = 0, \forall j < k : A_j = A_0) \text{ with probability 1.} \end{aligned} \right\} \quad (S4^*)$$

*The first requirement of  $S_4^*$  essentially means that the frequency of protocol-adherent incident cases in the  $k$ th window is proportional to the frequency of controls selected in this window. Under  $S_4^*$ ,  $S_4$  is met with  $\delta = \delta_k^* \Pr(Y_{k+1} = 1 | Y_k = 0, \forall j < k : A_j = A_0)$ , because*

$$\begin{aligned} &\Pr(S_k = 1 | \bar{L}_k, \bar{A}_k, \bar{Y}_k) \\ &= \Pr(S_k = 1 | Y_k = 0, \forall j < k : A_j = A_0) \\ &\quad \times (1 - Y_k) \times I(\forall j < k : A_j = A_0) \\ &= \frac{\Pr(S_k = 1)}{\Pr(Y_k = 0, \forall j < k : A_j = A_0)} \times (1 - Y_k) \times I(\forall j < k : A_j = A_0) \\ &= \frac{\delta_k^* \Pr(Y_{k+1} = 1, Y_k = 0, \forall j < k : A_j = A_0)}{\Pr(Y_k = 0, \forall j < k : A_j = A_0)} \\ &\quad \times (1 - Y_k) \times I(\forall j < k : A_j = A_0) \\ &= \delta_k^* \Pr(Y_{k+1} = 1 | Y_k = 0, \forall j < k : A_j = A_0) \\ &\quad \times (1 - Y_k) \times I(\forall j < k : A_j = A_0). \end{aligned}$$

*Similarly, condition  $S_4$  holds if, for some constant  $\delta_k^{**}$ ,*

$$\left. \begin{aligned} \Pr(S_k = 1) &= \delta_k^{**} \Pr(Y_{k+1} = 1, Y_k = 0) \text{ and} \\ S_k \perp\!\!\!\perp (\bar{L}_k, \bar{A}_k, \bar{Y}_k) | (Y_k = 0) \text{ and} \\ S_k = 1 &\Rightarrow Y_k = 0 \text{ with probability 1,} \end{aligned} \right\} \quad (S4^{**})$$

*in which case,  $\delta = \delta_k^{**} \Pr(Y_{k+1} = 1 | Y_k = 0)$ , because*

$$\begin{aligned} &\Pr(S_k = 1 | \bar{L}_k, \bar{A}_k, \bar{Y}_k) \\ &= \Pr(S_k = 1 | Y_k = 0) \times (1 - Y_k) \\ &= \frac{\Pr(S_k = 1)}{\Pr(Y_k = 0)} \times (1 - Y_k) \\ &= \frac{\delta_k^{**} \Pr(Y_{k+1} = 1, Y_k = 0)}{\Pr(Y_k = 0)} \times (1 - Y_k) \\ &= \delta_k^{**} \Pr(Y_{k+1} = 1 | Y_k = 0) \times (1 - Y_k). \end{aligned}$$

**Theorem 10.6** (Risk-set sampling for marginal per-protocol effect). *Suppose SCE and  $S_4$  hold. If*

$$\Pr(Y_{k+1}(\bar{a}) = 1 | Y_k(\bar{a}) = 0) = \theta_a \quad (\text{H4})$$

for  $a = 0, 1$  and some constants  $\theta_0, \theta_1$ , then

$$\begin{aligned} & \frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = 1)W_k I(Y_{k+1} = 1, Y_k = 0) | Y_K = 1, (\forall j : Y_j = 0 \Rightarrow A_j = A_0)]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = 0)W_k I(Y_{k+1} = 1, Y_k = 0) | Y_K = 1, (\forall j : Y_j = 0 \Rightarrow A_j = A_0)]} \\ &= \frac{\mathbb{E}[I(A_0 = 1) \sum_{k=0}^{K-1} W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]}{\mathbb{E}[I(A_0 = 0) \sum_{k=0}^{K-1} W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]} \\ &= \frac{\Pr(Y_{k+1}(\bar{1}) = 1 | Y_k(\bar{1}) = 0)}{\Pr(Y_{k+1}(\bar{0}) = 1 | Y_k(\bar{0}) = 0)}, \end{aligned}$$

where

$$W_k = \prod_{j=0}^k \frac{1}{\Pr(A_j = a_j | \bar{L}_j, \bar{A}_{j-1}, Y_j = 0, S_j = 1)} \Big|_{a_j = A_j}.$$

*Proof.* First, observe that  $\Pr(A_k = a' | \bar{L}_k, (\forall j < k : A_j = a), Y_k = 0, S_k = 1) = \Pr(A_k = a' | \bar{L}_k, (\forall j < k : A_j = a), Y_k = 0)$  for  $a', a = 0, 1$ , because

$$\begin{aligned} & \Pr(A_k = a' | \bar{L}_k, (\forall j < k : A_j = a), Y_k = 0, S_k = 1) \\ &= \frac{\Pr(S_k = 1 | \bar{L}_k, (\forall j < k : A_j = a), A_k = a', Y_k = 0) \times \Pr(A_k = a' | \bar{L}_k, (\forall j < k : A_j = a), Y_k = 0)}{\Pr(S_k = 1 | \bar{L}_k, (\forall j < k : A_j = a), Y_k = 0)} \\ &= \frac{\delta}{\delta} \Pr(A_k = a' | \bar{L}_k, (\forall j < k : A_j = a), Y_k = 0). \quad (\text{by S4}) \end{aligned}$$

Hence, if  $\forall j < k : A_j = A_0$ , then

$$W_k = \prod_{j=0}^k \frac{1}{\Pr(A_j = a_j | \bar{L}_j, \bar{A}_{j-1}, Y_j = 0)} \Big|_{a_j = A_j}.$$

For the numerator of the main result of Theorem 10.6, we thus have

$$\begin{aligned} & \frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = 1)W_k I(Y_{k+1} = 1, Y_k = 0) | Y_K = 1, (\forall j : Y_j = 0 \Rightarrow A_j = A_0)]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = 0)W_k I(Y_{k+1} = 1, Y_k = 0) | Y_K = 1, (\forall j : Y_j = 0 \Rightarrow A_j = A_0)]} \\ &= \frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a)W_k I(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = A_0)]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a')W_k I(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = A_0)]} \end{aligned}$$

$$\begin{aligned}
&= \frac{\sum_{k=0}^{K-1} \mathbb{E}[W_k Y_{k+1} (1 - Y_k) I(\forall j \leq k : A_j = a)]}{\sum_{k=0}^{K-1} \mathbb{E}[W_k Y_{k+1} (1 - Y_k) I(\forall j \leq k : A_j = a')]} \\
&= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \frac{\Pr(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = a, \bar{L}_k = \bar{l}_k)}{\prod_{j=0}^k \Pr(A_j = a | Y_j = 0, \bar{L}_k = \bar{l}_k, \forall i < j : A_i = a)}}{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \frac{\Pr(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = a', \bar{L}_k = \bar{l}_k)}{\prod_{j=0}^k \Pr(A_j = a' | Y_j = 0, \bar{L}_k = \bar{l}_k, \forall i < j : A_i = a')}} ,
\end{aligned}$$

where

$$\begin{aligned}
&\sum_{\bar{l}_k} \frac{\Pr(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = a, \bar{L}_k = \bar{l}_k)}{\prod_{j=0}^k \Pr(A_j = a | Y_j = 0, \bar{L}_k = \bar{l}_k, \forall i < j : A_i = a)} \\
&= \sum_{\bar{l}_k} \Pr(Y_{k+1} = 1 | Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a) \\
&\quad \times \Pr(L_k = l_k | Y_k = 0, \bar{L}_{k-1} = \bar{l}_{k-1}, \forall j < k : A_j = a) \\
&\quad \times \prod_{j=0}^{k-1} \Pr(Y_{j+1} = 1 | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i \leq j : A_i = a) \\
&\quad \times \Pr(L_j = l_j | Y_j = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \\
&= \sum_{\bar{l}_k} \Pr(Y_{k+1}(\bar{a}) = 1 | Y_k(\bar{a}) = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a) \\
&\quad \times \Pr(L_k = l_k | Y_k(\bar{a}) = 0, \bar{L}_{k-1} = \bar{l}_{k-1}, \forall j < k : A_j = a) \\
&\quad \times \prod_{j=0}^{k-1} \Pr(Y_{j+1}(\bar{a}) = 1 | Y_j(\bar{a}) = 0, \bar{L}_j = \bar{l}_j, \forall i \leq j : A_i = a) \\
&\quad \times \Pr(L_j = l_j | Y_j(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \\
&\hspace{15em} \text{(by consistency)} \\
&= \sum_{\bar{l}_k} \Pr(Y_{k+1}(\bar{a}) = 1 | Y_k(\bar{a}) = 0, \bar{L}_k = \bar{l}_k, \forall j < k : A_j = a) \\
&\quad \times \Pr(L_k = l_k | Y_k(\bar{a}) = 0, \bar{L}_{k-1} = \bar{l}_{k-1}, \forall j < k : A_j = a) \\
&\quad \times \prod_{j=0}^{k-1} \Pr(Y_{j+1}(\bar{a}) = 1 | Y_j(\bar{a}) = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a) \\
&\quad \times \Pr(L_j = l_j | Y_j(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \\
&\hspace{15em} \text{(by sequential conditional exchangeability)}
\end{aligned}$$

