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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

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For the estimation of controlled direct effects (i.e., direct effects controlling intermediates that are set at a fixed level for all members of the population) without bias, two fundamental assumptions must hold: the absence of unmeasured confounding factors for treatment and outcome and for intermediate variables and outcome. Even if these assumptions hold, one would nonetheless fail to estimate direct effects using standard methods, for example, stratification or regression modeling, when the treatment influences confounding factors. For such situations, the sequential g-estimation method for structural nested mean models has been developed for estimating controlled direct effects in point-treatment situations. In this study, we demonstrate that this method can be applied to longitudinal data with time-varying treatments and repeatedly measured intermediate variables. We sequentially estimate the parameters in two structural nested mean models: one for a repeatedly measured intermediate and the other one for direct effects of a time-varying treatment. The method was applied to data from a large primary prevention trial for coronary events, in which pravastatin was used to lower the cholesterol levels in patients with moderate hypercholesterolemia.

Keywords: direct effects; longitudinal data; structural nested mean model; time-dependent confounding; causal inference

1. Introduction

For making inferences about causal mechanisms of the treatment effect in both experimental and observational studies, one can estimate direct effects of a treatment with respect to a hypothesized intermediate variable involved in the causal pathway between treatment and outcome. Formally, direct effects can be defined as the contrast between outcomes under different treatments whilst keeping intermediate variables at the same level and are therefore termed 'controlled' direct effects [1]. For example, it may be of interest whether the benefit of statins (cholesterol-lowering drugs) for the primary and secondary prevention of coronary heart disease (CHD) [2, 3] can be obtained if patients' cholesterol levels were set at a fixed level for all members of the population, which is also known as statin's 'pleiotropic' effects.

Inspired by the seminal work of Robins and Greenland [4] on the separation of the total effect into direct and indirect effects, introductive discussions on the topic have premised the fact that estimating controlled direct effects without bias requires two fundamental assumptions to hold: the absence of unmeasured confounding factors for treatment and outcome and for intermediate variables and outcome [1, 5–8]. This implies that even if data were obtained from a randomized controlled trial, unbiased estimates of direct effects could not be obtained without the unverifiable assumption for unmeasured

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variables, because the study design does not ensure the absence of confounding between a post-baseline intermediate variable and outcome. In addition, even if these assumptions hold, standard statistical methods such as stratification or regression modeling would fail to provide unbiased estimates of direct effects if treatment itself influences confounding factors [4–8]. For inference on controlled direct effects in such scenarios, Robins had developed a g-computation algorithm for direct effects [4, 9, 10] and introduced two classes of causal models, direct-effect marginal structural models (MSMs) [11] and direct-effect structural nested mean models (SNMMs) [12].

Although these methods have been originally intended to cope with longitudinal settings where treatment changes during the follow-up period and intermediate variables also change over time, most studies demonstrated these methods on point-treatment or point-intermediate situations or both [4, 6, 8, 13–18]. In the presence of repeated measures data, treatment itself is likely to be confounded by covariates that are affected by prior treatment, which results in a time-dependent confounding problem [19]. These time-dependent confounders for treatment changes also need to be explicitly accounted for in the analysis. G-computation can be directly applied to repeated measures data especially by parametric modeling of covariate densities followed by Monte Carlo simulation [20–22]. Direct-effect MSMs [11] have also been illustrated to define controlled (and 'natural' [1, 4]) direct effects in repeated measures data [13] that can be estimated through inverse-probability weighted model fitting (and additional assumptions and steps) [13–15].

On the other hand, Robins's original method to estimate SNMMs for controlled direct effects that analyze repeated measures data is based on complex estimating equations with estimated weights [12]. As a result, SNMMs for controlled direct effects were not applied until Vansteelandt and colleagues [16–18] developed the 'sequential' g-estimation method, which solves two estimating equations sequentially (fitting two regression models in the simplest case) in a point-treatment setting. In this study, we demonstrate that the sequential g-estimation method can be applied to data with time-varying treatments and repeatedly measured intermediates by analyzing data from a large primary prevention trial for coronary events, the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study.

In the next section, we describe the MEGA Study and introduce notations for the observed variables. In Section 3, the controlled direct effects are defined using counterfactual variables [23]. In Section 4, we introduce direct-effect SNMMs for time-varying treatments. The sequential g-estimation method for estimating parameters and identifiability assumptions are provided in Section 5. In Section 6, the method is applied to data from the MEGA Study. Finally, in Section 7, we discuss our findings and make concluding remarks.

2. Data and notations

The rationale, design, and results of the MEGA Study have been reported previously [24, 25]. The MEGA Study was a prospective, randomized, open-label, blinded-endpoint-designed controlled trial conducted in Japan to evaluate the primary preventive effect of pravastatin against CHD in daily clinical practice. Men and postmenopausal women aged 40–70 years with moderate hypercholesterolemia (total cholesterol [TC] level: 220–270 mg/dl) and with no history of CHD or stroke were randomized to dietary therapy only treatment (diet group; $n = 3966$) or diet plus 10–20 mg daily pravastatin treatment (diet-plus-pravastatin group; $n = 3866$). The primary composite endpoint was the first occurrence of CHD, including fatal and nonfatal myocardial infarction, angina, cardiac and sudden death, and a coronary revascularization procedure. The study protocol stated that patients in the diet group could switch to pravastatin treatment if they had no reduction in their cholesterol levels and patients in the diet-plus-pravastatin group could discontinue pravastatin treatment when a reduction in the cholesterol level was observed. As a result, 790 (19.9%) and 2064 (53.4%) patients in the diet and diet-plus-pravastatin groups, respectively, switched to the other treatment at least once during the first 5 years [26]. Despite considerable treatment switching during the 5-year follow-up period, CHD occurred in 85 patients in the diet group and in 57 patients in the diet-plus-pravastatin group. An intention-to-treat risk ratio of 0.69 (95% CI: 0.49–0.96) demonstrated the beneficial effect of pravastatin on CHD prevention within 5 years. Our aim in this paper is to estimate the controlled direct effects of pravastatin at each visit on CHD occurrence within 5 years (using the risk-ratio scale) after adjustment for treatment switching and while controlling cholesterol levels at a fixed value among hypercholesterolemia patients receiving dietary treatment.

