Understanding Marginal Structural Models for Time-Varying Exposures: Pitfalls and Tips

Tomohiro Shinozaki¹ and Etsuji Suzuki²

¹Department of Information and Computer Technology, Faculty of Engineering, Tokyo University of Science, Tokyo, Japan
²Department of Epidemiology, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama University, Okayama, Japan

Received May 27, 2020; accepted July 6, 2020; released online July 18, 2020

ABSTRACT

Epidemiologists are increasingly encountering complex longitudinal data, in which exposures and their confounders vary during follow-up. When a prior exposure affects the confounders of the subsequent exposures, estimating the effects of the time-varying exposures requires special statistical techniques, possibly with structural (ie, counterfactual) models for targeted effects, even if all confounders are accurately measured. Among the methods used to estimate such effects, which can be cast as a marginal structural model in a straightforward way, one popular approach is inverse probability weighting. Despite the seemingly intuitive theory and easy-to-implement software, misunderstandings (or “pitfalls”) remain. For example, one may mistakenly equate marginal structural models with inverse probability weighting, failing to distinguish a marginal structural model encoding the causal parameters of interest from a nuisance model for exposure probability, and thereby failing to separate the problems of variable selection and model specification for these distinct models. Assuming the causal parameters of interest are identified given the study design and measurements, we provide a step-by-step illustration of generalized computation of standardization (called the g-formula) and inverse probability weighting, as well as the specification of marginal structural models, particularly for time-varying exposures. We use a novel hypothetical example, which allows us access to typically hidden potential outcomes. This illustration provides steppingstones (or “tips”) to understand more concretely the estimation of the effects of complex time-varying exposures.

Key words: causal inference; g-formula; inverse probability weighting; marginal structural model; time-varying exposure

BACKGROUND ON THE TOPIC

When we try to say something meaningful about a specific exposure–outcome causal relationship, counterfactual models are among the most popular and widely accepted approaches in the epidemiologic community.¹,² A counterfactual approach not only formalizes the language of cause and effect,³⁴ but has also triggered the explosive development of novel analytic methods, including propensity scores (ie, the probability of exposure conditional on measured confounders)¹⁴–¹⁹ and regression model-based estimation methods (ie, multivariable-adjusted outcome modeling, possibly followed by averaging predicted risks under distinct exposure statuses),²⁰,²¹ which have been evolved into doubly robust estimation.²²–²⁸ More importantly, a counterfactual approach has spurred extensive discussion on the assumptions for inferring causality from data and the conditions for specific statistical methods to work using, for example, causal diagrams.²–⁴,⁶,²⁹–³⁵ Yet, the most striking illustration brought about by the counterfactual approach may be that it can offer an elegant solution to the controversy surrounding the definition and estimability of the effects of exposures that vary over time. For example, initiated antiretroviral therapy (exposure) for acquired immunodeficiency syndrome may be intermitted after looking at the symptoms of pneumonia, which is a predictor of clinical outcomes (eg, death) but affected by the prior exposure, and thus considered as a part of the exposure’s effects. While no existent theory (at the time) in the statistics literature had offered clear guidance for adjusting or not adjusting for such intermediate variables to estimate the effect of time-varying exposures, new causal methodologies emerged in the 1980s. These include Robins’ unified approach, which is comprised of the generalized computational algorithm formula (abbreviated as g-formula) and estimation methods (ie, inverse probability weighting and g-estimation) of two classes of counterfactual, or structural, models.³⁶–⁴²

In 2000, marginal structural models were introduced as a tool to make the effects of such time-varying exposures easily estimable.⁴³–⁴⁵ Specifically, a marginal structural model is an equation to demonstrate prespecified assumptions on the causal effects to be estimated (ie, causal estimands). Thanks to the series of Robins and Hernán’s seminal works,⁴⁶–⁵¹ as well as others’ tutorials on the topic with intuitive theory and easy-to-implement software,⁵²–⁵⁹ marginal structural models have been widely applied to longitudinal data. Herein, we illustrate the use of marginal structural models, parameters of which can be estimated in a comparative way using inverse probability weighting and the
g-formula in certain situations, featuring hypothetical data with a time-varying exposure to point out common pitfalls as well as serve as a stepping stone to better understand the use of these methods.

CONCEPTUAL PITFALLS

If readers feel confused with the following statements, they could be trapped by the pitfalls around the methodology considered in this paper:

1. Marginal structural models should be distinguished from inverse probability weighting.
2. A marginal structural model is an equation to show prespecified assumptions on causal estimands, however, we rarely encounter such pedagogic examples of time-varying exposure.
3. As a marginal structural model and exposure probability model (for inverse probability weighting) are used for different purposes, mis specification of these models would lead to biases in different ways.
4. Principles for variable selection for marginal structural models are distinct from that for exposure probability models, and thus model specification of them raises different challenges.
5. Inverse probability weighting shares identifiability assumptions with the g-formula and can be used to fit marginal structural models when the assumptions are met, although g-formula can be used to fit them only when the models are saturated.

Although some of these pitfalls have been appreciated previously, we aim to discuss them from a different perspective. Before entering these subtleties, it would be helpful to seize the rationale of the specialized causal methods elaborated for time-varying exposures with simple worked examples without relying on computerized packages. Unlike point-exposure settings, however, we rarely encounter such pedagogic examples of time-varying exposures, including counterfactual data that explicate causal estimands and underlying conditions. Although there are at least four excellent numerical examples appropriate for exercise, they rely on either the external causal knowledge (ie, causal diagrams without explicit estimands) or “g-null” theorem implied by a causal diagram and observed data or “true” parameters for simulated data. In this paper, we provide a step-by-step illustration, or tips, using a novel, hypothetical numerical example dataset that includes potential outcomes, which directly incorporates minimal information to explicitly define causal estimands and conditions for their identification. One may consider a causal diagram would be helpful to understand the structure of the dataset. As noted later, however, causal diagrams typically include more causal assumptions than sufficient conditions to identify causal effects. That is why we do not start by drawing causal diagrams and use them only complementarily in our illustration, despite the fact that they are indeed useful tools for explicating our assumptions in real data analysis.

The following “tips” emanate from two introductory subsections regarding the effects of point exposures and time-varying exposures. Then, we step into the main contents to understand the unique role of and distinction between inverse probability weighting, marginal structural models, and regression/exposure probability models.

### Hypothetical cohort data with potential outcomes under point-exposure

| Stratum | N | Potential outcome | Observed outcome |
|---------|---|------------------|-----------------|
|         |   | Y0 = 1 | Y1 = 1 | Y = 1 | E[Y|A, L] |
| 1 1     | 280 | 168 0.6 | 210 0.75 | 210 0.75 |
| 1 0     | 720 | 432 0.6 | 540 0.75 | 432 0.6 |
| 0 1     | 180 | 45 0.25 | 60 0.333 | 60 0.333 |
| 0 0     | 60  | 15 0.25 | 20 0.333 | 15 0.25 |

*Unobservable counterfactual distributions. Bold numbers are observed as Y = 1 (by consistency) in each stratum.

### TIPS TO UNDERSTAND WHAT, WHY, AND HOW OF MARGINAL STRUCTURAL MODELS

**Prerequisite: identification of point-exposure effects**

As many epidemiologists become familiarized with a potential-outcome framework for a single time point, or a point-exposure setting, we just briefly review it here; readers unfamiliar with the basic concepts and notation may refer to Part 1 of Causal Inference: What If or concise introduction papers. Suppose that exposure A (eg, antihypertensive drug), outcome Y (eg, the occurrence of cardiovascular disease), and set of covariates L (eg, current/prior health conditions, unhealthy behaviors, and social support) are observed for individual i = 1, ..., n. Let Y^i denote the possibly unobserved, potential outcome that would be observed if, possibly counterfactually, exposure A was set to level a = 0 (unexposed) or 1 (exposed) (hereafter, we may omit subscript i if no confusion will occur). Then, the average causal effect of exposure A on outcome Y may be defined as E[Y^1 − E[Y^0]], which compares counterfactual expectations (or risks for a binary outcome) Y^1 and Y^0 in the same population along the difference-scale.

Suppose a hypothetical cohort (Table 1) of 1,240 members whose E[Y^0] = 660/1,240 = 0.532 and E[Y^1] = 830/1,240 = 0.669, indicating moderate risk increase (causal risk difference of 13.7%) by exposure A. Note that in a counterfactual framework, because either Y^0 or Y^1 can be observed as Y_i according to actual exposure status A_i, we can observe neither E[Y^0] nor E[Y^1] directly in the data. Thus, we need the set of assumptions to identify the causal effect: (1) consistency (ie, if A_i = a then Y_i = Y^a_i for all a), positivity (ie, 0 < P(A = a|L) almost everywhere, for all a), and the following conditional exchangeability given covariates, say, L.