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$$\begin{aligned}
 &= \sum_{\bar{l}_{k-1}} \Pr(Y_{k+1}(\bar{a}) = 1 | Y_k(\bar{a}) = 0, \bar{L}_{k-1} = \bar{l}_{k-1}, \forall j < k : A_j = a) \\
 &\quad \times \prod_{j=0}^{k-1} \Pr(Y_{j+1}(\bar{a}) = 1 | Y_j(\bar{a}) = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a) \\
 &\quad \times \Pr(L_j = l_j | Y_j(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \\
 &= \sum_{\bar{l}_{k-1}} \Pr(Y_{k+1}(\bar{a}) = 1, Y_k(\bar{a}) = 0 | Y_{k-1}(\bar{a}) = 0, \bar{L}_{k-1} = \bar{l}_{k-1}, \forall j < k : A_j = a) \\
 &\quad \times \Pr(L_{k-1} = l_{k-1} | Y_{k-1}(\bar{a}) = 0, \bar{L}_{k-2} = \bar{l}_{k-2}, \forall j < k-1 : A_j = a) \\
 &\quad \times \prod_{j=0}^{k-2} \Pr(Y_{j+1}(\bar{a}) = 1 | Y_j(\bar{a}) = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a) \\
 &\quad \times \Pr(L_j = l_j | Y_j(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \\
 &\quad \vdots \\
 &\text{(by repeating previous three steps, under sequential conditional exchangeability)} \\
 &= \Pr(Y_{k+1}(\bar{a}) = 1, Y_k(\bar{a}) = 0)
 \end{aligned}$$

and, similarly,

$$\begin{aligned}
 &\sum_{\bar{l}_k} \frac{\Pr(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = a', \bar{L}_k = \bar{l}_k)}{\prod_{j=0}^k \Pr(A_j = a' | Y_j = 0, \bar{L}_k = \bar{l}_k, \forall i < j : A_i = a')} \\
 &= \Pr(Y_{k+1}(\bar{a}') = 1, Y_k(\bar{a}') = 0).
 \end{aligned}$$

Hence,

$$\begin{aligned}
 &\frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a) W_k I(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = A_0)]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a') W_k I(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = A_0)]} \\
 &= \frac{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(\bar{a}) = 1, Y_k(\bar{a}) = 0)}{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(\bar{a}') = 1, Y_k(\bar{a}') = 0)} \\
 &= \frac{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(\bar{a}) = 1 | Y_k(\bar{a}) = 0) \prod_{j=1}^k \Pr(Y_j(\bar{a}) = 0 | Y_{j-1}(\bar{a}) = 0)}{\sum_{k=0}^{K-1} \Pr(Y_{k+1}(\bar{a}') = 1 | Y_k(\bar{a}') = 0) \prod_{j=1}^k \Pr(Y_j(\bar{a}') = 0 | Y_{j-1}(\bar{a}') = 0)} \\
 &= \frac{\sum_{k=0}^{K-1} \theta_a (1 - \theta_a)^k}{\sum_{k=0}^{K-1} \theta_{a'} (1 - \theta_{a'})^k} \tag{H4} \\
 &= \frac{1 - (1 - \theta_a)^K}{1 - (1 - \theta_{a'})^K} \quad (\text{since } (1 - r) \sum_{k=l}^u ar^k = a(r^l - r^{u+1}) \text{ for any real } a, r)
 \end{aligned}$$

For the denominator, we have

$$\begin{aligned}
& \frac{\mathbb{E}[I(A_0 = a) \sum_{k=0}^{K-1} W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]}{\mathbb{E}[I(A_0 = a') \sum_{k=0}^{K-1} W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]} \\
&= \frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a) W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a') W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]} \\
&= \frac{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a) W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]}{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a') W_k S_k | \forall j : Y_j = 0 \Rightarrow A_j = A_0]} \\
&= \frac{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a) W_k S_k | Y_k = 0, \forall j \leq k : A_j = A_0]}{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a') W_k S_k | Y_k = 0, \forall j \leq k : A_j = A_0]} \\
&\quad \times \frac{\Pr(Y_k = 0 | \forall j : Y_j = 0 \Rightarrow A_j = A_0)}{\Pr(Y_k = 0 | \forall j : Y_j = 0 \Rightarrow A_j = A_0)} \tag{by S4} \\
&= \frac{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a) W_k S_k | Y_k = 0, \forall j \leq k : A_j = A_0]}{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a') W_k S_k | Y_k = 0, \forall j \leq k : A_j = A_0]} \\
&\quad \times \frac{\Pr(Y_k = 0 | \forall j : Y_j = 0 \Rightarrow A_j = A_0)}{\Pr(Y_k = 0 | \forall j : Y_j = 0 \Rightarrow A_j = A_0)} \\
&= \frac{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a) W_k S_k | Y_k = 0, \forall j \leq k : A_j = A_0]}{\sum_{k=0}^{K-1} \mathbb{E}[I(A_k = a') W_k S_k | Y_k = 0, \forall j \leq k : A_j = A_0]} \\
&\quad \times \frac{\Pr(Y_k = 0, \forall j \leq k : A_j = A_0)}{\Pr(Y_k = 0, \forall j \leq k : A_j = A_0)} \\
&= \frac{\sum_{k=0}^{K-1} \mathbb{E}[W_k S_k | Y_k = 0, \forall j \leq k : A_j = a] \Pr(Y_k = 0, \forall j \leq k : A_j = a)}{\sum_{k=0}^{K-1} \mathbb{E}[W_k S_k | Y_k = 0, \forall j \leq k : A_j = a'] \Pr(Y_k = 0, \forall j \leq k : A_j = a')} \\
&= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \mathbb{E}[S_k | Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a]}{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \mathbb{E}[S_k | Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a]} \\
&\quad \times \frac{\Pr(Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a)}{\prod_{j=0}^k \Pr(A_j = a | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a)} \\
&= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \mathbb{E}[S_k | Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a']}{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \mathbb{E}[S_k | Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a']} \\
&\quad \times \frac{\Pr(Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a')}{\prod_{j=0}^k \Pr(A_j = a' | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a')} \\
&= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \frac{\Pr(Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a)}{\prod_{j=0}^k \Pr(A_j = a | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a)}}{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \frac{\Pr(Y_k = 0, \bar{L}_k = \bar{l}_k, \forall j \leq k : A_j = a')}{\prod_{j=0}^k \Pr(A_j = a' | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i < j : A_i = a')}} \tag{by S4} \\
&= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \prod_{j=0}^k \frac{\Pr(Y_j = 0, L_j = l_j | Y_{j-1} = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a)}{\Pr(Y_j = 0, L_j = l_j | Y_{j-1} = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a')}}{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \prod_{j=0}^k \frac{\Pr(Y_j = 0, L_j = l_j | Y_{j-1} = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a')}{\Pr(Y_j = 0, L_j = l_j | Y_{j-1} = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a')}}
\end{aligned}$$

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$$\begin{aligned}
 & \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \prod_{j=0}^k \Pr(L_j = l_j | Y_j = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \times \Pr(Y_j = 0 | Y_{j-1} = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a)}{\sum_{k=0}^K -1 \sum_{\bar{l}_k} \delta \prod_{j=0}^k \Pr(L_j = l_j | Y_j = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a') \times \Pr(Y_j = 0 | Y_{j-1} = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a')} \\
 &= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \prod_{j=0}^k \Pr(L_j = l_j | Y_j(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \times \Pr(Y_j(\bar{a}) = 0 | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a)}{\sum_{k=0}^{K-1} \sum_{\bar{l}_k} \delta \prod_{j=0}^k \Pr(L_j = l_j | Y_j(\bar{a}') = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a') \times \Pr(Y_j(\bar{a}') = 0 | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a')} \\
 & \hspace{15em} \text{(by consistency)} \\
 &= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-1}} \delta \prod_{j=0}^k \Pr(Y_j(\bar{a}) = 0 | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a) \times \Pr(L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a)}{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-1}} \delta \prod_{j=0}^k \Pr(Y_j(\bar{a}') = 0 | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j : A_i = a') \times \Pr(L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a')} \\
 &= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-1}} \delta \prod_{j=0}^k \Pr(Y_j(\bar{a}) = 0 | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j-1 : A_i = a) \times \Pr(L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a)}{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-1}} \delta \prod_{j=0}^k \Pr(Y_j(\bar{a}') = 0 | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-1} = \bar{l}_{j-1}, \forall i < j-1 : A_i = a') \times \Pr(L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a')} \\
 & \hspace{15em} \text{(by sequential conditional exchangeability)} \\
 &= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-1}} \delta \prod_{j=0}^k \Pr(Y_j(\bar{a}) = 0, L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a)}{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-1}} \delta \prod_{j=0}^k \Pr(Y_j(\bar{a}') = 0, L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a')} \\
 &= \frac{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-2}} \delta \prod_{j=0}^{k-1} \Pr(Y_j(\bar{a}) = 0, L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}) = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a) \times \Pr(Y_k(\bar{a}) = 0 | Y_{k-1}(\bar{a}) = 0, \bar{L}_{k-2} = \bar{l}_{k-2}, \forall i < k-1 : A_i = a)}{\sum_{k=0}^{K-1} \sum_{\bar{l}_{k-2}} \delta \prod_{j=0}^{k-1} \Pr(Y_j(\bar{a}') = 0, L_{j-1} = l_{j-1} | Y_{j-1}(\bar{a}') = 0, \bar{L}_{j-2} = \bar{l}_{j-2}, \forall i < j-1 : A_i = a') \times \Pr(Y_k(\bar{a}') = 0 | Y_{k-1}(\bar{a}') = 0, \bar{L}_{k-2} = \bar{l}_{k-2}, \forall i < k-1 : A_i = a')} \\
 & \hspace{15em} \text{(by sequential conditional exchangeability)} \\
 & \vdots
 \end{aligned}$$