Let $k = 0, 1, 2, \ldots, K(= 12)$ denote each patient's scheduled follow-up visit at time t_k after randomization. Each patient was randomized at $t_0 = 0$ and uniformly followed up at $t_1 = 1$, $t_2 = 3$, $t_3 = 6$, $t_4 = 12, \ldots$, until $t_K = 54$ months. Let T be an observed time to CHD event measured. We define $Y(k) \equiv I[T < t_k]$ as an event indicator at k (by definition, $Y(0) = 0$ for all patients); in particular, $Y(K+1)$ is the CHD outcome of interest at year 5. Let $A(k)$ be an indicator for pravastatin treatment (>10 mg daily) and at visit $k \geqslant 0$ and $M(k)$ be an intermediate variable measured at $k > 0$. One of the following variables is considered an intermediate in each analysis: TC, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and non-HDL cholesterol.

Let $L(k)$ be a vector of time-dependent covariates measured at k for both the effects of pravastatin treatment and cholesterol levels—which comprise systolic and diastolic blood pressure; body weight; compliance to dietary therapy; and TC, LDL cholesterol, and HDL cholesterol measures other than M (k) (blood pressure is known to be an independent risk factor for CHD, weight and compliance are proxies for lifestyle factors, and treatment in the study was changed in response to the whole panel of cholesterol levels that potentially impact CHD). All of these factors could be used to predict pravastatin treatment and cholesterol levels in subsequent visits (time-dependent confounders) and could also be affected by previous levels of these variables. Let $L(0)$ represent all measured baseline covariates: sex, age, body mass index, triglycerides, diabetes mellitus, hypertension, previous medication for hypercholesterolemia, current smoking status, and current drinking status. We represent the set of the variable-history as $\bar{A}(k) = \{A(0), A(1), \ldots, A(k)\}$ and the set of future variable as $\underline{A}(k) = \{A(k), A(k+1), \ldots, A(K)\}$. We assume a sampling model in which an independent and identically distributed random vector $(\bar{A}_i(K), \bar{M}_i(K), \bar{L}_i(K), \bar{Y}_i(K+1))$ for patient $i = 1, \ldots, n(= 7832)$ is observed.

A causal directed acyclic graph (Figure 1) depicts the relationships between the outcome $Y(K+1)$ and the other variables up to the second treatment $A(1)$ (apart from the baseline variables $L(0)$). Note that U represents unmeasured time-related or time-unrelated, independent predictors of $Y(k)$ and $L(k)$ but not of $A(k)$ and $M(k)$. We assume the temporal ordering of each measurement as $(Y(k), L(k), M(k), A(k))$ within each visit k as shown in Figure 1. If $Y(k) = 1$, we assign $Y(k+1) = 1$ and $A(k) = M(k) = 0$ thereafter, because a patient could neither receive treatment nor be influenced by intermediates after visit k.

3. Controlled direct effects with counterfactuals

We introduce deterministic counterfactual variables [27] that are assumed to be observed without error if the corresponding interventions were assigned to that patient. We let $g_A(k) = \bar{a}(k) = \{a(0), a(1), \ldots, a(k)\}$ (1 for pravastatin-treated, 0 for untreated) and $g_M(k) = \bar{m}(k) = \{m(1), m(2), \ldots, m(k)\}$ denote 'intervention' sequences through visit k for $\{A(0), A(1), \ldots, A(k)\}$ and $\{M(0), M(1), \ldots, M(k)\}$, respectively. Let $Y_{g_A(K)=\bar{a}, g_M(K)=\bar{m}}(K+1)$ be a counterfactual at $K+1$, which, possibly contrary to the factual variable, would have been experienced if the patient had followed $g_A(K) = \bar{a} = \{a(0), a(1), \ldots, a(K)\}$ and $g_M(K) = \bar{m} = \{m(1), m(2), \ldots, m(K)\}$. For the

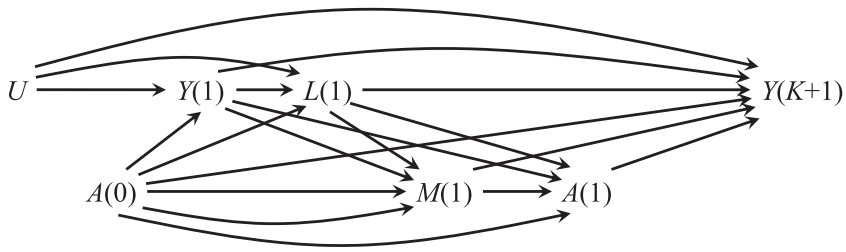

Figure 1. A causal directed acyclic graph assumed in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study. $A(k)$, pravastatin treatment at k; $M(k)$, cholesterol levels at k measured as an intermediate; $L(k)$, time-dependent confounders at k for A-Y and M-Y; $Y(k)$, coronary heart disease occurrence at k; $Y(K+1)$, coronary heart disease occurrence at the end of the trial; and U, unmeasured predictors of $Y(k)$. Note that the baseline confounders $L(0)$ that affect all variables except for U but are affected by U were omitted for graphical simplicity.

definition and identification of the SNMM introduced in the next section, we define the counterfactual $A_{g_A(k-1)=\bar{a}(k-1),g_M(k)=\bar{m}(k)}(k)$ in the same way.

We are interested in the controlled direct effects, on the risk-ratio scale, on the outcome $Y(K+1)$ of treatment $A(k)=a(k)$ in an arbitrary treatment sequence $\bar{a}=\{a(0),a(1),\ldots,a(K)\}$ while controlling intermediates fixed at $\bar{m}=\{m(1),m(2),\ldots,m(K)\}$ [12]:

$$\frac{\mathrm{E}\left[Y_{g_A(K)=\{\bar{a}(k),\underline{0}(k+1)\},g_M(K)=\bar{m}}(K+1)\right]}{\mathrm{E}\left[Y_{g_A(K)=\{\bar{a}(k-1),\underline{0}(k)\},g_M(K)=\bar{m}}(K+1)\right]}$$

where $\{\bar{a}(k),\underline{0}(k+1)\}=\{a(0),a(1),\ldots,a(k),0,\ldots,0\}$ comprises the first k treatment sequences in $\bar{a}$ and subsequent discontinuation of the treatment. This measures the effect of a final 'blip' $a(k)$ of the intervention $g_A(K)=\{\bar{a}(k),\underline{0}(k+1)\}$ at visit k, whereas the intermediate's values are set to $\bar{m}$ throughout the follow-up period. Note that the controlled direct effects of $a(k)$ may interact with prior treatment values in $\bar{a}(k-1)$ or any component of $\bar{m}$.