Table 1 also presents the observed distribution of (L, A_i, Y_i) in accordance with potential outcome Y^a_i (a = 0, 1) under consistency. In Table 1, potential risk under a = 0 in the exposed E[Y^0|A = 1] = 213/460 = 0.463 is not equal to that in the unexposed E[Y^0|A = 0] = 447/780 = 0.573, and the same is true for potential risk under a = 1, E[Y^1|A]. When A is associated with Y^a as previously, marginal (unconditional) exchangeability is violated and the A−Y association (observed risk difference) is said to be confounded: E[Y|A = 1] − E[Y|A = 0] = 270/460 − 447/780 = 1.4%, indicating almost null association. Fortunately, within every strata of L, we can verify from Table 1 (“Risk” columns) that E[Y|A = 0, L = l] = E[Y^a|A = 1, L = l] (a = 0, 1 and l = 0, 1) and thus equal to E[Y^0|L = l]. This condition is called “conditional exchangeability given L” and the sets of covariates that satisfy the condition are said to be confounders.
Under the condition, a weighted mean, or standardized risk, $\sum_{i} E[Y^0,i|A] = a, L = l|P(L = l)$ is equal to $E[Y^0]|$; that is, causal effects are identifiable. In our data, standardized risks for $A = 0$ and $A = 1$ are

$$0.61(1000/1240) + 0.25(240/1240) = 0.532 = E[Y^0]$$
$$0.75(1000/1240) + 0.333(240/1240) = 0.669 = E[Y^1],$$

respectively.

The next subsection extends the definitions for and the conditions sufficient to identify causal effects for time-varying settings. To focus on the complexity of conditional exchangeability in time-varying settings, we suppose throughout this paper that consistency and positivity assumptions, as well as the time-varying versions of them, are met in our data.

**Definition and identification of effects of time-varying exposures**

**Targeted effects of time-varying exposure**

If an exposure varies over time, the aforementioned definition of effects should be refined. Consider a simple case with 2 time points. At time 1, baseline confounders $L_{1j}$ are measured and then exposure $A_{1j}$ is commenced; at time 2, confounder set $L_{2j}$ is measured and exposure is changed to $A_{2j}$; finally, outcome $Y$ is measured. Thus, the observed data are $(L_{1j}, A_{1j}, L_{2j}, A_{2j}, Y_j)$ for $i = 1, \ldots, n$. Note that $A_1$ and $A_2$ may represent the same exposure (eg, start/stop anti-hypertensive drugs) or different exposures introduced sequentially (eg, first-line and second-line chemotherapy for cancer patients). Likewise, $L_1$ and $L_2$ may consist of the same set of variables or (partly or entirely) distinct sets of variables.

For time-varying exposure, potential outcome can be defined by the combination of intervention on a joint exposure $(A_{1j}, A_{2j})$: let $Y^{a_{1j},a_{2j}}$ denote the potential outcome that would be observed if exposure $A_{1j}$ and $A_{2j}$ were set to level $a_1$ and $a_2$, respectively. We assume that exposure at each time takes on 0 (unexposed) or 1 (exposed), leading to 4 different potential outcomes—$Y^{0,0}, Y^{0,1}, Y^{1,0}, Y^{1,1}$ for each individual $i$. The average causal effect of exposure on outcome may be defined as any contrast between counterfactual expectations $E[Y^{a_{1j},a_{2j}}]$; eg, $E[Y^{0,1}] - E[Y^{0,0}]$. We can also consider $E[Y^{1,0}] - E[Y^{0,0}]$, which is referred to as the “controlled direct effect” of $A_1$ while $A_2$ set at 0.”

Note that joint exposure $(A_1, A_2)$ can affect not only outcome $Y$, but also $L_2$ (by $A_1$), which is measured after exposure initiation. Under the implausible assumption of no effect of (the part of) exposure on (the part of) the following confounders, the effect of $(A_1, A_2)$ can solely be seen as a multivalued exposure at a single time-point; as shown earlier, $\sum_{i,j} E[Y^0,A_i = a_1, A_2 = a_2, L_1 = l_1, L_2 \equiv l_2|P(L = l_1) = l_1, L_2 = l_2]$ is equal to $E[Y^{a_{1j},a_{2j}}]$ if the corresponding exchangeability assumptions for point-exposure hold. In the following hypothetical data, however, there is no single set of confounders for joint effects of $A_1$ and $A_2$. Rather, $L_1$ is a sufficient set of confounders for $A_1$, and $(L_1, A_2)$ is a sufficient set of confounders for $A_2$. This condition would enable us to identify $E[Y^{a_{1j},a_{2j}}]$ but the usual standardization formula, $\sum_{i,j} E[Y^0,A_i = a_1, A_2 = a_2, L_1 = l_1, L_2 = l_2|P(L = l_1) = l_1, L_2 = l_2]$ leads to biased estimates unless the aforementioned implausible assumption of no-effect of past exposures on time-varying confounders holds.

### A hypothetical cohort

For simplicity, consider a hypothetical cohort with empty $L_1$. The situation would arise if $A_1$ is randomized at baseline, but non-adherence occurs or another exposure is introduced during the follow-up, or if the cohort is restricted based on measured variables $L_1$. In either case, the following illustration is unaffected by including the diverse values of $L_1$, so let us ignore the adjustment for baseline confounders in our illustration.

Table 2 provides the data distribution of $(A_{1j}, L_{1j}, L_{2j}, A_{2j}, Y_j)$ augmented by unobserved potential outcome $Y^{a_{1j},a_{2j}}(a_1, a_2 = 0, 1)$ in the hypothetical cohort. As in Table 1, observed outcome $Y$ coincides with $Y^{a_{1j},a_{2j}}$ such that $(A_{1j}, A_{2j}) = (a_1, a_2)$ by consistency. We want to identify from observational data four expectations $E[Y^{a_{1j},a_{2j}}]”$ (“Total” row of “Risk” columns).

We note that neither unconditional nor conditional (given $L_2$) exchangeability holds for joint exposure $(A_1, A_2)$ in our data. For example, in the subgroups of $(A_1, A_2) = (1, 1)$ and $(0, 0)$, $E[Y^{0,0}|A_1 = 1, A_2 = 1] = 1.728/2.520 = 0.686$ differs from $E[Y^{0,0}|A_1 = 0, A_2 = 0] = 1.575/3.990 = 0.395$ (unconditional exchangeability fails). Likewise, $E[Y^{0,0}|A_1 = 1, L_2 = 0, A_2 = 1] = 0.6 \neq E[Y^{0,0}|A_1 = 0, L_2 = 0, A_2 = 0] = 0.3$ (conditional exchangeability fails). Readers can see other potential outcomes $Y^{a_{1j},a_{2j}}$ also differ on average between distinct subgroups of $(A_1, A_2)$. Next, let us see the bias in estimators ignoring or solely stratifying on $L_2$ as a “baseline” confounder.

### Naïve standardization vs the g-formula

Table 3 shows the observable part of Table 2 in a different layout, adding some candidate estimates from observed data. “$L_2$-collapsed” estimates are risks in subgroups of joint exposure, $E[Y|A_1 = a_1, A_2 = a_2]$ without considering $L_2$. These are away from $E[Y^{a_{1j},a_{2j}}]$ in Table 2 because of the lack of unconditional exchangeability. On the other hand, “naïve standardization” uses standardization formula in point-exposure settings: $\sum_{i,j} E[Y^0,A_i = 0$.

---

**Table 2.** Hypothetical cohort data with potential outcomes under time-varying exposure

| Stratum | $A_1$ | $L_2$ | $A_2$ | $N$ | Potential outcome* | Observed outcome |
|---------|-------|-------|-------|-----|--------------------|-----------------|
|         |       |       |       |     | $Y^{0,0} = 1$ Risk | $Y^{0,1} = 1$ Risk | $Y^{1,0} = 1$ Risk | $Y^{1,1} = 1$ Risk | $Y = 1$ | $E[Y|A_1, L_2, A_2]$ |
| 1       | 1     | 1     | 1     | 720 | 648 0.9 648 0.9    | 432 0.6 576 0.8  | 576 0.8 |
| 1       | 1     | 1     | 2     | 642 | 0.9 162 0.9       | 444 0.8 720 0.4  | 720 0.4 |
| 1       | 0     | 1     | 1     | 1,800 | 908 0.9 900 0.55 | 900 0.5 720 0.5  | 900 0.5 |
| 1       | 0     | 0     | 1     | 1,800 | 900 0.5 900 0.55 | 900 0.5 720 0.5  | 900 0.5 |
| 0       | 1     | 1     | 1     | 5,670 | 5,103 0.9 4,536 0.8 | 2,835 0.5 3,402 0.6  | 4,536 0.8 |
| 0       | 0     | 1     | 1     | 630  | 567 0.9 504 0.55 | 315 0.5 378 0.6  | 567 0.9 |
| 0       | 0     | 0     | 1     | 840  | 252 0.3 294 0.35 | 462 0.55 252 0.3  | 294 0.35 |
| 0       | 0     | 0     | 0     | 3,360 | 1,008 0.3 1,176 0.35 | 1,848 0.55 1,008 0.3  | 1,008 0.3  |

*Unobservable counterfactual distributions. Bold numbers are observed as $Y = 1$ (by consistency) in each stratum.