$$\begin{aligned}
 &= \frac{\sum_{k=0}^{K-1} \delta \Pr(Y_k(\bar{a}) = 0)}{\sum_{k=0}^{K-1} \delta \Pr(Y_k(\bar{a}') = 0)} \\
 &= \frac{\sum_{k=0}^{K-1} \Pr(Y_k(\bar{a}) = 0)}{\sum_{k=0}^{K-1} \Pr(Y_k(\bar{a}') = 0)} \\
 &= \frac{1 + \sum_{k=1}^{K-1} \prod_{j=1}^k \Pr(Y_j(\bar{a}) = 0 | Y_{j-1}(\bar{a}) = 0)}{1 + \sum_{k=1}^{K-1} \prod_{j=1}^k \Pr(Y_j(\bar{a}') = 0 | Y_{j-1}(\bar{a}') = 0)} \\
 &= \frac{1 + \sum_{k=1}^{K-1} (1 - \theta_a)^k}{1 + \sum_{k=1}^{K-1} (1 - \theta_{a'})^k} \tag{by H4} \\
 &= \frac{1 + [1 - \theta_a - (1 - \theta_a)^{K-1}] / \theta_a}{1 + [1 - \theta_{a'} - (1 - \theta_{a'})^{K-1}] / \theta_{a'}} \\
 &\quad \text{(since } (1 - r) \sum_{k=l}^u ar^k = a(r^l - r^{u+1}) \text{ for any real } a, r) \\
 &= \frac{\theta_{a'}(1 - (1 - \theta_a)^{K-1})}{\theta_a(1 - (1 - \theta_{a'})^{K-1})}.
 \end{aligned}$$

Hence,

$$\begin{aligned}
 &\frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a)W_k I(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = A_0) | Y_K = 1]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = 1 - a)W_k I(Y_{k+1} = 1, Y_k = 0, \forall j \leq k : A_j = A_0) | Y_K = 1]} \\
 &\quad \frac{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = a)W_k S_k]}{\mathbb{E}[\sum_{k=0}^{K-1} I(A_k = 1 - a)W_k S_k]} \\
 &= \frac{1 - (1 - \theta_a)^{K-1}}{1 - (1 - \theta_{a'})^{K-1}} \times \frac{\theta_a(1 - (1 - \theta_{a'})^{K-1})}{\theta_{a'}(1 - (1 - \theta_a)^{K-1})} \\
 &= \theta_a / \theta_{a'},
 \end{aligned}$$

which completes the proof.  $\square$

### S10.3 Identification results for exact 1:M matching strategies

#### *Intention-to-treat effect*

In this subsection, cases are defined by  $Y_K = 1$  and have baseline exposure  $A_0$ . All cases are assigned a (possibly variable) number  $M \geq 0$  of control exposures  $A'_i$ ,  $i = 1, \dots, M$ , subject to

$$\left. \begin{aligned}
 &\Pr(M > 0 | Y_K = 1) > 0 \text{ and} \\
 &M \perp\!\!\!\perp A_0 | (L_0, Y_K = 1) \text{ and} \\
 &\forall l, a, a' : \Pr(A'_i = a' | L_0 = l, A_0 = a, Y_K = 1, M, M > 0) \\
 &\quad = \Pr(A_0 = a' | L_0 = l),
 \end{aligned} \right\} \tag{M1}$$

or

$$\left. \begin{aligned} & \Pr(M > 0 | Y_K = 1) > 0 \text{ and} \\ & M \perp\!\!\!\perp A_0 | (L_0, Y_K = 1) \text{ and} \\ \forall l, a, a' : & \Pr(A'_i = a' | L_0 = l, A_0 = a, Y_K = 1, M, M > 0) \\ & = \Pr(A_0 = a' | L_0 = l, Y_K = 0), \end{aligned} \right\} \quad (\text{M2})$$

or

$$\left. \begin{aligned} & \Pr(M > 0 | Y_K = 1) > 0 \text{ and} \\ & M \perp\!\!\!\perp A_0 | (L_0, Y_K = 1, J) \text{ and} \\ \forall l, a, a' : & \Pr(A'_i = a' | L_0 = l, A_0 = a, \bar{Y}_K, J = j, M, M > 0) \\ & = \Pr(A_0 = a' | L_0 = l, Y_j = 0), \\ & \text{where } J = \max\{k = 0, 1, \dots, K : Y_k = 0\}. \end{aligned} \right\} \quad (\text{M3})$$

That is, cases are matched with subjects that have the same baseline covariate level and who are alive at baseline (M1), at the end of study (M2), or whenever the case is alive (M3).

For simplicity, it is assumed below that the variables are discrete. The results can however be extended to more general distributions.

**Theorem 10.7** (Case-base sampling for marginal intention-to-treat effect). *If M1 and BCE hold and*

$$\frac{\Pr(Y_K = 1 | L_0 = l, A_0 = 1)}{\Pr(Y_K = 1 | L_0 = l, A_0 = 0)} = \theta \quad (\text{H1})$$

for all  $l$  and some constant  $\theta$ , then

$$\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1) | Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0) | Y_K = 1, M > 0]} = \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}.$$

*Proof.* We have

$$\begin{aligned} & \frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1) | Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0) | Y_K = 1, M > 0]} \\ & = \frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0) | A_0 = 1, Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1) | A_0 = 0, Y_K = 1, M > 0]} \\ & \quad \times \text{Odds}(A_0 = 1 | Y_K = 1, M > 0), \end{aligned}$$

where

$$\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0) | A_0 = 1, Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1) | A_0 = 0, Y_K = 1, M > 0]}$$

$$\begin{aligned}
& \frac{\mathbb{E}[\sum_{i=1}^m I(A'_i = 0) | A_0 = 1, Y_K = 1, M = m]}{\times \Pr(M = m | A_0 = 1, Y_K = 1, M > 0)} \\
= & \frac{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 1) | A_0 = 0, Y_K = 1, M = m]}{\times \Pr(M = m | A_0 = 0, Y_K = 1, M > 0)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A'_i = 0 | L_0 = l, A_0 = 1, Y_K = 1, M = m)}{\times \Pr(M = m, L_0 = l | A_0 = 1, Y_K = 1, M > 0)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A'_i = 1 | L_0 = l, A_0 = 0, Y_K = 1, M = m)}{\times \Pr(M = m, L_0 = l | A_0 = 0, Y_K = 1, M > 0)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A_0 = 0 | L_0 = l)}{\times \Pr(M = m, L_0 = l | A_0 = 1, Y_K = 1, M > 0)} \quad (\text{by M1}) \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A_0 = 1 | L_0 = l)}{\times \Pr(M = m, L_0 = l | A_0 = 0, Y_K = 1, M > 0)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A_0 = 0 | L_0 = l)}{\times \Pr(M = m, L_0 = l, A_0 = 1 | Y_K = 1)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A_0 = 1 | L_0 = l)}{\times \Pr(M = m, L_0 = l, A_0 = 0 | Y_K = 1)} \\
& \times \frac{1}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \Pr(Y_K = 1 | L_0 = l, A_0 = 1)}{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \Pr(Y_K = 1 | L_0 = l, A_0 = 0)} \\
& \times \frac{1}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)} \\
& \quad (\text{under M1 and definition of } q(l, m) \text{ (see below)}) \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \theta \Pr(Y_K = 1 | L_0 = l, A_0 = 0)}{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \Pr(Y_K = 1 | L_0 = l, A_0 = 0)} \\
& \times \frac{1}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)} \quad (\text{by H1}) \\
= & \frac{\theta}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)}
\end{aligned}$$

where  $q(l, m) = \Pr(M = m | L_0 = l, Y_K = 1) \Pr(A_0 = 0 | L_0 = l) \Pr(A_0 = 1 | L_0 = l) \Pr(L_0 = l)$ .