4. Direct-effect and total-effect structural nested mean models

We assume a multiplicative direct-effect SNMM [12] for the conditional version of the controlled direct effects given the history of all variables up to k and $Y(k)=0$ as follows:

$$\begin{aligned}
&\log \mathrm{E}\left[\left.Y_{g_A(K)=\{\bar{a}(k),\underline{0}(k+1)\},g_M(K)=\bar{m}}(K+1)\right| \bar{A}(k-1)=\bar{a}(k-1),\bar{L}(k),\bar{M}(k)=\bar{m}(k),Y(k)=0\right]\\
&-\log \mathrm{E}\left[\left.Y_{g_A(K)=\{\bar{a}(k-1),\underline{0}(k)\},g_M(K)=\bar{m}}(K+1)\right| \bar{A}(k-1)=\bar{a}(k-1),\bar{L}(k),\bar{M}(k)=\bar{m}(k),Y(k)=0\right] \qquad (1)\\
&=\gamma_k\left[\bar{a}(k),\bar{m},\bar{L}(k);\psi\right]
\end{aligned}$$

where $\bar{a}(k)$ and $\bar{m}(k)$ are the first k components in $\bar{a}$ and $\bar{m}$, respectively. $\gamma_k\left[\bar{a}(k),\bar{m},\bar{L}(k);\psi\right]$ is a known 'blip' function, which is selected such that it takes 0 if a direct effect parameter vector $\psi=0$, that is, $\gamma_k\left[\bar{a}(k),\bar{m},\bar{L}(k);0\right]\equiv 0$; it takes 0 if $a(k)=0$, in which case the two expectations are exactly the same, that is, $\gamma_k\left[\bar{a}(k-1),a(k)=0,\bar{m},\bar{L}(k);\psi\right]\equiv 0$; and it is linear in ψ. This is the same model as Robins's original direct-effect SNMMs [12], where $\gamma_k\left[\bar{a}(k),\bar{m},\bar{L}(k);\psi\right]$ measures the direct effects of a blip $a(k)$ in subgroups defined by all variables measured up to k. The SNMM (1) allows interaction or effect modification by the history of treatment $\bar{A}(k-1)=\bar{a}(k-1)$, intermediates $\bar{M}(k)=\bar{m}(k)$, and covariates $\bar{L}(k)$, as well as interactions with future intermediate values in $\bar{m}$. In the simplest form, that is, the direct effects of $A(k)=a(k)$ neither depend on time nor other variables, the blip function is $\gamma_k\left[\bar{a}(k),\bar{m},\bar{L}(k);\psi\right]=a(k)\psi$.

Here, the outcome was originally measured as the time to event T. In such cases, accelerated structural failure time models of joint effects [28, 29] or structural nested cumulative failure time models (SNCFTMs) [30, 31] are both suitable models. In this paper, we focus on the effects on the outcome at the last visit, $Y(K+1)$, and ignore the censoring owing to non-CHD causes in order to illustrate the sequential g-estimation in a simple class of structural nested models for time-varying treatments. Nevertheless, the method described in the next section can be applied to SNCFTMs (but not to accelerated structural failure time models) using estimating equations to fit the models. We discuss the modification in Section 7.

Parameters in the SNMM (1) cannot be obtained by the usual g-estimation procedure [12]. Instead, in point-treatment settings, Vansteelandt and colleagues [16–18] presented SNMMs for the *total* effect of an intermediate variable in addition to direct-effect SNMMs, which enables the estimation of parameters in direct-effect SNMMs by sequential application of g-estimation (described in Section 5.2). We extend their second SNMM to be a SNMM of the total effect of repeatedly measured intermediates $M(k)$ as follows:

$$\begin{aligned}
&\log \mathrm{E}\left[Y_{g_M(K)=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1) \,\middle|\, \bar{M}(k-1)=\bar{m}(k-1), \bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k), Y(k)=0 \right] \\
&-\log \mathrm{E}\left[Y_{g_M(K)=\{\bar{m}(k-1),\underline{0}(k)\}}(K+1) \,\middle|\, \bar{M}(k-1)=\bar{m}(k-1), \bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k), Y(k)=0 \right] \\
&=\delta_k\left[\bar{m}(k), \bar{a}(k-1), \bar{L}(k); \theta\right]
\end{aligned} \tag{2}$$

where $\delta_k\left[\bar{m}(k), \bar{a}(k-1), \bar{L}(k); \theta\right]$ is a known blip function of the history of measured variables, selected such that $\delta_k\left[\bar{m}(k), \bar{a}(k-1), \bar{L}(k); 0\right] = \delta_k\left[\bar{m}(k-1), m(k)=0, \bar{a}(k-1), \bar{L}(k); \theta\right] \equiv 0$ and linear in θ. We removed $g_A(K)$ from $Y(K+1)$ so that $Y_{g_M(K)}(K+1)$ is defined independently from the treatment intervention and is instead only determined by $g_M(K)$ in the subgroups defined in (2). Equivalence between (2) and the SNMM written in the more rigorous counterfactual notation of $Y_{g_A(K),g_M(K)}(K+1)$ with counterfactuals of $A(k)$ in $g_A(K)$ is explained in Appendix A.

The following must be noted: the SNMMs (1) and (2) constrain the parameter space for each other. For example, if we assume the direct-effect SNMM (1) as $\gamma_k\left[\bar{a}(k), \bar{m}, \bar{L}(k); \psi\right] = a(k)\left[\psi_1 + L(k)\psi_2 + m(k+1)\psi_3\right]$, it forces the SNMM (2) to include the interaction term $a(k-1)m(k)$; the interaction parameter θ_3 of $a(k-1)m(k)$ must equal ψ_3. Furthermore, two SNMMs must condition the same set of history of covariates $L(k)$, even if the subset of $L(k)$ history only confounds $A(k)$ but not $M(k)$ or vice versa; effect modification by such a subset that is not a confounder must be considered. A rule of thumb for the parameterization of blip functions is to retain coherence of the interaction of $a(k)$ with $m(k+s)$ in the SNMMs (1) and (2) with the same set of covariates $L(k)$, for $s > 0$.