---

**Table 3.** Hypothetical cohort data with potential outcomes under time-varying exposure
However, this estimate is (and other estimates are) again biased because it is not exchangeable (see Appendix A for more technical notes on the topic). In Table 3 averages the stratified risks $E[Y|A_1, L_2]$ for joint exposure, we can easily check the following conditions.

### Conditions for identification of the effects

Instead of conditional exchangeability $E[Y^{a_1,a_2}|A_1, L_2] = E[Y^{a_1,a_2}|L_2]$ for joint exposure, we can easily check the following conditions:

\[
E[Y^{a_1,a_2}|A_1 = 1] = E[Y^{a_1,a_2}|A_1 = 0] \quad \text{(C1)}
\]

\[
E[Y^{a_1,a_2}|A_1 = a_1, L_2, A_2 = 1] = E[Y^{a_1,a_2}|A_1 = a_1, L_2, A_2 = 0], \quad \text{(C2)}
\]

for all $a_1$ and $a_2$, from upper four rows vs lower four rows (for (C1)) and every 2 rows within the same stratum of $(A_1, L_2)$ (for (C2)) in Table 2. These conditions are collectively called the sequential exchangeability for $(A_1, A_2)$, which are typically easier to hold than joint conditional exchangeability but are neither necessary nor sufficient condition for joint conditional exchangeability (see Appendix A for more technical notes on the conditions). The covariates that satisfy (C2) through their stratification (ie, $L_2$ here) are called time-varying confounders. In fact, slightly strong condition (C2) $E[Y^{a_1,a_2}|A_1, L_2, A_2 = 1] = E[Y^{a_1,a_2}|A_1, L_2, A_2 = 0]$ (which requires conditional independence in all $A_1$ supports instead of only in $A_1 = a_1$) compatible with intervention on $Y^{a_1,a_2}$ also holds in our example, while this is not required for the g-formula to be equal to $E[Y^{a_1,a_2}]$. The g-formula equals $E[Y^{a_1,a_2}]$ if sequential exchangeability (C1) and (C2) holds.

### Table 3. Estimates of effect of time-varying exposure from hypothetical cohort data

| $L_2$ | $A_1 = 0$ | $A_2 = 0$ | $A_1 = 1$ | $A_2 = 0$ | $A_1 = 1$ | $p(L_2) | A_1$ | $p(L_2)$ |
|-------|-----------|-----------|-----------|-----------|-----------|--------------|-----------|
|       | $N$ | $Y = 1$ | Risk | $N$ | $Y = 1$ | Risk | $N$ | $Y = 1$ | Risk | $N$ | $Y = 1$ | Risk |
| 1     | 630 | 567 | 0.9 | 5,670 | 4,536 | 0.8 | 0.6 | 180 | 108 | 0.6 | 720 | 576 | 0.8 | 0.2 | 0.48 |
| 0     | 3,360 | 1,008 | 0.3 | 840 | 294 | 0.35 | 0.4 | 1,800 | 900 | 0.5 | 1,800 | 720 | 0.4 | 0.8 | 0.52 |

Estimates of $E[Y^{a_1,a_2}]$:

- $L_2$-collapsed b
- Naive standardization c
- G-formula d

### Notes

1. $a_1, A_2 = a_2, L_2 = l_2|P(L_2 = l_2)$, where $P(L_2 = 1) = 0.48$ and $P(L_2 = 0) = 0.52$. For example, standardized risk in $(A_1, A_2) = (0, 0)$ can be obtained as $(567/630)0.48 + (1,008/3,360)0.52 = (0.9)0.48 + (0.3)0.52 = 0.59$.

2. However, this estimate is (and other estimates are) again biased because it is not exchangeable (see $E[Y^{a_1,a_2}] = 0.66$ and other $E[Y^{a_1,a_2}]$ in Table 2) owing to the violation of conditional exchangeability given $L_2$.

3. Instead of using $P(L_2 = l_2)$ in the stratification formula, the “g-formula” in Table 3 averages the stratified risks $E[Y|A_1, L_2 = l_2, A_2]$ using the weights $P(L_2 = l_2|A_1)$:

$$\sum_{l_2} E[Y|A_1 = a_1, L_2 = l_2, A_2 = a_2|P(L_2 = l_2|A_1 = a_1).$$

4. Unlike the previous two naïve estimates, we can see that these values are equal to $E[Y^{a_1,a_2}]$ in Table 2. As elaborated in the next subsection, the g-formula is one expression of $E[Y^{a_1,a_2}]$ in terms of observed distribution under the condition that is different from unconditional/conditional exchangeability.

5. It is helpful to depict the conditions in causal diagrams, namely, causal directed acyclic graphs (DAGs) and single-world intervention graphs (SWIGs), which are typically unfamiliar with these graphical terminology and rules (eg, opening/blocking paths, d-separation, the backdoor criterion) to refer to introductory articles, and book chapters on the topic. Informally, variables are d-separated if they are not connected with each other or connected only through paths on which at least one unadjusted “colliders” or adjusted “non-colliders” exist. If a supposed exposure is d-separated from a supposed outcome by adjusting for non-descendant variables of the exposure (in an original graph) after deletion of arrows emanating from the exposure, then we would say the backdoor criterion is satisfied. Figure 1, which is adopted from Part 3 of Causal Inference: What If, represents the causal diagrams that imply (C1) and (C2). Note that the typical strategy for causal inference in practice starts by drawing a causal DAG (eg, Figure 1(a)) or a SWIG (eg, Figure 1(c)) assumed for the data-generating process. Then, (conditional) independences between potential and observed variables, such as (C1) and (C2), are deduced from the graph. Here, we go backward; we start with counterfactual data (Table 2) in which (C1) and (C2) hold and proceed to causal DAGs/SWIGs that are compatible with those conditions.

6. In Figure 1(a), there is no non-descendant variable set that blocks all backdoor paths from collective nodes $(A_1, A_2)$ to $Y$ (ie, satisfies the backdoor criterion). On the contrary, the backdoor paths to $Y$ from $A_1$ and $A_2$ are separately blocked by distinct sets of variables: empty set for $A_1$ and $(A_1, A_2)$ for $A_2$. The arguments can be more directly depicted using potential variables in Figure 1(c), which is a “template” of the SWIG representing each intervention ($a_1$, $a_2$) on $(A_1, A_2)$.

In Figure 1(a), there is no non-descendant variable set that blocks all backdoor paths from collective nodes $(A_1, A_2)$ to $Y$ (ie, satisfies the backdoor criterion). On the contrary, the backdoor paths to $Y$ from $A_1$ and $A_2$ are separately blocked by distinct sets of variables: empty set for $A_1$ and $(A_1, A_2)$ for $A_2$. The arguments can be more directly depicted using potential variables in Figure 1(c), which is a “template” of the SWIG representing each intervention ($a_1$, $a_2$) on $(A_1, A_2)$.

In Figure 1(a), there is no non-descendant variable set that blocks all backdoor paths from collective nodes $(A_1, A_2)$ to $Y$ (ie, satisfies the backdoor criterion). On the contrary, the backdoor paths to $Y$ from $A_1$ and $A_2$ are separately blocked by distinct sets of variables: empty set for $A_1$ and $(A_1, A_2)$ for $A_2$. The arguments can be more directly depicted using potential variables in Figure 1(c), which is a “template” of the SWIG representing each intervention ($a_1$, $a_2$) on $(A_1, A_2)$.