It follows that

$$\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1) | Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0) | Y_K = 1, M > 0]} = \frac{\Pr(Y_K = 1 | L_0, A_0 = 1)}{\Pr(Y_K = 1 | L_0, A_0 = 0)}$$

$$\begin{aligned}
 &= \frac{\Pr(Y_K(1) = 1|L_0, A_0 = 1)}{\Pr(Y_K(0) = 1|L_0, A_0 = 0)} \\
 &\quad \text{(by consistency)} \\
 &= \frac{\Pr(Y_K(1) = 1|L_0)}{\Pr(Y_K(0) = 1|L_0)} \\
 &\quad \text{(by baseline conditional exchangeability)} \\
 &= \frac{\Pr(Y_K(1) = 1)}{\Pr(Y_K(0) = 1)}.
 \end{aligned}$$

□

**Theorem 10.8** (Survivor sampling for conditional intention-to-treat effect).  
 Suppose M2 and BCE hold. If

$$\frac{\text{Odds}(Y_K = 1|L_0, A_0 = 1)}{\text{Odds}(Y_K = 1|L_0, A_0 = 0)} = \theta \tag{H5}$$

for some constant  $\theta$ , then

$$\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)|Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)|Y_K = 1, M > 0]} = \frac{\text{Odds}(Y_K(1) = 1|L_0)}{\text{Odds}(Y_K(0) = 1|L_0)}.$$

*Proof.* We have

$$\begin{aligned}
 &\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)|Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)|Y_K = 1, M > 0]} \\
 &= \frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0)|A_0 = 1, Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1)|A_0 = 0, Y_K = 1, M > 0]} \\
 &\quad \times \text{Odds}(A_0 = 1|Y_K = 1, M > 0),
 \end{aligned}$$

where

$$\begin{aligned}
 &\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0)|A_0 = 1, Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1)|A_0 = 0, Y_K = 1, M > 0]} \\
 &= \frac{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 0)|A_0 = 1, Y_K = 1, M = m] \times \Pr(M = m|A_0 = 1, Y_K = 1)}{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 1)|A_0 = 0, Y_K = 1, M = m] \times \Pr(M = m|A_0 = 0, Y_K = 1)}
 \end{aligned}$$

$$\begin{aligned}
&= \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A'_i = 0 | L_0 = l, A_0 = 1, Y_K = 1, M = m) \times \Pr(M = m, L_0 = l | A_0 = 1, Y_K = 1, M > 0)}{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A'_i = 1 | L_0 = l, A_0 = 0, Y_K = 1, M = m) \times \Pr(M = m, L_0 = l | A_0 = 0, Y_K = 1, M > 0)} \\
&= \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A_0 = 0 | L_0 = l, Y_K = 0) \times \Pr(M = m, L_0 = l | A_0 = 1, Y_K = 1, M > 0)}{\sum_{m>0} \sum_{i=1}^m \sum_l \Pr(A_0 = 1 | L_0 = l, Y_K = 0) \times \Pr(M = m, L_0 = l | A_0 = 0, Y_K = 1, M > 0)} \quad (\text{by M2}) \\
&= \frac{\sum_{m>0} \sum_{i=1}^m \sum_l \frac{\Pr(Y_K = 0 | L_0 = 0, A_0 = 0) \Pr(A_0 = 0 | L_0 = l) \times \Pr(M = m, L_0 = l, A_0 = 1 | Y_K = 1)}{\Pr(Y_K = 0 | L_0 = l)}}{\sum_{m>0} \sum_{i=1}^m \sum_l \frac{\Pr(Y_K = 0 | L_0 = 0, A_0 = 1) \Pr(A_0 = 1 | L_0 = l) \times \Pr(M = m, L_0 = l, A_0 = 0 | Y_K = 1)}{\Pr(Y_K = 0 | L_0 = l)}} \\
&\quad \times \frac{1}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)} \\
&= \frac{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \frac{\Pr(Y_K = 1 | L_0 = l, A_0 = 1)}{\Pr(Y_K = 0 | L_0 = 0, A_0 = 0)}}{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \frac{\Pr(Y_K = 1 | L_0 = l, A_0 = 0)}{\Pr(Y_K = 0 | L_0 = 0, A_0 = 1)}} \\
&\quad \times \frac{1}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)} \\
&\quad \quad (\text{under M2 and definition of } q(l, m) \text{ (see below)}) \\
&= \frac{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \theta \Pr(Y_K = 1 | L_0 = l, A_0 = 0) \times \Pr(Y_K = 0 | L_0 = 0, A_0 = 1)}{\sum_{m>0} \sum_{i=1}^m \sum_l q(l, m) \Pr(Y_K = 1 | L_0 = l, A_0 = 0) \times \Pr(Y_K = 0 | L_0 = 0, A_0 = 1)} \\
&\quad \times \frac{1}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)} \quad (\text{by H5}) \\
&= \frac{\theta}{\text{Odds}(A_0 = 1 | Y_K = 1, M > 0)}
\end{aligned}$$

where  $q(l, m) = \Pr(M = m | L_0 = l, Y_K = 1) \Pr(A_0 = 0 | L_0 = l) \Pr(A_0 = 1 | L_0 = l) \Pr(L_0 = l) / \Pr(Y_K = 0 | L_0 = l)$ .

From the definition of  $\theta$ , it follows that

$$\begin{aligned}
 \frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)|Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)|Y_K = 1, M > 0]} &= \frac{\text{Odds}(Y_K(1) = 1|L_0, A_0 = 1)}{\text{Odds}(Y_K(0) = 1|L_0, A_0 = 0)} \\
 &\quad \text{(by consistency)} \\
 &= \frac{\text{Odds}(Y_K(1) = 1|L_0)}{\text{Odds}(Y_K(0) = 1|L_0)} \\
 &\quad \text{(by baseline conditional exchangeability)} \\
 &= \frac{\text{Odds}(Y_K(1) = 1)}{\text{Odds}(Y_K(0) = 1)}.
 \end{aligned}$$

□

**Theorem 10.9** (Risk-set sampling for conditional intention-to-treat effect).  
*Suppose M3 and BCE hold. If*

$$\frac{\Pr(Y_{j+1} = 1|L_0, A_0 = 1, Y_j = 0)}{\Pr(Y_{j+1} = 1|L_0, A_0 = 0, Y_j = 0)} = \theta \tag{H6}$$

for  $j = 0, 1, \dots, K$  and some constant  $\theta$ , then

$$\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)|Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)|Y_K = 1, M > 0]} = \frac{\Pr(Y_{j+1}(1) = 1|L_0, Y_j(1) = 0)}{\Pr(Y_{j+1}(0) = 1|L_0, Y_j(0) = 0)}.$$

*Proof.* If  $J = \max\{k = 0, 1, \dots, K : Y_k = 0\}$ , then

$$\begin{aligned}
 &\frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)|Y_K = 1, M > 0]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)|Y_K = 1, M > 0]} \\
 &= \frac{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 0, A_0 = 1)|Y_K = 1, M = m] \times \Pr(M = m|Y_K = 1, M > 0)}{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 1, A_0 = 0)|Y_K = 1, M = m] \times \Pr(M = m|Y_K = 1, M > 0)} \\
 &= \frac{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 0, A_0 = 1)|Y_K = 1, M = m] \times \Pr(M = m, Y_K = 1)}{\sum_{m>0} \mathbb{E}[\sum_{i=1}^m I(A'_i = 1, A_0 = 0)|Y_K = 1, M = m] \times \Pr(M = m, Y_K = 1)}
 \end{aligned}$$