5. Parameter estimation

5.1. Assumptions and identifiability in g-estimation

To estimate the parameters in the SNMMs (1) and (2), three identifying assumptions must be made. (i) The consistency assumption: if $\bar{A} = \bar{a}$ and $\bar{M} = \bar{m}$, then $Y(K+1) = Y_{g_A(K)=\bar{a},g_M(K)=\bar{m}}(K+1)$ for all $\bar{a}$ and $\bar{m}$; if $\bar{A}(k-1) = \bar{a}(k-1)$ and $\bar{M}(k) = \bar{m}(k)$, then $A(k) = A_{g_A(k-1)=\bar{a}(k-1),g_M(k)=\bar{m}(k-1)}(k)$ for all $\bar{a}(k-1)$ and $\bar{m}(k)$. (ii) The following no-unmeasured confounders assumption for $A(k)$ and $M(k)$, represented as the conditional independence of counterfactual outcomes given the history of variables:

$$Y_{g_A(K)=\bar{a},g_M(K)=\bar{m}} \quad (K+1)\coprod A(k) \,\middle|\, \bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k), \bar{M}(k)=\bar{m}(k), Y(k)=0 \tag{3}$$

$$Y_{g_A(K)=\bar{a},g_M(K)=\bar{m}} \quad (K+1)\coprod M(k) \,\middle|\, \bar{M}(k-1)=\bar{m}(k-1), \bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k), Y(k)=0 \tag{4}$$

for $k > 0$ and for all $\bar{a}$ and $\bar{m}$ ($\bar{a}(k)$ and $\bar{m}(k)$ are the first k components therein). (iii) The correct specification of all structural and regression models. If we assume SNMMs with different parameter vectors ψ_k or θ_k at each k, we need the positivity assumption to hold: if $f_{\bar{A}(k-1),\bar{L}(k),\bar{M}(k)|Y(k)}\left[\bar{a}(k-1), \bar{l}(k), \bar{m}(k)\,|0\right]\Pr[Y(k)=0] \neq 0$, then $\Pr\left[A(k)=a(k)\,\middle|\,\bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k)=\bar{l}(k), \bar{M}(k)=\bar{m}(k), Y(k)=0\right] > 0$ for all $a(k)$; and if $f_{\bar{M}(k-1),\bar{A}(k-1),\bar{L}(k)|Y(k)}\left[\bar{m}(k-1), \bar{a}(k-1), \bar{l}(k)\,|0\right]\Pr[Y(k)=0] \neq 0$, then $f_{M(k)|\bar{M}(k-1),\bar{A}(k-1),\bar{L}(k),Y(k)}\left[m(k)\,|\bar{m}(k-1), \bar{a}(k-1), \bar{l}(k), 0\right] > 0$ for all $m(k)$, where $f_{V|W}[v|w]$ is the conditional density of V given W evaluated at v and w, respectively [31]. However, as long as we assume unsaturated SNMMs with respect to visit k, we do not require the positivity at every k because our estimates can rely on some extrapolations from the models [19,31,32]. Under these assumptions, we first estimate the parameter θ in the SNMM (2) and then sequentially estimate the parameter ψ in the direct-effect SNMM (1) using the estimated $\hat{\theta}$. Each estimator is based on the standard g-estimation procedure [19,32–34] described in the next subsection.

We define the following 'pseudo'-outcome for patient i whose $Y_i(k) = 0$ as if $M_i(t)$ after k $(> t)$ are set to zero under the model (2) as a function of any parameter value θ:

$$H_{i,k}(\theta) = Y_i(K+1) \exp\left\{-\sum_{t=k}^{K} \delta_t\left[\bar{M}_i(t), \bar{A}_i(t-1), \bar{L}_i(t); \theta\right]\right\}$$

Note that we can compute $H_{i,k}(\theta)$ from observed data $\{\bar{A}_i(K), \bar{M}_i(K), \bar{L}_i(K), \bar{Y}_i(K+1)\}$ for all i and k for which $Y_i(k) = 0$ by substituting an arbitrary value for θ. From the SNMM (2) and the consistency assumption, under the correct specification of θ as the true value, we obtain the following result [32–34]:

$$\begin{aligned}\log \mathrm{E}\left[H_k(\theta) \,\middle|\, \bar{M}(k-1) = \bar{m}(k-1), \bar{A}(k-1) = \bar{a}(k-1), \bar{L}(k), Y(k) = 0\right] \\ = \log \mathrm{E}\left[\begin{array}{l} Y_{g_M(K)=\{\bar{m}(k-1),\underline{0}(k)\}}(K+1) \\ \left| \bar{M}(k-1) = \bar{m}(k-1), \bar{A}(k-1) = \bar{a}(k-1), \bar{L}(k), Y(k) = 0 \right. \end{array}\right]\end{aligned} \tag{5}$$

where $H_k(\theta)$ on the left-hand side is the function of observed data, whereas the right-hand side represents counterfactual risks contrasted in the SNMM (2). As described in the next section, the no-unmeasured confounders assumption (4) and Equation (5) make θ identifiable in the g-estimation method.

We now illustrate that the sequential g-estimation method [16–18] can be extended to time-varying treatments. From the SNMMs (1) and (2) and the consistency assumption, we can show (Appendix B) that

$$\begin{aligned}\log \mathrm{E}\left[H_k^*(\theta, \psi) \,\middle|\, \bar{A}(k-1) = \bar{a}(k-1), \bar{L}(k), \bar{M}(k) = \bar{m}(k), Y(k) = 0\right] \\ = \log \mathrm{E}\left[\begin{array}{l} Y_{g_A(K)=\{\bar{a}(k-1),\underline{0}(k)\},g_M(K)=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1) \\ \left| \bar{A}(k-1) = \bar{a}(k-1), \bar{L}(k), \bar{M}(k) = \bar{m}(k), Y(k) = 0 \right. \end{array}\right],\end{aligned} \tag{6}$$

$$H_{i,k}^*(\theta, \psi) = H_{i,k+1}(\theta) \exp\left\{-\sum_{t=k}^{K} \gamma_t\left[\bar{A}_i(t), \bar{M}_i(t), \underline{m}(t+1) = \underline{0}(t+1), \bar{L}_i(t); \psi\right]\right\}$$

where $\underline{m}(t+1) = \{m(t+1), \ldots, m(K)\}$ represents the set of $\bar{m}$ after $t+1$; we set $\underline{m}(t+1) = \{0, \ldots, 0\}$ in every $\gamma_t[\cdot]$. This result means that, in order to obtain a g-estimate of ψ, we simply have to conduct the general g-estimation procedure (as used for estimating the total effect) by regarding $H_{k+1}(\theta)$ as an outcome, because we no longer have to consider the interaction between $A(k)$ and $M(k+s)$ $(s > 0)$, even if the SNMM (1) allows it.