In Figure 1(a), there is no non-descendant variable set that blocks all backdoor paths from collective nodes $(A_1, A_2)$ to $Y$ (ie, satisfies the backdoor criterion). On the contrary, the backdoor paths to $Y$ from $A_1$ and $A_2$ are separately blocked by distinct sets of variables: empty set for $A_1$ and $(A_1, A_2)$ for $A_2$. The arguments can be more directly depicted using potential variables in Figure 1(c), which is a “template” of the SWIG representing each intervention ($a_1$, $a_2$) on $(A_1, A_2)$.
Different view of the g-formula: inverse probability weighting

We have seen that under the sequential exchangeability (C1) and (C2), the g-formula is equivalent to the averages of potential outcome. If baseline confounders \( L_1 \) exist, the g-formula is

\[
E[\mathbb{E}[Y|A_1 = a_1, L_2 = a_2, A_2 = a_2]|A_1 = a_1, L_1 = l_1, a_2]
\]

\[
= \sum_{i} p_i \mathbb{E}[Y|A_1 = a_1, L_2 = a_2, A_2 = a_2] \times p(L_2 = a_2|L_1 = l_1, A_1 = a_1) p(L_1 = l_1),
\]

which is equivalent to \( E[Y^{a_1, a_2}] \) if (C1) and (C2) hold by additionally conditioning on \( L_1 \). The left-hand side of equation (1) is a representation of the iterative conditional expectation of the g-formula.

The alternative expression of \( E[Y^{a_1, a_2}] \) under (C1) and (C2) is inverse probability weighting:

\[
E \left[ \frac{I(A_1 = a_1, A_2 = a_2)}{p(A_1|L_1)p(A_2|A_1, L_1, L_2)} Y \right],
\]

where \( I(A_1 = a_1, A_2 = a_2) \) is an indicator function that takes 1 if individual \( i \) has joint exposure level \( (a_1, a_2) \) and 0 otherwise, \( p(a_1|l_1) = p(A_1 = a_1|L_1 = l_1) \) is a conditional probability function of first exposure having level \( a_1 \) and \( p(a_2|l_1, a_1, l_2) = p(A_2 = a_2|L_1 = l_1, A_1 = a_1, L_2 = l_2) \) is a conditional probability function of second exposure having level \( a_2 \) given past exposure and covariates. Accordingly, \( p(A_1|L_1) \) and \( p(A_2|L_1, A_1, L_2) \) in formula (2) are functions of individual data.

These two expressions are equivalent forms of \( E[Y^{a_1, a_2}] \) under sequential exchangeability (C1) and (C2), as well as the time-varying versions of consistency and positivity. Despite the equivalence of these identification formulas, the estimator that plugs each estimate into (1) is called a g-formula estimator and that based on (2) is an inverse probability weighted estimator. The arguments can be extended to “dynamic regimes” with stronger conditions (Appendix B).

Now, let us obtain inverse probability weighted estimates from Table 2. First, we garner the probability of actually received exposure given past exposure and covariates separately for \( A_1 \) and \( A_2 \). As \( L_1 \) is empty to achieve sequential exchangeability, \( p(A_1) \) and \( p(A_2|A_1, L_2) \) for each combination of \( (A_1, L_2, A_2) \) are provided in Table 4. Next, calculate the “inverse probability weights” \( 1/[P(A_1)p(A_2|A_1, L_2)] \) and multiply the numbers of combinations \( (A_1, L_2, A_2) \) by the weights. Note that the sum of the weights \( P(A_1 = a_1, A_2 = a_2)/[P(A_1)p(A_2|A_1, L_2)] \) for each \( (a_1, a_2) \) equals total sample size (ie, \( n = 15,000 \) in our data). Hence, formula (2) indicates that we only have to estimate the probability

| \( A_1 \) | \( L_2 \) | \( A_2 \) | Unweighted | \( p(A_1) \) | \( p(A_2|A_1, L_2) \) | IPW | Number multiplied by IPW |
|---|---|---|---|---|---|---|---|
| 1 | 1 | 1 | 720 | 0.3 | 0.8 | 4.17 | 3,000 |
| 1 | 1 | 0 | 180 | 0.3 | 0.2 | 16.67 | 3,000 |
| 1 | 0 | 1 | 1,800 | 0.3 | 0.5 | 6.67 | 12,000 |
| 1 | 0 | 0 | 1,300 | 0.3 | 0.5 | 6.67 | 12,000 |
| 0 | 1 | 1 | 5,670 | 0.7 | 0.9 | 1.59 | 9,000 |
| 0 | 1 | 0 | 630 | 0.7 | 0.1 | 14.29 | 9,000 |
| 0 | 0 | 1 | 840 | 0.7 | 0.2 | 7.14 | 6,000 |
| 0 | 0 | 0 | 3,360 | 0.7 | 0.8 | 1.79 | 6,000 |

IPW, inverse probability weight.
of \( Y = 1 \) for every combination of \((a_1, a_2)\) in these multiplied numbers, or the inverse probability weighted population:

\[
E_{\text{IPW}}[Y|A_1 = 1, A_2 = 1] = \frac{(2,400 + 4,800)/(3,000 + 12,000)}{7.200/15.000} = 0.48,
\]

\[
E_{\text{IPW}}[Y|A_1 = 1, A_2 = 0] = \frac{(1,800 + 6,000)/(3,000 + 12,000)}{7.800/15.000} = 0.52,
\]

\[
E_{\text{IPW}}[Y|A_1 = 0, A_2 = 1] = \frac{(7,200 + 2,100)/(9,000 + 6,000)}{9.300/15.000} = 0.62,
\]

\[
E_{\text{IPW}}[Y|A_1 = 0, A_2 = 0] = \frac{(8,100 + 1,800)/(9,000 + 6,000)}{9.900/15.000} = 0.66.
\]

**Marginal structural models**

We have estimated four distinct \( E[Y^{a_1,a_2}] \) separately via g-formula (1) or inverse probability weighting (2). No approximation, or model, has been used.

Now, carefully look at the true values \( E[Y^{a_1,a_2}] \) in the last row of Table 2. We can see that \( E[Y^{1,0}] - E[Y^{0,0}] = 0.52 - 0.66 = 0.48 - 0.62 = E[Y^{1,1}] - E[Y^{0,1}] \); the difference between \( a_1 = 1 \) vs \( a_1 = 0 \) is \(-14\%\), irrespective of the value of \( a_2 \). Likewise, review \( E[Y^{0,1}] - E[Y^{0,0}] = 0.62 - 0.66 = 0.48 - 0.52 = E[Y^{1,1}] - E[Y^{0,0}] \) and the causual risk difference of \( a_2 = 1 \) vs \( a_2 = 0 \) is \(-4\%\). We can collectively write the counterfactual expectations as follows: \( E[Y^{a_1,a_2}] = 0.66 - 0.14a_1 - 0.04a_2 \). More generally, we may describe the relation between \( E[Y^{a_1,a_2}] \) and \((a_1, a_2)\) as

\[
E[Y^{a_1,a_2}] = \beta_0 + \beta_1a_1 + \beta_2a_2.
\]

This is the correctly specified marginal structural model; if we have the data in Table 2, the parameters of marginal structural model (3) can be unbiasedly estimated by, for example, the least-squares or maximum-likelihood methods. The marginal structural models are the simplified expressions of \( E[Y^{a_1,a_2}] \) by restricting the possible values of \( E[Y^{a_1,a_2}] \). In equation (3), the left-hand side can take any four values, but the right-hand side expresses them by only three parameters. Model (3) is marginal because the expectations are taken with the marginal distributions of \( Y^{a_1,a_2} \) unconditional on other observed variables (though the condition is relaxed later) and other potential outcomes \( Y^{a_1,a_2} \) other than \((a_1, a_2)\) (thus, we need not consider any cross-world joint distributions under different interventions). Model (3) is also structural because it imposes restrictions on potential outcomes \( Y^{a_1,a_2} \) rather than observed distributions.