$$\begin{aligned}
& \frac{\sum_{m>0} \sum_{j=0}^{K-1} \sum_l \mathbb{E}[\sum_{i=1}^m I(A'_i = 0, A_0 = 1) | L_0 = l, J = j, M = m]}{\Pr(L_0 = l, J = j, M = m)} \\
= & \frac{\sum_{m>0} \sum_{j=0}^{K-1} \sum_l \mathbb{E}[\sum_{i=1}^m I(A'_i = 1, A_0 = 0) | L_0 = l, J = j, M = m]}{\times \Pr(L_0 = l, J = j, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \mathbb{E}[I(A'_i = 0, A_0 = 1) | L_0 = l, J = j, M = m]}{\times \Pr(L_0 = l, J = j, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \mathbb{E}[I(A'_i = 1, A_0 = 0) | L_0 = l, J = j, M = m]}{\times \Pr(L_0 = l, J = j, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \mathbb{E}[I(A'_i = 0, A_0 = 1) | L_0 = l, Y_j = 0, Y_{j+1} = 1, M = m]}{\times \Pr(L_0 = l, Y_j = 0, Y_{j+1} = 1, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \mathbb{E}[I(A'_i = 1, A_0 = 0) | L_0 = l, Y_j = 0, Y_{j+1} = 1, M = m]}{\times \Pr(L_0 = l, Y_j = 0, Y_{j+1} = 1, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \Pr(A'_i = 0 | L_0 = l, A_0 = 1, Y_j = 0, Y_{j+1} = 1, M = m)}{\times \Pr(L_0 = l, A_0 = 1, Y_j = 0, Y_{j+1} = 1, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \Pr(A'_i = 1 | L_0 = l, A_0 = 0, Y_j = 0, Y_{j+1} = 1, M = m)}{\times \Pr(L_0 = l, A_0 = 0, Y_j = 0, Y_{j+1} = 1, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \Pr(A_0 = 0 | L_0 = l, Y_j = 0)}{\times \Pr(L_0 = l, A_0 = 1, Y_j = 0, Y_{j+1} = 1, M = m)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l \Pr(A_0 = 1 | L_0 = l, Y_j = 0)}{\times \Pr(L_0 = l, A_0 = 0, Y_j = 0, Y_{j+1} = 1, M = m)} \\
& \text{(by M3)} \\
= & \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l q_j(l, m) \Pr(Y_{j+1} = 1 | L_0 = l, A_0 = 1, Y_j = 0)}{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l q_j(l, m) \Pr(Y_{j+1} = 1 | L_0 = l, A_0 = 0, Y_j = 0)} \\
& \text{(under M3 and definition of } q_j(l, m) \text{ (see below))} \\
= & \theta \frac{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l q_j(l, m) \Pr(Y_{j+1} = 1 | L_0 = l, A_0 = 0, Y_j = 0)}{\sum_{m>0} \sum_{i=1}^m \sum_{j=0}^{K-1} \sum_l q_j(l, m) \Pr(Y_{j+1} = 1 | L_0 = l, A_0 = 0, Y_j = 0)} \\
& \text{(by H6)} \\
= & \theta.
\end{aligned}$$

where  $q_j(l, m) = \Pr(M = m | L_0 = l, Y_j = 0) \Pr(A_0 = 1 | L_0 = l, Y_j = 0) \Pr(A_0 =$

$$0|L_0 = l, Y_j = 0) \Pr(L_0 = l, Y_j = 0).$$

Thus,

$$\begin{aligned} & \frac{\mathbb{E}[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)|Y_K = 1]}{\mathbb{E}[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)|Y_K = 1]} \\ &= \frac{\Pr(Y_{j+1} = 1|L_0, A_0 = 1, Y_j = 0)}{\Pr(Y_{j+1} = 1|L_0, A_0 = 0, Y_j = 0)} \\ &= \frac{\Pr(Y_{j+1}(1) = 1|L_0, A_0 = 1, Y_j(1) = 0)}{\Pr(Y_{j+1}(0) = 1|L_0, A_0 = 0, Y_j(0) = 0)} \quad (\text{by consistency}) \\ &= \frac{\Pr(Y_{j+1}(1) = 1|L_0, Y_j(1) = 0)}{\Pr(Y_{j+1}(0) = 1|L_0, Y_j(0) = 0)}. \end{aligned}$$

(by baseline conditional exchangeability)

□

### Per-protocol effect

In this subsection, an individual qualifies as a case if and only if  $Y_K = 1$  and the subject adheres to the protocol that was assigned at baseline (i.e.,  $A_k = A_0$  for all  $k = 0, 1, \dots, K$  if  $Y_k = 0$ ). All cases are assigned a (possibly variable) number  $M \geq 0$  control exposures  $A'_i$ ,  $i = 1, \dots, M$ , subject to

$$\left. \begin{aligned} & \Pr(M > 0|Y_K = 1, \forall j : (Y_j = 0 \Rightarrow A_j = A_0)) > 0 \text{ and} \\ & M \perp\!\!\!\perp A_0|(J, Y_K = 1, \bar{L}_J = \bar{l}_J, \forall i \leq J : A_i = A_0) \text{ and} \\ & \forall \bar{l}, a : \Pr(A'_i = a'|\bar{L}_J = \bar{l}_J, \forall j \leq J : A_j = A_0, A_0 = a, \\ & \quad Y_J = 0, J, M, M > 0) \\ & = \Pr(A_J = a'|\bar{L}_J = \bar{l}_J, \forall j \leq J : A_j = A_0, Y_J = 0), \\ & \text{where } J = \max\{k = 0, 1, \dots, K : Y_k = 0\}. \end{aligned} \right\} \quad (\text{M4})$$

**Theorem 10.10** (Risk-set sampling for conditional per-protocol effect). *Suppose M4 holds. If*

$$\frac{\Pr(Y_{j+1} = 1|\bar{L}_j = \bar{l}_j, Y_j = 0, \forall i \leq j : A_i = 1)}{\Pr(Y_{j+1} = 1|\bar{L}_j = \bar{l}_j, Y_j = 0, \forall i \leq j : A_i = 0)} = \theta \quad (\text{H7})$$

for all  $j, \bar{l}_j$  and some constant  $\theta$ , then

$$\frac{\mathbb{E}\left[\sum_{i=1}^M I(A'_i = 0, A_0 = 1)\middle|Y_K = 1, \forall j : (Y_j = 0 \Rightarrow A_j = A_0), M > 0\right]}{\mathbb{E}\left[\sum_{i=1}^M I(A'_i = 1, A_0 = 0)\middle|Y_K = 1, \forall j : (Y_j = 0 \Rightarrow A_j = A_0), M > 0\right]}$$

$$= \frac{\Pr(Y_{j+1}(\bar{1}) = 1 | \bar{L}_j = \bar{l}_j, Y_j(\bar{1}) = 0, \forall i \leq j : A_i = 1)}{\Pr(Y_{j+1}(\bar{0}) = 1 | \bar{L}_j = \bar{l}_j, Y_j(\bar{0}) = 0, \forall i \leq j : A_i = 0)}.$$

*Proof.* Let  $J = \max\{k = 0, 1, \dots, K : Y_k = 0\}$ . Then, for  $a = 0, 1$ ,

$$\begin{aligned} & \mathbb{E} \left[ \sum_{i=1}^M I(A'_i = 1 - a, A_0 = a) \middle| Y_K = 1, \forall j \leq J : A_j = A_0, M > 0 \right] \\ &= \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \mathbb{E} \left[ \sum_{i=1}^M I(A'_i = 1 - a, A_0 = a) \middle| \right. \\ & \quad \left. \bar{L}_j = \bar{l}_j, J = j, Y_K = 1, \forall j \leq J : A_j = A_0, M > 0 \right] \\ & \quad \times \Pr(\bar{L}_j = \bar{l}_j, J = j | Y_K = 1, \forall i \leq J : A_i = A_0, M > 0) \\ &= \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \mathbb{E} \left[ \sum_{i=1}^M I(A'_i = 1 - a, A_0 = a) \middle| \right. \\ & \quad \left. \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1, \forall j \leq J : A_j = A_0, M > 0 \right] \\ & \quad \times \Pr(\bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1 | Y_K = 1, \forall i \leq J : A_i = A_0, M > 0) \\ &= \sum_{m>0} \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \mathbb{E} \left[ \sum_{i=1}^m I(A'_i = 1 - a, A_0 = a) \middle| \right. \\ & \quad \left. \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1, \forall j \leq J : A_j = A_0, M = m \right] \\ & \quad \times \Pr(M = m, \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1 | \forall j \leq J : A_j = A_0, M > 0) \\ &= \sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \mathbb{E} \left[ I(A'_u = 1 - a, A_0 = a) \middle| \right. \\ & \quad \left. \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1, \forall j \leq J : A_j = A_0, M = m \right] \\ & \quad \times \Pr(M = m, \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1 | \forall j \leq J : A_j = A_0, M > 0) \\ &= \sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(A'_u = 1 - a | \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1, \\ & \quad \forall j \leq J : A_j = a, M = m) \end{aligned}$$

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$$\begin{aligned}
 & \times \Pr(M = m, A_0 = a, \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1 | \\
 & \quad \forall j \leq J : A_j = A_0, M > 0) \\
 = & \sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(A_0 = 1 - a | Y_j = 0, \bar{L}_j = \bar{l}_j, \\
 & \quad \forall i \leq j : A_i = A_0) \\
 & \quad \times \Pr(M = m, A_0 = a, \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1 | \\
 & \quad \forall j \leq J : A_j = A_0, M > 0) \tag{by M4} \\
 = & \sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(A_0 = 1 - a | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i \leq j : A_i = A_0) \\
 & \quad \times \Pr(M = m, \bar{L}_j = \bar{l}_j, A_0 = a, Y_{j+1} = 1, Y_j = 0, \forall i \leq j : A_i = A_0) \\
 & \quad \times \Pr(Y_K = 1, \forall i : (Y_i = 0 \Rightarrow A_i = A_0), M > 0)^{-1} \\
 = & \sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, A_0 = a, Y_j = 0, \forall i \leq j : A_i = A_0) \\
 & \quad \times q_j(\bar{l}_j, m) \Pr(Y_K = 1, \forall i : (Y_i = 0 \Rightarrow A_i = A_0), M > 0)^{-1}, \\
 & \tag{under M4}
 \end{aligned}$$

where

$$\begin{aligned}
 q_j(\bar{l}_j, m) &= \Pr(M = m | \bar{L}_j = \bar{l}_j, Y_j = 0, Y_{j+1} = 1, \forall i \leq j : A_i = A_0) \\
 & \quad \times \Pr(A_0 = 1 - a | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i \leq j : A_i = A_0) \\
 & \quad \times \Pr(A_0 = a | Y_j = 0, \bar{L}_j = \bar{l}_j, \forall i \leq j : A_i = A_0) \\
 & \quad \times \Pr(\bar{L}_j = \bar{l}_j, Y_j = 0, \forall i \leq j : A_i = A_0).
 \end{aligned}$$