5.2. *Sequential g-estimation*

We assume a regression model for the conditional mean of an intermediate $M(k)$ given the previous variables as

$$\mathrm{E}\left[M(k) \,\middle|\, \bar{L}(k), \bar{A}(k-1), \bar{M}(k-1), Y(k) = 0\right] = \mu_k\left[\bar{L}(k), \bar{A}(k-1), \bar{M}(k-1); \alpha\right]$$

for example, as a linear model for continuous $M(k)$ or as a logistic model for binary $M(k)$. Assumption (4) implies that $M(k)$ and any counterfactual outcome are mean-independent conditional on the variable history. According to the result of Equation (5), $H_k(\theta)$ is equal to one of the counterfactual outcomes on expectation, which results in the following unbiased (mean-zero) 'g'-estimating function for each patient i:

$$U_{1i}(\theta) = \sum_{k=1}^{K} [1 - Y_i(k)]\left\{M_i(k) - \mu_k\left[\bar{L}_i(k), \bar{A}_i(k-1), \bar{M}_i(k-1); \alpha\right]\right\} Q_{i,k} H_{i,k}(\theta) \tag{7}$$

where $Q_{i,k} = q_k\left[\bar{L}_i(k), \bar{A}_i(k-1), \bar{M}_i(k-1)\right]$ is an arbitrary random vector function with the same dimensions as parameter θ. The choice of $q_k[\cdot]$ does not affect the consistency of the estimators but does affect their efficiency [32–34]. After substituting regular and asymptotically linear estimates $\hat{\alpha}$ (by maximum likelihood or generalized estimating equations), the resulting g-estimator $\hat{\theta}$ from $\sum_{i=1}^{n} U_{1i}(\theta) = 0$ consistently estimates θ.

To obtain the g-estimates of ψ, we use $H_{k+1}(\hat{\theta})$ evaluated at a g-estimate as a pseudo-outcome instead of $Y(K+1)$ itself for treatment $A(k)$. We assume a regression model for the conditional probability of treatment $A(k)=1$ given previous variables (i.e., a propensity score) as follows:

$$\Pr\left[A(k)=1 \,\middle|\, \bar{A}(k-1), \bar{L}(k), \bar{M}(k), Y(k)=0\right] = \pi_k\left[\bar{A}(k-1), \bar{L}(k), \bar{M}(k); \beta\right]$$

Therefore, from assumption (4) and the result of Equation (6), we can derive the g-estimating function for ψ in the same way as in (7) for i as follows:

$$U_{2i}(\psi, \hat{\theta}) = \sum_{k=1}^{K} [1-Y_i(k)]\left\{A_i(k) - \pi_k\left[\bar{A}_i(k-1), \bar{L}_i(k), \bar{M}_i(k); \hat{\beta}\right]\right\} Q^*_{i,k} H^*_{i,k}(\psi, \hat{\theta}) \qquad (8)$$

where $Q^*_{i,k} = q^*_k\left[\bar{A}_i(k-1), \bar{L}_i(k), \bar{M}_i(k)\right]$ is an arbitrary vector function with the same dimensions as parameter ψ and $\hat{\beta}$ is a regular and asymptotically linear estimate of the regression parameter β. The conservative asymptotic covariance matrix of the g-estimator $(\hat{\theta}^T, \hat{\psi}^T)^T$ is obtained with a sandwich estimator using the joint g-estimating function $U_i = \left\{U_{1i}(\theta)^T, U_{2i}(\psi, \theta)^T\right\}^T$:

$$n^{-1}\hat{\mathrm{E}}\left[\frac{\partial U}{\partial(\psi^T, \theta^T)}\right]^{-1} \hat{\mathrm{E}}\left[UU^T\right] \hat{\mathrm{E}}\left[\frac{\partial U}{\partial(\psi^T, \theta^T)}\right]^{-1,T}$$

which the g-estimates $(\hat{\theta}^T, \hat{\psi}^T)^T$ are substituted for [33]. The estimated expectations are computed using the empirical distribution of the sample.

6. Data analysis

The sequential g-estimation method for time-varying treatments was applied to data from the MEGA Study. As an intermediate variable $M(k)$, we separately considered the achieved cholesterol level (mg/dl) and the reduction from the baseline value (mg/dl) for TC, LDL cholesterol, HDL cholesterol, and non-HDL cholesterol in each analysis (centered at target levels, $m(k)$, in Tables I and II).

First, we estimated ψ and θ in the 1-parameter SNMMs $\gamma_k[\bar{a}(k), \bar{m}, \bar{L}(k); \psi] = a(k)(t_{k+1}-t_k)\psi$ and $\delta_k[\bar{m}(k), \bar{a}(k-1), \bar{L}(k-1); \theta] = m(k)(t_{k+1}-t_k)\theta$. As patients were followed up in non-constant intervals (1, 2, and 3 months between the first four visits and 6 months thereafter), we rescaled treatment and intermediate values by the duration between each visit $t_{k+1}-t_k$ (year); the parameters in these SNMMs represent 1-year cumulative effects of $A(k)$ and $M(k)$ on CHD risk at year 5. The following regression models were fitted separately for each patient visit:

$$\pi_k\left[\bar{A}(k-1), \bar{L}(k), \bar{M}(k); \beta\right] = \left\{1+\exp\left[-\beta_{0,k} - \beta_{1,k}A(k-1) - \beta_{2,k}M(k) - \beta^T_{3,k}L(k) - \beta^T_{4,k}L(0)\right]\right\}^{-1},$$

$$\mu_k\left[\bar{L}(k), \bar{A}(k-1), \bar{M}(k-1); \alpha\right] = \alpha_{0,k} + \alpha_{1,k}A(k-1) + \alpha_{2,k}M(k-1) + \alpha^T_{3,k}L(k) + \alpha^T_{4,k}L(0)$$

For the time-dependent confounders $L(k)$, systolic blood pressure; diastolic blood pressure; body-weight; dietary habit; and TC, LDL cholesterol, and HDL cholesterol measures other than $M(k)$ were assumed (we removed HDL cholesterol when $M(k)$ was non-HDL cholesterol). $L(0)$ represents all measured baseline confounders described in Section 2. When we omitted cholesterol measures from $L(k)$ and instead included these baseline measures in $L(0)$, the results presented here were not changed qualitatively.