There are other possibilities for specification of marginal structural models. For example, we can fit the simpler additive model

\[
E[Y^{a_1,a_2}] = \beta_0 + \beta_1(a_1 + a_2),
\]

which has only two parameters assuming that \( A_1 \) and \( A_2 \) have the same effect (risk difference) on \( Y \), or a multiplicative marginal structural model

\[
\log E[Y^{a_1,a_2}] = \beta_0 + \beta_1a_1 + \beta_2a_2,
\]

where \( \exp(\beta_1) \) and \( \exp(\beta_2) \) represent the (common) risk ratios \( E[Y^{1,a_2}]/E[Y^{0,a_2}] \) \((a_2 = 0, 1)\) and \( E[Y^{a_1,1}]/E[Y^{a_1,0}] \) \((a_1 = 0, 1)\), respectively. However, these are incorrectly specified or misspecified marginal structural models because any parameter values \((\hat{\beta}_0, \hat{\beta}_1)\) or \((\hat{\beta}_0, \hat{\beta}_1, \hat{\beta}_2)\) in the right-hand sides of (4) and (5) cannot exactly express the left-hand sides. A marginal structural model is correctly specified in multiplicative scale by making it saturated by, for example, including an interaction term of \( a_1 \) and \( a_2 \):

\[
\log E[Y^{a_1,a_2}] = \beta_0 + \beta_1a_1 + \beta_2a_2 + \beta_1a_2a_1. \tag{6}
\]

We estimate these marginal structural models through inverse probability weighting from observed data in Table 3, where sequential exchangeability (C1) and (C2) holds. Of course, models (4) and (5) are misspecified and necessarily result in biased estimates of \( E[Y^{a_1,a_2}] \). Nevertheless, the estimates of misspecified marginal structural models may well approximate the true \( E[Y^{a_1,a_2}] \) unless the model forms differ significantly from the true relationship between \( E[Y^{a_1,a_2}] \) and \((a_1, a_2)\). A typical estimation process is as follows: 1) calculate the inverse probability weight, \( 1/(p(A_1)p(A_2)\mid A_{10}, L_{20}) \), for each variable pattern \((A_{10}, L_{20}, A_{20})\) as in Table 4; 2) fit the regression model for \( E[Y\mid A_1 = a_1, A_2 = a_2] \) with the same functional form of the marginal structural models; and 3) obtain confidence intervals by the sandwich estimator or bootstrap. The SAS and Stata codes to create a dataset and replicate the results are provided in Appendix C and Supplementary Material, respectively. Table 5 shows the parameter estimates of these models. Expectations \( E[Y^{a_1,a_2}] \) are also estimated by linear combination of these estimates in the corresponding models; eg, \( E[Y^{1,0}] = \beta_0 \) (models 3 and 4) or \( \exp(\beta_0) \) (models 5 and 6), and \( E[Y^{1,1}] = \beta_0 + \beta_1 + \beta_2 \) (model 3), \( \exp(\beta_0 + \beta_1 + \beta_2) \) (model 5), or \( \exp(\beta_0 + \beta_1 + \beta_2) \) (model 6).

Why do we need to model \( E[Y^{a_1,a_2}] \) by taking the risk to cause bias? Consider exposures can change at an additional one time point. Without models, we need to estimate \( 3^2 = 8 \) (double of our case) distinct \( E[Y^{a_1,a_2}] \). If we have six time points, the task requires 64 estimates from the limited amount of data. Furthermore, if we have continuous exposure, we have to rely on the dose-response curves irrespective of the number of exposure time points. Given we always have a limited amount of data, our estimation task must rely on the dimension reduction of parameter space by imposing restriction on the possible values of counterfactual outcome means. In Table 5, despite both models (3) and (6) being correctly specified and unbiasedly estimated, the estimates of \( E[Y^{a_1,a_2}] \) from model (3) (3 parameters) have slightly narrower confidence intervals than those from model (6) (four parameters). The efficiency gain owing to dimension reduction will be modest as the number of time points increases.

Note that models (3)–(6) do not require covariate information, though can incorporate baseline confounders \( L_1 \) for examining effect modifications by certain variables in specific scales (eg, risk difference or ratio). The convenient choice that is commonly seen in practice may be the simplest model assuming a common exposure effect across time and baseline confounder strata:

\[
E[Y^{a_1,a_2}\mid L_1 = l_1] = \beta_0 + \beta_1(a_1 + a_2) + \beta_2^TL_1,
\]

which imposes more restriction than the marginal structural model (4), which is agnostic about (ie, does not assume) no-effect modification by \( L_1 \). To assess effect modification by baseline confounders, the model can be modified as

\[
E[Y^{a_1,a_2}\mid L_1 = l_1] = \beta_0 + \beta_1(a_1 + a_2) + \beta_2^TL_1 + \beta_3^T(a_1 + a_2)l_1,
\]

though this is still generally stricter than model (4) because the effect of exposure is restricted to be linearly modified by \( L_1 \).

**Dealing with high-dimensional covariates**

In our example, we have no baseline confounder and only one
Table 5. Inverse probability weighted estimates of marginal structural models from observed hypothetical cohort data (Table 3)

| Risk difference or ratio | MSM (3): Correct | MSM (4): Incorrect | MSM (5): Incorrect | MSM (6): Correct |
|--------------------------|-------------------|-------------------|-------------------|-------------------|
| Estimate \(a\) | 95% CI \(b\) | Estimate \(a\) | 95% CI \(b\) | Estimate \(a\) | 95% CI \(b\) | Estimate \(a\) | 95% CI \(b\) |
| \(A_1 (a_1 = 1 \text{ vs } 0)\) | \(-0.140\) | \((-0.160, -0.120)\) | \(-0.090\) | \((-0.104, -0.076)\) | \(0.781\) | \((0.753, 0.810)\) | \(0.788^c\) | \((0.746, 0.832)\) |
| \(A_2 (a_2 = 1 \text{ vs } 0)\) | \(-0.040\) | \((-0.060, -0.020)\) | \(-0.090\) | \((-0.104, -0.076)\) | \(0.932\) | \((0.900, 0.965)\) | \(0.939^c\) | \((0.903, 0.978)\) |
| \(A_1A_2\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(\ldots\) | \(0.983^f\) | \((0.914, 1.057)\) | \(\ldots\) | \(\ldots\) |

Potential outcome mean

- \(E[Y^{0,0}]\): \(0.660\), \((0.643, 0.677)\)
- \(E[Y^{1,0}]\): \(0.620\), \((0.605, 0.635)\)
- \(E[Y^{1,1}]\): \(0.520\), \((0.501, 0.539)\)
- \(E[Y^{1,1}]\): \(0.480\), \((0.463, 0.497)\)

- \(E[Y^{1,0}]\): \(0.781\), \((0.753, 0.810)\)
- \(E[Y^{1,1}]\): \(0.788^c\), \((0.746, 0.832)\)
- \(E[Y^{1,1}]\): \(0.803^f\), \((0.767, 0.840)\)
- \(E[Y^{1,1}]\): \(0.832^d\), \((0.795, 0.869)\)

Cl, confidence interval; MSM, marginal structural model.

*Risk differences \(\beta\) (MSMs (3) and (4)) or risk ratios \(\exp(\beta)\) (MSMs (5) and (6)) in the upper part.

Using sandwich estimator.

*Common risk difference for \(A_1\) and \(A_2\).

*Risk ratio for \(A_1\) when controlling \(A_2\) at 0: \(E[Y^{1,0}]/E[Y^{0,0}]\).

*Risk ratio for \(A_2\) when controlling \(A_1\) at 0: \(E[Y^{1,1}]/E[Y^{0,1}]\).

*Interaction between \(A_1\) and \(A_2\) in risk ratio scale: \(E[Y^{1,1}]/E[Y^{0,0}]\).
be adopted in practice to account for the large numbers of baseline and time-varying confounders, which usually do not have implications on marginal structural modeling (pitfalls 2 and 4). We also show the biases based on the misspecification of exposure probability models and misspecification of marginal structural models separately (pitfall 3). Note that while inverse probability weighting and the g-formula are applicable to estimate marginal counterfactual means (ie, saturated marginal structural models), only the former can estimate general, unsaturated marginal structural models (pitfall 5). Although running into these pitfalls may not necessarily lead to large biases in practical analysis, failure to recognize these subtleties would advocate unprincipled and suboptimal strategies for causal inference.

We would conclude this section with additional emphases of two pitfalls. First, variable selection and model specification are generally different tasks in modeling for causal inference. By inverse probability weighting, exposure probability models should select confounders, stratification of which is sufficient to achieve sequential exchangeability. In our example, all analyses with or without an exposure probability model include all confounder(s), $L_2$. Even if the models include all confounders, however, they may be misspecified as in the analysis in Table 6. The same is true for regression models for the g-formula. On the contrary, it is unnecessary for marginal structural models to include confounders; only covariates (need not to be confounders but should be conditioned in propensity score) that may modify the exposure effect of interest may be included in marginal structural models.

Second, doubly robust estimators can alleviate the bias from misspecification of regression and exposure probability models, but not the bias owing to the misspecification of marginal structural models nor other causal models (that are not introduced in this paper). For example, Table 6 provides the biased estimates using a misspecified exposure probability model for correct/incorrect marginal structural models. Among them, bias in the estimates of correct marginal structural models (3) and (6) would be mitigated by doubly robust methods, by including outcome regression models via the iterative model-fitting algorithm of Bang and Robins, while the fitting of incorrect marginal structural models (4) and (5) must result in biased estimates. Hence, even with doubly robust methods, the careful consideration of marginal structural models is needed, especially for long-term follow-up study with many time points at which exposure can change. Marginal structural models for dynamic regimes may also have to depend on strong modeling assumptions, even when exposure is binary and change at several time points.