It follows that

$$\begin{aligned}
 & \frac{\mathbb{E} \left[ \sum_{i=1}^M I(A'_i = 0, A_0 = 1) \middle| Y_K = 1, \forall j : (Y_j = 0 \Rightarrow A_j = A_0), M > 0 \right]}{\mathbb{E} \left[ \sum_{i=1}^M I(A'_i = 1, A_0 = 0) \middle| Y_K = 1, \forall j : (Y_j = 0 \Rightarrow A_j = A_0), M > 0 \right]} \\
 &= \frac{\sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, A_0 = 1, Y_j = 0, \forall i \leq j : A_i = A_0) \\
 & \quad \times q_j(\bar{l}_j, m) \Pr(Y_K = 1, \forall i : (Y_i = 0 \Rightarrow A_i = A_0), M > 0)^{-1}}{\sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, A_0 = 0, Y_j = 0, \forall i \leq j : A_i = A_0) \\
 & \quad \times q_j(\bar{l}_j, m) \Pr(Y_K = 1, \forall i : (Y_i = 0 \Rightarrow A_i = A_0), M > 0)^{-1}}
 \end{aligned}$$

$$\begin{aligned}
 & \frac{\sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, A_0 = 1, Y_j = 0, \forall i \leq j : A_i = A_0)}{\sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, A_0 = 1, Y_j = 0, \forall i \leq j : A_i = A_0)} \\
 &= \theta \frac{\sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, Y_j = 0, \forall i \leq j : A_i = 0)}{\sum_{m>0} \sum_{u=1}^m \sum_{j=0}^{K-1} \sum_{\bar{l}_j} \Pr(Y_{j+1} = 1 | \bar{L}_j = \bar{l}_j, Y_j = 0, \forall i \leq j : A_i = 0)} \\
 & \hspace{20em} \text{(by H7)} \\
 &= \theta.
 \end{aligned}$$

The desired results follows by consistency. □

### S10.4 Parametric identification by conditional logistic regression for exact or partial 1:M matching

We now allow for the possibility that cases ( $Y_K = 1$ ) are matched to  $M \geq 0$  controls on only part of  $L_0$ . That part of  $L_0$  on which exact matching is done will be denoted  $L_0^*$ ; the other part is denoted  $L'_0$ , so that  $L_0 = (L_0^*, L'_0)$ . The identification result below rests on the assumption that cases are assigned  $M \geq 0$  pairs  $(A'_i, L'_i)$  of baseline exposure and baseline covariate data,  $i = 1, \dots, M$ , subject to

$$\left. \begin{aligned}
 & \Pr(M > 0 | Y_K = 1) > 0 \text{ and} \\
 & M \perp\!\!\!\perp (A_0, L_0) | (L_0^*, Y_K = 1) \text{ and} \\
 & \forall l, l', a : \Pr(A'_i = a, L'_i = l' | L_0^* = l, L'_0, A_0, Y_K = 1, M, M > 0) \\
 & \quad = \Pr(A_0 = a, L'_0 = l' | L_0^* = l, Y_K = 0) \text{ and} \\
 & (L'_0, A_0), (L'_1, A'_1), \dots, (L'_M, A'_M) \text{ are mutually independent} \\
 & \text{given } (L_0^*, Y_K = 1, M > 0).
 \end{aligned} \right\} \text{(M2*)}$$

It is assumed below that the variables are discrete with finite support for simplicity. The results can however be extended to more general distributions.

**Theorem 10.11** (Conditional logistic regression for conditional intention-to-treat effect). *Suppose BCE and M2\* hold. For some known real-valued functions  $f_j$ ,*

$j = 1, \dots, p$ , assume the following model:

$$\text{logit Pr}(Y_K(a) = 1|L_0) = \alpha + \sum_{j=1}^p f_j(a, L_0^*, L'_0)\beta_j \quad (\text{Outcome Model})$$

For  $i = 0, \dots, M$ , let  $X_{i,j} = f_j(A'_i, L_0^*, L'_i) - f_j(A_0, L_0^*, L'_0)$ , with  $A'_0 = A_0$ , and assume for any  $\gamma_1, \dots, \gamma_p \in \mathbb{R}$ , not all zero, that

$$\Pr\left(\bigvee_{i=1}^M \left[\sum_{j=1}^p \gamma_j X_{i,j} \neq 0\right] \middle| Y_K = 1, M > 0\right) > 0, \quad (\text{Linear Independence})$$

where  $\bigvee$  denotes the logical OR operator (i.e., given any indexed collection  $(P_i)_{i \in I}$  of propositions,  $\bigvee_{i \in I} P_i$  is the proposition that  $P_i$  is true for at least one  $i \in I$ ). Then,

$$\mathbb{E}\left[-\log\left(1 + \sum_{i=1}^M \exp\left[\sum_{j=1}^p X_{i,j}\tilde{\beta}_j\right]\right)^{-1} \middle| Y_K = 1, M > 0\right]$$

is uniquely maximized at  $\tilde{\beta} = \beta$ .

*Proof.* We first demonstrate that

$$\mathbb{E}\left[-\log\left(1 + \sum_{i=1}^M \exp\left[\sum_{j=1}^p X_{i,j}\tilde{\beta}_j\right]\right)^{-1} \middle| Y_K = 1, M > 0\right]$$

has at most one maximum by showing that it is strictly concave as a function of  $\tilde{\beta}$ . Let  $X = (X_1, \dots, X_M)$  and  $X_i = (X_{i,1}, \dots, X_{i,p})$ ,  $i = 1, \dots, M$ . To show that function  $f$ ,

$$\begin{aligned} f(\beta) &= \mathbb{E}\left[\log\left(1 + \sum_{i=1}^M \exp\left[\sum_{j=1}^p X_{i,j}\beta_j\right]\right)^{-1} \middle| Y_K = 1, M > 0\right] \\ &= \sum_{m>0} \sum_x \log\left(1 + \sum_{i=1}^m \exp\left[\sum_{j=1}^p x_{i,j}\beta_j\right]\right)^{-1} \\ &\quad \times \Pr(X = x|Y_K = 1, M = m) \Pr(M = m|Y_K = 1, M > 0), \end{aligned}$$

is convex (and  $-f$  concave) it suffices to show that its Hessian is positive semidefinite, i.e., that  $\sum_{t=1}^p \sum_{u=1}^p \beta_k \beta_l H_{k,l}(\beta) \geq 0$  for all  $\beta \in \mathbb{R}^p$ , where

$$H_{k,l}(\beta) = \frac{\partial}{\partial \beta_l} \frac{\partial}{\partial \beta_k} f(\beta).$$

Positive definiteness of the Hessian, i.e.,  $\sum_{k=1}^p \sum_{l=1}^p \beta_k \beta_l H_{k,l}(\beta) > 0$  for all  $\beta \in \mathbb{R}^p$  such that  $\beta_k \neq 0$  for some  $k \in \{1, \dots, p\}$ , implies strict convexity of  $f$  (and  $-f$  strictly concave).