Because we fitted 1-parameter SNMMs, including no-interaction terms between $A(k)$ and $M(k+s)$, we can present the 'indirect' effect by subtracting the controlled direct effect estimates $\hat{\psi}$ from the estimates of the total effect η. In general, indirect effects are not equal to the differences between total effects and controlled direct effects if an interaction exists between A and M. Therefore, we have to estimate pure (natural) direct effects to obtain the corresponding indirect effects [1, 4]. Under the 1-parameter

SNMMs (1) and (2), however, the controlled direct effects do not depend on an intermediate and, hence, coincide with the pure direct effect. We estimated η (log risk-ratio) on the basis of the 1-parameter g-estimating function:

$$U_{3i}(\eta)=\sum_{k=1}^{K}[1-Y_i(k)]\left\{A_i(k)-\pi_k\left[\bar{A}_i(k-1),\bar{L}_i(k),\bar{M}_i(k);\hat{\beta}\right]\right\}Y_i\exp\left\{-\sum_{j=k}^{K}A_i(j)(t_{j+1}-t_j)\eta\right\}$$

and the covariance matrix of g-estimates by using the sandwich formula:

$$n^{-1}\hat{\mathrm{E}}\left[\frac{\partial U}{\partial(\psi,\theta,\eta)}\right]^{-1}\hat{\mathrm{E}}\left[UU^T\right]\hat{\mathrm{E}}\left[\frac{\partial U}{\partial(\psi,\theta,\eta)}\right]^{-1,T}$$

where $U_i=(U_{1i}(\theta),U_{2i}(\psi,\theta),U_{3i}(\eta))^T$, for which the g-estimates were substituted.

At visit $k=1$, only 0.7% in the diet group started pravastatin treatment, but 43.6% in the diet plus pravastatin group did not achieve 10 mg daily dose of pravastatin. At each k thereafter, 3.5–5.8% of patients started pravastatin treatment (i.e., $A(k-1)=0$ and $A(k)=1$) except for 12.5% at $k=2$, and 7.7–11.9% of patients discontinued pravastatin treatment (i.e., $A(k-1)=1$ and $A(k)=0$). None of the cholesterol levels in $L(k)$ were significantly associated with $A(k)$ (increase in the odds by up to 1.1 times per 10 mg/dl). Note that as our g-estimates of assumed SNMMs do not depend on the positivity assumption of $A(k)$ nor $M(k)$, these data are provided as reference for the readers.

The g-estimate of the total effect (risk ratio) of 1 year pravastatin use on CHD was 0.75 (95% [CI]: 0.62–0.91). Table I shows the results of the initial analysis using the 1-parameter SNMMs. Although the direct effects were larger than the indirect effects for all cholesterol measures considered, the indirect effects through achieved LDL cholesterol levels were slightly larger than those through other measures. For all cholesterol measures, there were small differences between the results of achieved values and those of reductions from baseline.

We next fitted 2-parameter SNMMs, including an interaction term between pravastatin treatment and the cholesterol level immediately after treatment, that is, $[\psi_1+\psi_2 m(k+1)]a(k)(t_{k+1}-t_k)$ and $[\theta_1+\theta_2 a(k-1)]m(k)(t_{k+1}-t_k)$ for SNMMs (1) and (2), respectively. We sequentially solved the following g-estimating equations:

Table I. Sequential g-estimates for controlled direct and indirect effects of 1 year use of pravastatin on CHD at year 5 with 1-parameter structural nested mean models (using data from the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study).

Intermediate $M(k)$ ($m(k)$ at which $M(k)$ is controlled)	Direct effect (RR)	95% CI	Indirect effect (RR)	95% CI
TC				
Achieved (210 mg/dl)	0.78	0.63–0.96	0.95	0.86–1.04
Reduction from baseline (30 mg/dl)	0.75	0.61–0.93	0.98	0.91–1.06
LDL-C				
Achieved (120 mg/dl)	0.83	0.68–1.02	0.89	0.81–0.99
Reduction from baseline (30 mg/dl)	0.77	0.62–0.95	0.96	0.88–1.05
HDL-C				
Achieved (60 mg/dl)	0.77	0.63–0.96	0.96	0.88–1.04
Increase from baseline (10 mg/dl)	0.77	0.63–0.94	0.97	0.91–1.02
Non-HDL-C				
Achieved (120 mg/dl)	0.80	0.64–0.99	0.93	0.83–1.04
Reduction from baseline (30 mg/dl)	0.76	0.61–0.94	0.98	0.90–1.05

CHD, coronary heart disease; RR, risk ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

$$\begin{pmatrix} 0 \\ 0 \end{pmatrix} = \sum_{i=1}^{n} U_{1i}(\theta_1, \theta_2)$$

$$= \sum_{i=1,k=1}^{i=n,k=K} \begin{pmatrix} 1 \\ A_i(k-1) \end{pmatrix} [1 - Y_i(k)]$$

$$\times \begin{bmatrix} \{M_i(k) - \mu_k [\bar{L}_i(k), \bar{A}_i(k-1), \bar{M}_i(k-1); \hat{\alpha}]\} \\ \times Y_i(K+1) \exp\left\{ -\sum_{j=k}^{K} [\theta_1 + \theta_2 A_i(j-1)] M_i(j)(t_{j+1} - t_j) \right\} \end{bmatrix},$$

$$0 = \sum_{i=1}^{n} U_{2i}\left(\psi_1, \hat{\theta}_1, \hat{\theta}_2\right)$$

$$= \sum_{i=1,k=1}^{i=n,k=K} [1 - Y_i(k)] \begin{bmatrix} \{A_i(k) - \pi_k [\bar{A}(k-1), \bar{L}(k), \bar{M}(k); \hat{\beta}]\} \\ \times Y_i(K+1) \exp \begin{Bmatrix} -\sum_{j=k+1}^{K} \left[\hat{\theta}_1 + \hat{\theta}_2 A_i(j-1)\right] M_i(j)(t_{j+1} - t_j) \\ -\sum_{j=k}^{K} \psi_1 A_i(j)(t_{j+1} - t_j) \end{Bmatrix} \end{bmatrix}$$

where the models μ_k and π_k fit to regressions of $A(k)$ and $M(k)$ are the same as in the first analysis. Note that because the interaction parameter ψ_2 in the direct-effect SNMM (1) is equal to θ_2 of the SNMM (2), we only need to solve the scalar function in the second sequence (Section 5.1). Covariance matrices were estimated using the sandwich formula with $U_i = (U_{1i}(\theta_1, \theta_2)^T, U_{2i}(\psi, \theta_1, \theta_2))^T$.