**FUTURE DIRECTIONS**

There is a relevant method other than the g-formula and inverse probability weighting that requires essentially the same assumptions to estimate causal effects of time-varying exposures: g-estimation. Like the relation of marginal structural modeling and inverse probability weighting, g-estimation is a method to estimate the parameters of structural nested models. Structural nested models and g-estimation indeed have attractive statistical properties (eg, robustness, efficiency, and flexible parameterization), which successfully work within Robins’ causal “interventionism” framework with minimal conditions. Despite its theoretical superiority, g-estimation has been underestimated in epidemiologic literature probably because of the complexity of background theory and interpretability of the
parameters.75 However, structural nested models are especially useful for dynamic regimes of time-varying exposures by modeling the effect modification by time-varying covariates,38,41,51 which cannot generally be included in marginal structural models.46,68

Besides the conceptual pitfalls considered in this paper, there are important pitfalls regarding specification and estimation of marginal structural models, which will often lead to mistakes in practice:

- One should always use the independence working correlations in marginal structural models of repeated-measures outcomes.47,67,77
- If “stabilized” weights include covariates in the numerator weights,43 they should be conditioned in the marginal structural models.50
- “Stabilization” of the weights is not always acceptable (eg, dynamic-regime marginal structural models.72–74).
- It is always important to check the fits of exposure probability models (eg, checking calibration or model-diagnostic measures76 and weight distributions50) and marginal structural models (eg, comparing the estimating equation-based quasi-likelihood information criterion with that for less restricted models79 or testing equivalence between asymptotic values of parameter estimates obtained through different weighting options80).

There are other practical concerns in real data analysis. For example, many follow-up studies compare time-to-event outcomes, which complicate the modeling and estimation process for the effects of time-varying exposure. In those settings, time-dependent Cox models or the risk-set switching Kaplan–Meier estimators would need unrealistic assumptions to yield causally interpretable estimates.43,81 In addition, censoring of the events must be taken with care by, for example, constructing the inverse probability weights to prevent attrition bias.44,45,51 Note that the idea of inverse probability of censoring weights appears in diverse causal inference fields; eg, adjustment for treatment discontinuation in clinical trials.82,83 estimation of the effects of dynamic regimes;72 and the effects of the treatment duration on survival.84

ACKNOWLEDGEMENTS

We greatly thank Drs. Stephen R. Cole, Yasuhiro Hagiwara, Tosiya Sato, Stijn Vansteelandt, Daniel Westreich, and Eiji Shinozaki T, et al. for their support and helpful comments.

Funding: This work was supported by Japan Society for the Promotion of Science (KAKENHI Grant Numbers JP20K11716 and JP20K10471).

Conflicts of interest: None declared.

APPENDIX A. EXCHANGEABILITY CONDITIONS FOR IDENTIFYING THE EFFECTS OF TIME-VARYING EXPOSURES

As shown in Figure 1, sequential exchangeability (C1) and (C2) is more likely in practice than conditional exchangeability $E[Y^{a_{1},a_{2}}|A_{1},L_{2},A_{2}] = E[Y^{a_{1},a_{2}}|L_{2}]$ for joint exposure $(A_{1}, A_{2})$; conditional exchangeability for joint exposure is not a necessary condition for sequential exchangeability, which would be intuitively understandable to many readers. Mathematically, however, conditional exchangeability for joint exposure itself is not a sufficient condition for sequential exchangeability, either. Nevertheless, these conditions are closely related with each other in other realistic situations, as shown subsequently.

First note that conditional exchangeability always implies (C2), which is rewritten as $E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}, A_{2}] = E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}]$. The right-hand side is $E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}] = \sum_{a_{2}} E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}, A_{2} = a_{2}] P(A_{2} = a_{2}|A_{1} = a_{1}, L_{2}) = E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}, A_{2} = a_{2}]$. On the other hand, the right-hand side of the equation $E[Y^{a_{1},a_{2}}|A_{1} = E[Y^{a_{1},a_{2}}|L_{2}]]$ (an equivalent form of (C1)) is $E[Y^{a_{1},a_{2}}|L_{2} = \sum_{a_{1}} E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}, A_{2} = a_{2}] P(A_{1} = a_{1}|L_{2}) = E[Y^{a_{1},a_{2}}|A_{1} = a_{1}, L_{2}, A_{2} = a_{2}] P(A_{1} = a_{1}, L_{2} = l_{2}, A_{2} = a_{2}|L_{2} = l_{2})$ (by conditional exchangeability) cannot further reduce to $E[Y^{a_{1},a_{2}}|A_{1}]$. However, we can see that if $A_{1}$ is independent of $Y^{a_{1},a_{2}}$ (as in Figure 1) or 2) if $P(L_{2} = l_{2}) = P(L_{2} = l_{2}|A_{1})$, that is, $A_{1}$ is independent of $L_{2}$ in observed data, then (C1) is also implied by conditional exchangeability. Moreover, if $A_{1}$ is randomized (ie, $(Y^{a_{1},a_{2}}, L_{2}^{a_{1}}) \perp A_{1}$ holds, where “$\perp$” means statistical independence), then the previous independence condition $P(L_{2} = l_{2}) = P(L_{2} = l_{2}|A_{1})$ is equivalent to (sharp) null effect of $A_{1}$ on $L_{2}$ by the “g-null” theorem under the faithfulness assumption.36,37 In this case of no-effect of randomized $A_{1}$ on time-varying confounders $L_{2}$, (C2) implies $E[Y^{a_{1},a_{2}}|L_{2}] = E[Y^{a_{1},a_{2}}|A_{1}, L_{2}]$ (by randomization) = $E[Y^{a_{1},a_{2}}|A_{1}, L_{2}, A_{2}]$; hence, sequential exchangeability also implies conditional exchangeability for joint exposure.

APPENDIX B. INDEPENDENCY ASSUMPTIONS ENCODED IN CAUSAL DIAGRAMS AND IDENTIFIABILITY OF GENERAL INTERVENTION REGIMES

Sequential exchangeability (C1) and (C2) is insufficient for identification of the effects of more general exposure interventions (also known as dynamic regimes or strategies) that may depend on (time-varying) covariates, say, $(L_{1}, L_{2})$. That identification is built on the identification of the distribution $f(Y^{a_{1},a_{2}}, L_{2}^{a_{1}})$, or generally, $f(Y^{j}, L_{2}^{j})$ with the intervention $g = (g(L_{1}), g(L_{1}, A_{1}, L_{2}))$, where $g(L_{1})$ corresponds to the intervention on $A_{1}$ possibly depending on past $A$ and $L$ values (rather than a prespecified value like $a_{1}$). Hence, we need more assumptions to identify the effects of a dynamic regime $g$, one of the sufficient conditions is

$(Y^{a_{1},a_{2}}, L_{2}^{a_{1}}) \perp A_{1}$ and $(Y^{a_{1},a_{2}}, L_{2}^{a_{1}}) \perp A_{1}|A_{1} = a_{1}, L_{2}$, (C3)

where $Z_{1} \perp Z_{2}|Z_{2}$ refers to statistical independence between $Z_{1}$ and $Z_{2}$ conditional on $Z_{2}$.51 However, our example is also compatible both with (C3) and the settings with $E[L_{2}^{a_{1}}|A_{1}] \neq E[L_{2}^{a_{1}}]$, in other words, agnostic about condition (C3). Thus, data in Table 2 themselves are not sufficient for the validity of the g-formula for effects of a general regime $g$.

On the contrary, causal diagrams would indicate whether condition (C3) holds and the assumptions encoded in the diagrams allow $f(Y^{j}, L_{2}^{j})$ to be identifiable. From the SWIG of Figure 1(c), we can read the independences $(Y^{a_{1},a_{2}}, L_{2}^{a_{1}}) \perp A_{1}$ and $(Y^{a_{1},a_{2}}, A_{1}^{a_{1}}) \perp A_{1}^{a_{1}}|A_{1} = a_{1}, L_{1}$, which imply (C3) by consistency under conditioning on $A_{1} = a_{1}$ (ie, the “world” represented by the
SWIG) in the second condition. Thus, the corresponding causal DAG of Figure 1(a) allows us to identify $E[Y^g]$. However, we cannot deduce (C3) from Figure 1(d) owing to a d-connected path between $L_2^{a_1}$ and $A_1$; hence, under the corresponding causal DAG of Figure 1(b), $E[Y^g]$ for a general regimes $g$ cannot be identified even though $E[Y^{a_1,a_2}]$ for non-dynamic exposure intervention $(a_1, a_2)$ is identified as illustrated in the main text. That is, Figure 1 is one of the examples of causal diagrams that are compatible with our example data, where the stronger causal assumptions are implicitly imposed on. As we have documented earlier, causal diagrams (when tied with underlying causal models) often represent the “finer” description of causal assumptions than counterfactual notation.