Letting  $g(X_i, \beta) = \exp \{ \sum_{j=1}^p X_{i,j} \beta_j \}$  for  $i = 1, \dots, M$ , we have

$$\begin{aligned}
H_{k,l}(\beta) &= \frac{\partial}{\partial \beta_l} \frac{\partial}{\partial \beta_k} f(\beta) \\
&= \frac{\partial}{\partial \beta_l} \sum_{m>0} \sum_x \frac{\sum_{i=1}^m x_{i,k} g(x_i, \beta)}{1 + \sum_{i=1}^m g(x_i, \beta)} \\
&\quad \times \Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0) \\
&= \frac{\partial}{\partial \beta_l} \sum_{m>0} \sum_x \frac{\sum_{i=1}^m x_{i,k} g(x_i, \beta)}{1 + \sum_{i=1}^m g(x_i, \beta)} \\
&\quad \times \Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0) \\
&= \sum_{m>0} \sum_x \left( 1 + \sum_{i=1}^m g(x_i, \beta) \right)^{-2} \\
&\quad \times \left[ \left( 1 + \sum_{i=1}^m g(x_i, \beta) \right) \left( \sum_{i=1}^m X_{i,k} X_{i,l} g(x_i, \beta) \right) \right. \\
&\quad \left. - \left( \sum_{i=1}^m X_{i,k} g(x_i, \beta) \right) \left( \sum_{i=1}^m X_{i,l} g(x_i, \beta) \right) \right] \\
&\quad \times \Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0),
\end{aligned}$$

so that, with  $v_i = \sqrt{g(x_i, \beta)}$  and  $w_i = \sum_{j=1}^p x_{i,j} \beta_j \sqrt{g(x_i, \beta)}$ ,

$$\begin{aligned}
&\sum_{k=1}^p \sum_{l=1}^p \beta_k \beta_l H_{k,l}(\beta) \\
&= \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{(1 + \sum_{i=1}^m g(x_i, \beta))^2} \\
&\quad \times \left[ \sum_{k=1}^p \sum_{l=1}^p \beta_k \beta_l \left( 1 + \sum_{i=1}^m g(x_i, \beta) \right) \left( \sum_{i=1}^m x_{i,k} x_{i,l} g(x_i, \beta) \right) \right. \\
&\quad \left. - \sum_{k=1}^p \sum_{l=1}^p \beta_k \beta_l \left( \sum_{i=1}^m x_{i,k} g(x_i, \beta) \right) \left( \sum_{i=1}^m x_{i,l} g(x_i, \beta) \right) \right] \\
&= \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{(1 + \sum_{i=1}^m g(x_i, \beta))^2}
\end{aligned}$$

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$$\begin{aligned}
 & \times \left[ \left( 1 + \sum_{i=1}^m g(x_i, \beta) \right) \left( \sum_{i=1}^m g(x_i, \beta) \left( \sum_{k=1}^p \beta_k x_{i,k} \right) \left( \sum_{l=1}^p \beta_l x_{i,l} \right) \right) \right. \\
 & \quad \left. - \left( \sum_{i=1}^m \sum_{k=1}^p \beta_k x_{i,k} g(x_i, \beta) \right) \left( \sum_{i=1}^m \sum_{l=1}^p \beta_l x_{i,l} g(x_i, \beta) \right) \right] \\
 = & \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{\left( 1 + \sum_{i=1}^m g(x_i, \beta) \right)^2} \\
 & \times \left[ \left( 1 + \sum_{i=1}^m g(x_i, \beta) \right) \left( \sum_{i=1}^m \left( \sum_{k=1}^p \beta_k x_{i,k} \sqrt{g(x_i, \beta)} \right)^2 \right) \right. \\
 & \quad \left. - \left( \sum_{i=1}^m \sum_{k=1}^p \beta_k x_{i,k} g(x_i, \beta) \right)^2 \right] \\
 = & \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{\left( 1 + \sum_{i=1}^m g(x_i, \beta) \right)^2} \\
 & \times \left[ \sum_{i=1}^m \left( \sum_{k=1}^p \beta_k x_{i,k} \sqrt{g(x_i, \beta)} \right)^2 + \left( \sum_{i=1}^m v_{i,j}^2 \right) \left( \sum_{i=1}^m w_{i,j}^2 \right) \right. \\
 & \quad \left. - \left( \sum_{i=1}^m v_{i,j} v_{i,j} \right)^2 \right] \\
 \geq & \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{\left( 1 + \sum_{i=1}^m g(x_i, \beta) \right)^2} \\
 & \times \sum_{i=1}^m \left( \sum_{k=1}^p \beta_k x_{i,k} \sqrt{g(x_i, \beta)} \right)^2. \quad (\text{by the Cauchy-Schwarz inequality})
 \end{aligned}$$

Now,

$$\begin{aligned}
 & \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{\left( 1 + \sum_{i=1}^m g(x_i, \beta) \right)^2} \\
 & \times \sum_{i=1}^m \left( \sum_{k=1}^p \beta_k x_{i,k} \sqrt{g(x_i, \beta)} \right)^2 \\
 = & \sum_{m>0} \sum_x \frac{\Pr(X = x | Y_K = 1, M = m) \Pr(M = m | Y_K = 1, M > 0)}{\left( 1 + \sum_{i=1}^m g(x_i, \beta) \right)^2} \\
 & \times \sum_{i=1}^m g(x_i, \beta) \left( \sum_{k=1}^p \beta_k x_{i,k} \right)^2
 \end{aligned}$$

$$= \mathbb{E} \left[ \left( 1 + \sum_{i=1}^M g(X_i, \beta) \right)^{-2} \sum_{i=1}^M g(X_i, \beta) \left( \sum_{k=1}^p \beta_k X_{i,k} \right)^2 \middle| Y_K = 1, M > 0 \right] \\ \geq 0$$

with strict inequality under Linear Independence. Thus,

$$\mathbb{E} \left[ -\log \left( 1 + \sum_{i=1}^M \exp \left[ \sum_{j=1}^p X_{i,j} \tilde{\beta}_j \right] \right)^{-1} \middle| Y_K = 1, M > 0 \right]$$

has at most one maximum.

It remains to be shown that

$$\mathbb{E} \left[ -\log \left( 1 + \sum_{i=1}^M \exp \left[ \sum_{j=1}^p X_{i,j} \tilde{\beta}_j \right] \right)^{-1} \middle| Y_K = 1, M > 0 \right]$$

is maximized at  $\tilde{\beta} = \beta$ , i.e.,  $\partial/\partial\tilde{\beta}_k f(\tilde{\beta}) = 0$  for all  $k = 1, \dots, p$  at  $\tilde{\beta} = \beta$ .

Now,

$$\frac{\partial}{\partial\tilde{\beta}_k} f(\tilde{\beta}) = \mathbb{E} \left[ \frac{\sum_{i=1}^M X_{i,k} g(X_i, \tilde{\beta})}{1 + \sum_{i=1}^M g(X_i, \tilde{\beta})} \middle| Y_K = 1, M > 0 \right] \\ = \sum_{l^*} \sum_{m>0} \mathbb{E} \left[ \frac{\sum_{i=1}^m X_{i,k} g(X_i, \tilde{\beta})}{1 + \sum_{i=1}^m g(X_i, \tilde{\beta})} \middle| L_0^* = l^*, Y_K = 1, M = m \right] \\ \times \Pr(L_0^* = l^*, M = m | Y_K = 1, M > 0),$$

where

$$\mathbb{E} \left[ \frac{\sum_{i=1}^m X_{i,k} g(X_i, \tilde{\beta})}{1 + \sum_{i=1}^m g(X_i, \tilde{\beta})} \middle| L_0^* = l^*, Y_K = 1, M = m \right] \\ = \sum_{l_0, \dots, l_m} \sum_{a_0, \dots, a_m} \frac{\sum_{i=1}^m [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \\ \times \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}} \\ \times \Pr(A_0 = a_0, A_1' = a_1, \dots, A_m = a_m, L_0' = l_0, \dots, L_m' = l_m | \\ L_0^* = l^*, Y_K = 1, M = m) \\ = \sum_{l_0, \dots, l_m} \sum_{a_0, \dots, a_m} \frac{\sum_{i=1}^m [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \\ \times \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}}$$

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$$\begin{aligned}
 & \times h(a_0, \dots, a_M, l_0, \dots, l_M) \\
 & \times \Pr \left( A_0 = a_0, A'_1 = a_1, \dots, A_M = a_M, L'_0 = l_0, \dots, L'_m = l_m \mid \right. \\
 & \left. \bigvee_{\sigma} [(A_0 = a_{\sigma(0)}, L'_0 =_{\sigma(0)}, A'_1 = a_{\sigma(1)}, L'_1 =_{\sigma(1)}, \dots, A_m = a_{\sigma(m)}, L'_m =_{\sigma(m)}] \right), \\
 & L_0^* = l^*, Y_K = 1, M = m),
 \end{aligned}$$

where permutation  $\sigma$  denotes a bijection from  $\{0, 1, \dots, M\}$  to itself and

$$\begin{aligned}
 & h(a_0, \dots, a_M, l_0, \dots, l_M) \\
 & = \Pr \left( \bigvee_{\sigma} [(A_0 = a_{\sigma(0)}, L'_0 =_{\sigma(0)}, A'_1 = a_{\sigma(1)}, L'_1 =_{\sigma(1)}, \dots, A_m = a_{\sigma(m)}, \right. \\
 & \quad \left. L'_m =_{\sigma(m)}] \mid L_0^* = l^*, Y_K = 1, M = m \right).
 \end{aligned}$$