Table II provides the controlled direct effects (risk ratios) of pravastatin when each cholesterol level was controlled at a specified value ($= \exp(\psi_1)$) and there was an interaction with a 10 mg/dl increase in the subsequent cholesterol values ($= \exp(10\psi_2)$). Estimates of the controlled direct effects were similar to the results of the first analysis, because the size of the interaction was close to 1 for all cholesterol measures. Other biologically plausible SNMMs, for example, models including the interaction term between $A(k)$ and cholesterol levels immediately before it, $M(k)$ (i.e., $[\psi_1 + \psi_2 m(k)]a(k)(t_{k+1} - t_k)$ for SNMM (1)), the time trend of the intermediate effect parameter (i.e., $[\theta_1 + \theta_2 t_k]m(k)(t_{k+1} - t_k)$ for SNMM (2)), or the interaction with the cumulative exposure for intermediate $M(k)$ (i.e., $[\theta_1 + \theta_2 \sum_{j=1}^{k} m(j)(t_{j+1} - t_j)]m(k)(t_{k+1} - t_k)$ for SNMM (2)) provided similar estimates for ψ as those in Table II (i.e., minimal interaction in each SNMM). Reversing the assumed temporal order from ($L(k)$, $M(k)$) to ($M(k)$, $L(k)$) had only a small effect on all estimates (results not shown).

Table II. Sequential g-estimates for controlled direct effects of 1 year use of pravastatin on CHD risk at year 5 with 2-parameter SNMMs that allow interactions between pravastatin $A(k)$ and cholesterol levels $M(k+1)$.

Intermediate $M(k)$ ($m(k)$ at which $M(k)$ is controlled)	Direct effect (RR)*	95% CI	Interaction (RR) with a 10 mg/dl increase in subsequent cholesterol level	95% CI
TC				
Achieved (210 mg/dl)	0.77	0.62–0.96	1.02	0.93–1.11
Reduction from baseline (30 mg/dl)	0.75	0.61–0.93	1.04	0.95–1.14
LDL-C				
Achieved (120 mg/dl)	0.82	0.65–1.04	1.01	0.89–1.15
Reduction from baseline (30 mg/dl)	0.76	0.62–0.95	1.06	0.96–1.17
HDL-C				
Achieved (60 mg/dl)	0.75	0.58–0.97	0.89	0.51–1.54
Increase from baseline (10 mg/dl)	0.70	0.54–0.92	0.86	0.65–1.15
Non-HDL-C				
Achieved (120 mg/dl)	0.73	0.47–1.14	1.02	0.93–1.13
Reduction from baseline (30 mg/dl)	0.77	0.62–0.95	1.04	0.97–1.13

CHD, coronary heart disease; RR, risk ratio; CI, confidence interval; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
*Estimated direct effects when the cholesterol levels $M(k)$ were controlled at $m(k)$ as shown in the first column.

7. Discussion

This paper illustrates the sequential g-estimation method [16–18] for direct-effect SNMMs [12] using longitudinal data with time-varying treatments and repeatedly measured intermediates. The method is as intuitive as the ordinary g-estimation method for time-varying treatments and can be implemented by using widely distributed optimization routines such as the Newton–Raphson method.

Our SNMMs are also valid if the outcome is continuous or dichotomous, which is evaluated only at the end of the study (in such cases, $Y(k)$ in the g-estimating functions represents the 'drop-out' process and equals 0 except for the final outcome $Y(K+1)$) but are generally inadequate if the outcome is time-to-event with differential follow-up lengths between patients. For such time-to-event outcomes, it might be better to assume SNCFTMs [30, 31] rather than the SNMMs (1) and (2) by replacing each counterfactual $Y_{g_A(K)=\bar{a},g_M(K)=\bar{m}}(K+1)$ by $Y_{g_A(s-1)=\bar{a}(s-1),g_M(s-1)=\bar{m}(s-1)}(s)$ for all s $(>k)$ and replacing $\gamma_k[\cdot]$ and $\delta_k[\cdot]$ by $\gamma_{s,k}[\cdot]$ and $\delta_{s,k}[\cdot]$, respectively. Although biologically plausible blip functions exist that are consistent with 1-parameter accelerated failure time models [28, 33] under certain assumptions (e.g., rare events under no-treatment) [30], the estimating equations based on SNCFTMs are smooth in their parameters, unlike accelerated structural failure time models [31]. For SNCFTMs under the rare disease assumption, g-estimation procedures have to be modified as described in Appendix C.

If there is loss to follow-up (censoring), each component of the g-estimating functions should be weighted by the reciprocal of the uncensoring probability [31, 33]. Although we did not adjust for censoring, owing to the limited number of patients who were lost to follow-up (<15% in 5 years) and the analytical evidence of independent censoring in the MEGA Study [35], we suspect that bias due to censoring is unlikely to change our estimates substantially.

In addition to the sequential g-estimation method of SNMMs, the inverse-probability weighted estimation of MSMs [13–15] and g-computation with Monte Carlo simulations after fitting the parametric models of each variable's conditional distribution using maximum likelihood methods (parametric g-formula) [20–22] may also be readily applicable methods for estimating controlled direct effects using standard software. Yet SNMMs [12], MSMs [11], and g-formula [9, 10] differ in causal parameters that analysts target for and in their modeling assumptions. In particular, estimation methods for SNMMs and MSMs operate through the different choice of full-data estimating functions [36]. Despite the conceptual dissociation of the underlying models and inference targets, it may be difficult or even impossible to estimate controlled direct effects under a single modeling assumption. We believe that additional observational data including time-varying treatment and intermediates are conducive to the development of sophisticated theories related to treatment mechanisms in conjunction with various methods that offer compatible results. We hope that our study contributes to the literature on longitudinal mediation analysis where the applicability of SNMMs has not been widely discussed.