The difficulty in identification of $E[Y^g]$ with $g = (g_1, g_2) = (g_1(L_1), g_2(L_1, A_1, L_2))$ is directly depicted in Appendix Figure 1(a) and (c), where $L_1$ is suppressed for simplicity but it can affect any variable in the graphs. A causal DAG of Appendix Figure 1(a) is the same as Figure 1(b), while the corresponding SWIGs are different. The structural distinction is the presence (Appendix Figure 1(c)) or absence (Figure 1(d)) of an arrow from $L_2$ to hypothetical intervention $(g_2$ or $a_2$, according to the dependence of intervention on covariates), respectively. We can easily see that dependence between $Y^g = Y^{g_1,g_2}$ and $A_1$ is either with or without conditioning on $L_2^{a_1} = L_2$ in Appendix Figure 1(c), which suggests that $E[Y^g]$ is not identifiable without referring to condition (C3).

Finally, we show a slightly modified causal DAG of Figure 1(b) in Appendix Figure 1(b), in which $L_1$ that is affected by $A_1$ also affects $Y$. The corresponding SWIG, Appendix Figure 1(d), reveals that $Y^{g_1,a_2}$ is d-connected either with or without conditioning on $L_2^{a_1} = L_2$; hence, the effects of dynamic regimes $g$ and non-dynamic exposure intervention $(a_1, a_2)$ is unidentifiable if the association between exposure and its effect lying on a path to the outcome is confounded by unobservables. Of course, our example data in Table 2 is incompatible with Appendix Figure 1(b) and (d) because of independence between $A$ and $Y^{g_1,a_2}$.

**APPENDIX C. SAS CODE FOR HYPOTHETICAL DATA ANALYSIS**

* Create a dataset;  
data MSM;  
input A1 L2 A2 N N1;  
cumA = A1 + A2;  
do i = 1 to N1; Y = 1; ID + 1; output; end;  
do i = N1 + 1 to N; Y = 0; ID + 1; output; end;  
drop i N N1;  
cards;  
1 1 1 720 576  
1 1 0 180 108  
1 0 1 1800 720  
1 0 0 1800 900  
0 1 1 5670 4536  
0 1 0 630 567  
0 0 1 840 294  
0 0 0 3360 1008  
;  
* Estimate sequential exposure probabilities;  
proc logistic data = MSM desc;  
model A1 = ;  
output out = MSM p = P1;  
run;  
proc logistic data = MSM desc;  
/* Use either of the following two commands */  
model A2 = A1 L2 A1*L2; *Fitting correct exposure probability model for Table 5;  
*model A2 = A1 L2; *Fitting misspecified exposure probability model for Table 6;  
output out = MSM p = P2;  
run;  
* Calculate inverse probability weights;  
data MSM;  
set MSM;  
IPW = (A1/P1 + (1 – A1)/(1 – P1))* (A2/P2 + (1 – A2)/*
(1 − P2));
run;
* Fit marginal structural model (3): Correct specification;
proc genmod data = MSM;
class ID;
model Y = A1 A2 /dist = normal;
weight IPW;
repeated sub = ID;
estimate "E[Y00]" int 1 A1 0 A2 0;
estimate "E[Y01]" int 1 A1 0 A2 1;
estimate "E[Y10]" int 1 A1 1 A2 0;
estimate "E[Y11]" int 1 A1 1 A2 1;
run;
* Fit marginal structural model (4): Misspecification;
proc genmod data = MSM;
class ID;
model Y = cumA /dist = normal;
weight IPW;
repeated sub = ID;
estimate "E[Y00]" int 1 cumA 0;
estimate "E[Y01]" int 1 cumA 1;
estimate "E[Y10]" int 1 cumA 0;
estimate "E[Y11]" int 1 cumA 2;
run;
* Fit marginal structural model (5): Misspecification;
proc genmod data = MSM;
class ID;
model Y = A1 A2 /dist = Poisson;
weight IPW;
repeated sub = ID;
estimate "A1" A1 1 / exp;
estimate "A2" A2 1 / exp;
estimate "Y00" int 1 A1 0 A2 0;
estimate "Y01" int 1 A1 0 A2 1;
estimate "Y10" int 1 A1 1 A2 0;
estimate "Y11" int 1 A1 1 A2 1;
run;
* Fit marginal structural model (6): Correct specification;
proc genmod data = MSM;
class ID;
model Y = A1 A2 A1*A2 /dist = Poisson;
weight IPW;
repeated sub = ID;
estimate "A1" A1 1 / exp;
estimate "A2" A2 1 / exp;
estimate "A1A2" A1*A2 1 / exp;
estimate "Y00" int 1 A1 0 A2 0 A1*A2 0;
estimate "Y01" int 1 A1 0 A2 1 A1*A2 0;
estimate "Y10" int 1 A1 1 A2 0 A1*A2 0;
estimate "Y11" int 1 A1 1 A2 1 A1*A2 1;
run;

APPENDIX D. SUPPLEMENTARY DATA
Supplementary data related to this article can be found at https://doi.org/10.2188/jca.JE20200226.

REFERENCES
1. Greenland S, Robins JM. Identifiability, exchangeability, and epidemiological confounding. Int J Epidemiol. 1986;15:413–419.
2. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology. 1999;10:37–48.
3. Greenland S, Brumback B. An overview of relations among causal modelling methods. Int J Epidemiol. 2002;31:1030–1037.
4. Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology, 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2008.
5. Greenland S. For and against methodologies: some perspectives on recent causal and statistical inference debates. Eur J Epidemiol. 2017;32:3–20.
6. Hernán MA, Robins JM. Causal Inference: What If. Boca Raton: Chapman & Hall/CRC; 2020.
7. Hernán MA. The C-word: scientific euphemisms do not improve causal inference from observational data. Am J Public Health. 2018;108:616–619.
8. Gatto NM, Campbell UB, Schwartz S. An organizational schema for epidemiologic causal effects. Epidemiology. 2014;25:88–97.
9. Suzuki E. Generalized causal measure: the beauty lies in its generality. Epidemiology. 2015;26:490–495.
10. Suzuki E, Tsuda T, Mitsushashi T, Mansournia MA, Yamamoto E. Errors in causal inference: an organizational schema for systematic error and random error. Ann Epidemiol. 2016;26:788–793.
11. Suzuki E, Mitsushashi T, Tsuda T, Yamamoto E. A typology of four notions of confounding in epidemiology. J Epidemiol. 2017;27:49–55.
12. Mansournia MA, Higgins JP, Sterne JA, Hernán MA. Biases in randomized trials: a conversation between trialists and epidemiologists. Epidemiology. 2017;28:54–59.
13. Shinozaki T, Hagiwara Y, Matsuyama Y. Re: Biases in randomized trials: a conversation between trialists and epidemiologists. Epidemiology. 2017;28:e40–e41.
14. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. Biometrika. 1983;70:41–55.
15. Robins JM, Mark SD, Newey WK. Estimating exposure effects by modelling the expectation of exposure conditional on confounders. Biometrics. 1992;48:479–495.
16. Lunceford JK, Davidian M. Stratification and weighting via the propensity score in estimation of causal treatment effects: a comparative study. Stat Med. 2004;23:2937–2960.
17. Li L, Greene T. A weighting analogue to pair matching in propensity score analysis. Int J Biostat. 2013;9:215–234.
18. Vansteelandt S, Daniel RM. On regression adjustment for the propensity score. Stat Med. 2014;33:4053–4072.
19. Shinozaki T, Nojima M. Misuse of regression adjustment for additional confounders following insufficient propensity score balancing. Epidemiology. 2019;30:541–548.
20. Robins JM, Greenland S. The role of model selection in causal inference from nonexperimental data. Am J Epidemiol. 1986;123:392–402.
21. Greenland S. Estimating standardized parameters from generalized linear models. Stat Med. 1991;10:1069–1074.
22. Robins JM, Rotnitzky A, Zhao LP. Estimation of regression coefficients when some regressors are not always observed. J Am Stat Assoc. 1994;89:846–866.
23. Scharfstein DO, Rotnitzky A, Robins JM. Adjusting for non-ignorable drop-out using semiparametric nonresponse models. J Am Stat Assoc. 1999;94:1096–1120.
24. Bang H, Robins JM. Doubly robust estimation in missing data and causal inference models. Biometrics. 2005;61:962–973.
25. Kang JDY, Schafer JL. Demystifying double robustness: a comparison of alternative strategies for estimating a population mean from incomplete data. Stat Sci. 2007;22:523–539.
26. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. Am J Epidemiol. 2011;173:761–767.
27. Rose S, van der Laan M. A doubly robust approach to causal effects in case-control studies. Am J Epidemiol. 2014;179:653–669.
28. Shinozaki T, Matsuyama Y. Brief report: doubly robust estimation of standardized risk difference and ratio in the exposed population. Epidemiology. 2015;26:873–877.
Marginal Structural Models: Pitfalls and Tips