Next, let  $B_0 = (L'_0, A_0)$  and  $B_i = (L'_i, A'_i)$ ,  $i = 1, 2, \dots, M$ . Let  $b_i = (l_i, a_i)$  for  $i = 0, \dots, M$ . We have

$$\begin{aligned}
 & \Pr \left( B_0 = b_0, \dots, B_M = b_M \mid \right. \\
 & \left. \bigvee_{\sigma} [(B_0, \dots, B_M) = (b_{\sigma(0)}, \dots, b_{\sigma(M)}], L_0^*, Y_K = 1, M, M > 0 \right) \\
 & = \frac{\Pr(B_0 = b_0, \dots, B_M = b_M \mid L_0^*, Y_K = 1, M > 0)}{\Pr \left( \bigvee_{\sigma} [B_0 = b_{\sigma(0)}, \dots, B_M = a_{\sigma(M)}] \mid L_0^*, Y_K = 1, M, M > 0 \right)} \\
 & \propto \frac{\Pr(B_0 = b_0, \dots, B_M = b_M \mid L_0^*, Y_K = 1, M > 0)}{\sum_{\sigma} \Pr \left( B_0 = b_{\sigma(0)}, \dots, B_M = a_{\sigma(M)} \mid L_0^*, Y_K = 1, M, M > 0 \right)} \\
 & = \frac{\prod_{i=0}^M \Pr(B_i = b_i \mid L_0^*, Y_K = 1, M, M > 0)}{\sum_{\sigma} \prod_{i=0}^M \Pr(B_i = b_{\sigma(i)} \mid L_0^*, Y_K = 1, M, M > 0)} \\
 & \quad \text{(by mutual independence of M2*)} \\
 & = \frac{\Pr(B_0 = b_0 \mid L_0^*, Y_K = 1) \prod_{i=1}^M \Pr(B_0 = b_i \mid L_0^*, Y_K = 0)}{\sum_{\sigma} \Pr(B_0 = b_{\sigma(0)} \mid L_0^*, Y_K = 1) \prod_{i=1}^M \Pr(B_0 = b_{\sigma(i)} \mid L_0^*, Y_K = 0)} \\
 & \quad \text{(by M2*)} \\
 & = \frac{\Pr(Y_K = 1 \mid B_0 = b_0, L_0^*) \prod_{i=1}^M [1 - \Pr(Y_K = 1 \mid B_0 = b_i, L_0^*)]}{\sum_{\sigma} \Pr(Y_K = 1 \mid B_0 = b_{\sigma(0)}, L_0^*) \prod_{i=1}^M [1 - \Pr(Y_K = 1 \mid B_0 = b_{\sigma(i)}, L_0^*)]}
 \end{aligned}$$

$$\begin{aligned}
& \frac{\Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)}{\times \prod_{i=1}^M [1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_i), A_0 = a_i)]} \\
= & \frac{\sum_{\sigma} \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(0)}), A_0 = a_{\sigma(0)})}{\times \prod_{i=1}^M [1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(i)}), A_0 = a_{\sigma(i)})]} \\
& \frac{\Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)}{1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)} \\
& \times \prod_{i=0}^M [1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_i), A_0 = a_i)] \\
= & \frac{\sum_{\sigma} \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(0)}), A_0 = a_{\sigma(0)})}{1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(0)}), A_0 = a_{\sigma(0)})} \\
& \times \prod_{i=0}^M [1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(i)}), A_0 = a_{\sigma(i)})] \\
& \frac{\Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)}{1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)} \\
= & \frac{\sum_{\sigma} \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(0)}), A_0 = a_{\sigma(0)})}{1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_{\sigma(0)}), A_0 = a_{\sigma(0)})} \\
& \frac{\Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)}{1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_0), A_0 = a_0)} \\
\propto & \frac{\sum_{i=0}^M \Pr(Y_K = 1|L_0 = (L_0^*, l_i), A_0 = a_i)}{1 - \Pr(Y_K = 1|L_0 = (L_0^*, l_i), A_0 = a_i)} \\
& \frac{\text{expit}\{\alpha + \sum_{j=1}^p f_j(a_0, L_0^*, l_0)\beta_j\}}{1 - \text{expit}\{\alpha + \sum_{j=1}^p f_j(a_0, L_0^*, l_0)\beta_j\}} \\
= & \frac{\sum_{i=0}^M \text{expit}\{\alpha + \sum_{j=1}^p f_j(a_i, L_0^*, l_i)\beta_j\}}{1 - \text{expit}\{\alpha + \sum_{j=1}^p f_j(a_i, L_0^*, l_i)\beta_j\}} \\
= & \frac{\exp[\sum_{j=1}^p f_j(a_0, L_0^*, l_0)\beta_j]}{\sum_{i=0}^M \exp[\sum_{j=1}^p f_j(a_i, L_0^*, l_i)\beta_j]} \\
= & \left( \sum_{i=0}^M \exp \left[ \sum_{j=1}^p [f_j(a_i, L_0^*, l_i) - f_j(a_0, L_0^*, l_0)]\beta_j \right] \right)^{-1} \\
= & \left( 1 + \sum_{i=1}^M \exp \left[ \sum_{j=1}^p [f_j(a_i, L_0^*, l_i) - f_j(a_0, L_0^*, l_0)]\beta_j \right] \right)^{-1}.
\end{aligned}$$

Thus,

$$\begin{aligned}
 & \mathbb{E} \left[ \frac{\sum_{i=1}^m X_{i,j} g(X_i, \tilde{\beta})}{1 + \sum_{i=1}^m g(X_i, \tilde{\beta})} \middle| L_0^* = l^*, Y_K = 1, M = m \right] \\
 & \propto \sum_{l_0, \dots, l_m} \sum_{a_0, \dots, a_m} \frac{\sum_{i=1}^m [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)]}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}} \\
 & \quad \times \frac{1}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \beta_k \}} \\
 & \quad \times h(a_0, \dots, a_M, l_0, \dots, l_M) \\
 & \propto \sum_{l_0, \dots, l_m} \sum_{a_0, \dots, a_m} h(a_0, \dots, a_M, l_0, \dots, l_M) \\
 & \quad \times \sum_{i=1}^m [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \\
 & \quad \times \frac{\exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \tilde{\beta}_k \}} \\
 & \quad \times \frac{1}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_0, l^*, l_0)] \beta_k \}} \\
 & \propto \sum_{\{(l_0, a_0), \dots, (l_m, a_m)\}} h(a_0, \dots, a_M, l_0, \dots, l_M) \\
 & \quad \times \sum_{u=1}^m \sum_{i=1}^m [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \\
 & \quad \times \frac{\exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \tilde{\beta}_k \}}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \tilde{\beta}_k \}} \\
 & \quad \times \frac{1}{1 + \sum_{i=1}^m \exp \{ \sum_{k=1}^p [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \beta_k \}} \\
 & = \sum_{\{(l_0, a_0), \dots, (l_m, a_m)\}} h(a_0, \dots, a_M, l_0, \dots, l_M) \\
 & \quad \times \sum_{u=1}^m \sum_{i=1}^m [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \\
 & \quad \times \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}}
 \end{aligned}$$

$$\begin{aligned}
&= \sum_{\{(l_0, a_0), \dots, (l_m, a_m)\}} h(a_0, \dots, a_M, l_0, \dots, l_M) \\
&\quad \times \left[ \sum_{u, i \in \{1, \dots, m\}: i > u} [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \right. \\
&\quad \times \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}} \\
&\quad + \sum_{u, i \in \{1, \dots, m\}: i < u} [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \\
&\quad \times \left. \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}} \right] \\
&= \sum_{\{(l_0, a_0), \dots, (l_m, a_m)\}} h(a_0, \dots, a_M, l_0, \dots, l_M) \\
&\quad \times \left[ \sum_{u, i \in \{1, \dots, m\}: i > u} [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \right. \\
&\quad \times \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}} \\
&\quad - \sum_{u, i \in \{1, \dots, m\}: i < u} [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \\
&\quad \times \left. \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}} \right] \\
&= \sum_{\{(l_0, a_0), \dots, (l_m, a_m)\}} h(a_0, \dots, a_M, l_0, \dots, l_M) \\
&\quad \times \sum_{u, i \in \{1, \dots, m\}: i > u} [f_k(a_i, l^*, l_i) - f_k(a_u, l^*, l_u)] \\
&\quad \times \left[ \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}} \right. \\
&\quad \left. - \frac{\exp \{ \sum_{k=1}^p f_k(a_u, l^*, l_u) \tilde{\beta}_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \tilde{\beta}_k \}} \frac{\exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}}{\sum_{i=0}^m \exp \{ \sum_{k=1}^p f_k(a_i, l^*, l_i) \beta_k \}} \right],
\end{aligned}$$

which is clearly zero when  $\tilde{\beta} = \beta$ . It follows that

$$\frac{\partial}{\partial \tilde{\beta}_k} f(\tilde{\beta}) = \mathbb{E} \left[ \frac{\sum_{i=1}^M X_{i,k} g(X_i, \tilde{\beta})}{1 + \sum_{i=1}^m g(X_i, \tilde{\beta})} \middle| Y_K = 1, M > 0 \right] = 0$$

## IDENTIFICATION OF CAUSAL EFFECTS IN CASE-CONTROL STUDIES

for all  $k = 1, \dots, p$  if and only if  $\tilde{\beta} = \beta$ .

□