29. Pearl J. Causal diagrams for empirical research. *Biometrika*. 1995; 82:669–688.

30. Hernández-Díaz S, Robins JM. A structural approach to selection bias. *Epidemiology*. 2004;15:615–625.

31. Richardson TS, Robins JM. Single world intervention graphs (SWIGs): a unification of the counterfactual and graphical approaches to causality. Center for Statistics and the Social Sciences, University of Washington, Working Paper. 2013:128.

32. Richardson TS, Robins JM. Single world intervention graphs: a primer. Second UAI workshop on causal structure learning, Bellevue, Washington. 2013.

33. Shipitse I, Tchetgen Tchetgen E. Causal inference with a graphical hierarchy of interventions. *Am Stat*. 2016;44:2433–2466.

34. Glymour MM. Using causal diagrams to understand common problems in social epidemiology. In: Oakes JM, Kaufman JS, eds. *Methods in Social Epidemiology*. 2nd ed. San Francisco, CA: Jossey-Bass; 2017:458–492.

35. Suzuki E, Shinozaki T, Yamamoto E. Causal diagrams: pitfalls and tips. *J Epidemiol*. 2020;30:153–162.

36. Robins J. A new approach to causal inference in mortality studies with a sustained exposure period: application to control of the healthy worker survivor effect. *Math Model*. 1986;7:1393–1512.

37. Robins J. A graphical approach to the identification and estimation of causal parameters in mortality studies with sustained exposure periods. *J Chronic Dis*. 1987;40(Suppl 2):1395–1618.

38. Robins JM. The analysis of randomized and non-randomized AIDS treatment trials using a new approach to causal inference in longitudinal studies. In: Sechrest L, Freeman H, Mulley A, eds. *Health Service Research Methodology: A Focus on AIDS*. Washington DC: U.S. Public Health Service, National Center for Health Services Research; 1989:113–159.

39. Robins JM, Blevins D, Ritter G, Wulfsohn M, eds. *Health Service Research Methodology: A Focus on AIDS*. Washington DC: U.S. Public Health Service, National Center for Health Services Research; 1989:113–159.

40. Witteman JC, De Stavola BL, Kenward MG, Sterne JA. Methods for dealing with time-dependent confounding. *Stat Med*. 2013;32:1584–1618.

41. Talbot D, Atherton J, Rossi AM, Bacon SL, Lefebvre G. A cautionary note concerning the use of standardized weights in marginal structural models. *Stat Med*. 2015;34:812–823.

42. Taguri M. Comments on ‘A cautionary note concerning the use of standardized weights in marginal structural models’ by D. Talbot, J. Atherton, A. M. Rossi, S. L. Bacon, and G. Lefebvre. *Stat Med*. 2015;34:1438–1439.

43. Breskin A, Cole SR, Westreich D. Exploring the subtleties of inverse probability weighting and marginal structural models. *Epidemiology*. 2018;29:352–355.

44. Naimi AI, Cole SR, Westreich DJ, Richardson DB. A comparison of methods to estimate the hazard ratio under conditions of time-varying confounding and nonpositivity. *Epidemiology*. 2011;22:718–723.

45. Naimi AI, Cole SR, Kennedy EH. An introduction to g methods. *Int J Epidemiol*. 2017;46:756–762.

46. Hernán MA. A definition of causal effect for epidemiological research. *J Epidemiol Community Health*. 2004;58:265–271.

47. Hernán MA, Robins JM. Estimating causal effects from epidemiological data. *J Epidemiol Community Health*. 2006;60:578–586.

48. Sato T, Matsuyama Y. Mysterious phenomenon called confounding and adjusted analysis of it: standardization and marginal structural models. *Am J Epidemiol*. 2011;32:S35–S49 (in Japanese).

49. Robins JM, Richardson TS. Alternative graphical causal models and the identification of direct effects. In: Shriout P, Keyes KM, Ornstein K, eds. *Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures*. New York: Oxford University Press; 2010:103–158.

50. Young JG, Hernán MA, Robins JM. Identification, estimation and approximation of risk under interventions that depend on the natural value of treatment using observational data. *Epidemiol Methods*. 2014;3:1–19.

51. Robins JM, Greenland S. Identification and exchangeability for direct and indirect effects. *Epidemiology*. 1992;3:143–155.

52. Pearl J. Direct and indirect effects. In: *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*. San Francisco, CA: Morgan Kaufmann; 2001:411–420.

53. Shinozaki T, Matsuyma Y, Ohashi Y. Estimation of controlled direct effects in time-varying treatments using structural nested mean models: application to a primary prevention trial for coronary events with pravastatin. *Stat Med*. 2014;33:3214–3228.

54. Robins JM, Hernán MA, Rotnitzky A. Effect modification by time-varying covariates. *Am J Epidemiol*. 2007;166:994–1002; discussion 1003–4.

55. Greenland S. Summarization, smoothing, and inference in epidemiologic analysis. *Scand J Soc Med*. 1993;21:227–232.

56. Greenland S. Smoothing observational data: a philosophy and implementation for the health sciences. *Int Stat Rev*. 2006;74:31–46.

57. Schulte PJ, Tsatis AA, Laber EB, Davidian M. Q- and A-learning methods for estimating optimal dynamic treatment regimes. *Stat Sci*. 2014;29:640–661.

58. Hernán MA, Lanoy E, Costagiolla D, Robins JM. Comparison of dynamic treatment regimes via inverse probability weighting. *Basic Clin Pharmacol Toxicol*. 2006;98:237–242.

59. Orellana L, Rotnitzky A, Robins JM. Dynamic regime marginal structural mean models for estimation of optimal dynamic treatment regimes. Part I: main content. *Int J Biostat*. 2010;6:8.

60. Hagiwara Y, Shinozaki T, Mukai H, Matsuyma Y. Sensitivity analysis for subsequent treatments in confirmatory oncology clinical
trials: a two-stage stochastic dynamic treatment regime approach. Biometrics. (In press).
75. Vansteelandt S, Joffe M. Structural nested models and g-estimation: the partially realized promise. Stat Sci. 2014;29:707–731.
76. Robins JM, Greenland S, Hu FC. Estimation of the causal effect of a time-varying exposure on the marginal mean of a repeated binary outcome. J Am Stat Assoc. 1999;94:687–700.
77. Tchetgen Tchetgen EJ, Glymour MM, Weuve J, Robins J. Specifying the correlation structure in inverse-probability-weighting estimation for repeated measures. Epidemiology. 2012;23:644–646.
78. Greenland S. Introduction to regression modeling. In: Rothman KJ, Greenland S, Lash TL, eds. Modern Epidemiology, 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2008:419–455.
79. Platt RW, Brookhart MA, Cole SR, Westreich D, Schisterman EF. An information criterion for marginal structural models. Stat Med. 2013;32:1383–1393.
80. Sall A, Aubé K, Trudel X, Brisson C, Talbot D. A test for the correct specification of marginal structural models. Stat Med. 2019;38:3168–3183.
81. Sjölander A. A cautionary note on extended Kaplan-Meier curves for time-varying covariates. Epidemiology. 2020;31:517–522.
82. Robins JM, Finkelstein DM. Correcting for noncompliance and dependent censoring in an AIDS Clinical Trial with inverse probability of censoring weighted (IPCW) log-rank tests. Biometrics. 2000;56:779–788.
83. Cain LE, Cole SR. Inverse probability-of-censoring weights for the correction of time-varying noncompliance in the effect of randomized highly active antiretroviral therapy on incident AIDS or death. Stat Med. 2009;28:1725–1738.
84. Hernán MA. How to estimate the effect of treatment duration on survival outcomes using observational data. BMJ. 2018;360:k182.