Appendix A: The structural nested mean model (2) with counterfactual outcomes defined under both $g_A(K)$ and $g_M(K)$

The SNMM (2) can be formally written as

$$\log \mathrm{E}\left[Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A(k-1)=\bar{a}(k-1),g_M(K)=\{\bar{m}(k),\underline{0}(k+1)\}}(k)\right\},g_M(K)=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1) \,\middle|\, \bar{M}(k-1)=\bar{m}(k-1), \bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k), Y(k)=0 \right]$$

$$-\log \mathrm{E}\left[Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A(k-1)=\bar{a}(k-1),g_M(K)=\{\bar{m}(k-1),\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),\underline{0}(k)\}}(K+1) \,\middle|\, \bar{M}(k-1)=\bar{m}(k-1), \bar{A}(k-1)=\bar{a}(k-1), \bar{L}(k), Y(k)=0 \right]$$

$$=\delta_k\left[\bar{m}(k),\bar{a}(k-1),\bar{L}(k);\theta\right]$$

where $\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k),\underline{0}(k+1)\}}(k)\right\}$ is the same as $\bar{a}$ up to $k-1$, but thereafter, treatment $A(t)(t \geqslant k)$ is determined by $g_A(k-1)=\bar{a}(k-1)$ and $g_M(K)=\{\bar{m}(k),\underline{0}(k+1)\}$. As a result, intervention $g_A(K)$ equals $\{a(0),\ldots,a(k-1),a^*(k),a^*(k+1),\ldots,a^*(K)\}$, such that $a^*(k)=A_{g_A(k-1)=\bar{a}(k-1),g_M(k)=\bar{m}(k)}(k)$, $a^*(k+1)=A_{g_A(k)=\{\bar{a}(k-1),a^*(k)\},g_M(k+1)=\{\bar{m}(k),0\}}(k+1)$, and so on. Thus, $g_A(K)$ are dynamic, but need to be nonrandom [22, 37], where interventions at each visit are assumed to be determined with probability 1, as a well-defined function of the history of measured variables. Note that because we have conditioned on $\bar{A}(k-1)=\bar{a}(k-1)$, we can remove

$g_A(k-1) = \bar{a}(k-1)$ from subscripts of counterfactual of $Y(K+1)$ by using the consistency assumption; components $a^*(t)(t \geq k)$ were determined with probability 1 by using these observed levels of $\bar{A}(k-1)$ and 'static' intervention $g_M(K) = \{\bar{m}(k), \underline{0}(k+1)\}$ under a deterministic model. Such $g_A(K)$ would be obtained if only $\bar{M}(K)$ had been intervened on. As a result, shorthand counterfactual notation in the SNMM (2) using only $g_M(K)$ is appropriate.

Appendix B: Derivation of Equations (5) and (6)

Here, we show the results (5) and (6), which are obtained from the SNMMs (1) and (2) under the identifying assumptions described in the text.

We show that the conditional mean counterfactual outcome in which the effect of $M(t)$ after visit k is eliminated is equal to the conditional mean of $H_k(\theta)$. First, by the law of iterative expectancy

$$\mathrm{E}\left[Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),\underline{0}(k)\}}(K+1) \,\middle|\, \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right]$$

$$= \mathrm{E}\left[\mathrm{E}\left\{ Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),\underline{0}(k)\}}(K+1) \,\middle|\, M(k) \right\} \,\middle|\, \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right]$$

$$= \mathrm{E}\left[\mathrm{E}\left\{ \begin{array}{l} Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k+1)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \end{array} \,\middle|\, M(k) \right\} \,\middle|\, \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right]$$

$$= \mathrm{E}\left[\begin{array}{l} Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \\ \left| \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right. \end{array} \right]$$

where the second equality follows the SNMM (2). Note that the condition $Y(k) = 0$ assures that only $A(k)$ and $M(k)$ are observable, but it does not assure that $M(k+1)$ is observable. However, because the aforementioned expectation can be rewritten as

$$\mathrm{E}\left[\mathrm{E}\left\{ \begin{array}{l} \mathrm{E}\left(\begin{array}{l} Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \end{array} \,\middle|\, Y(k+1)=0 \right) \\ \times \Pr(Y(k+1)=0) \\ +\mathrm{E}\left(\begin{array}{l} Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \end{array} \,\middle|\, Y(k+1)=1 \right) \\ \times \Pr(Y(k+1)=1) \end{array} \,\middle|\, A(k), M(k) \right\} \,\middle|\, \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right],$$

by the consistency for $A(k)$ and $Y(k+1)$, we obtain

$$\mathrm{E}\left[\mathrm{E}\left\{ \begin{array}{l} \mathrm{E}\left(\begin{array}{l} Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \\ \left| Y_{g_A(k)=\{\bar{a}(k-1),A(k)\},g_M(k)=\{\bar{m}(k-1),M(k)\}}(k+1)=0 \right. \end{array} \right) \\ \times \Pr\left(Y_{g_A(k)=\{\bar{a}(k-1),A(k)\},g_M(k)=\{\bar{m}(k-1),M(k)\}}(k+1)=0\right) \\ +\mathrm{E}\left(\begin{array}{l} Y_{g_A(K)=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M(K)=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \\ \left| Y_{g_A(k)=\{\bar{a}(k-1),A(k)\},g_M(k)=\{\bar{m}(k-1),M(k)\}}(k+1)=1 \right. \end{array} \right) \\ \times \Pr\left(Y_{g_A(k)=\{\bar{a}(k-1),A(k)\},g_M(k)=\{\bar{m}(k-1),M(k)\}}(k+1)=1\right) \end{array} \,\middle|\, A(k), M(k) \right\} \,\middle|\, \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right].$$

However, the consistency also implies that $Y_g(t) = 1(t > s+1)$ whenever $Y_{g(s)}(s+1) = 1$ for any regime g in which the first s components are $g(s)$, because the future part of the regime cannot influence the past outcome. Therefore, the aforementioned equation can be rearranged as follows:

$$\mathrm{E}\left[\mathrm{E}\left\{ \begin{array}{l} \mathrm{E}\left(\begin{array}{l} Y_{g_A=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1) \\ \times \exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \end{array} \,\middle|\, Y(k+1)=0 \right) \\ \times \Pr(Y(k+1)=0) \\ +\mathrm{E}\left(Y(k+1)\exp\left\{-\delta_k\left[\bar{M}(k), \bar{A}(k-1), \bar{L}(k); \theta\right]\right\} \,\middle|\, Y(k+1)=1\right) \\ \times \Pr(Y(k+1)=1) \end{array} \,\middle|\, A(k), M(k) \right\} \,\middle|\, \bar{L}(k), \bar{A}(k-1)=\bar{a}(k-1), \bar{M}(k-1)=\bar{m}(k-1), Y(k)=0 \right]$$

Because we imputed 0 for the missing values of $M(k+1)$ if the event occurs at $k+1$ in the patient,

$$\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y_{g_A=\left\{\bar{a}(k-1),\underline{A}_{g_A=\bar{a}(k-1),g_M=\{\bar{m}(k-1),M(k)\underline{0}(k)\}}(k)\right\},g_M=\{\bar{m}(k-1),M(k),\underline{0}(k+1)\}}(K+1)\\ \times\prod_{t=k}^{k+1}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}|Y(k+1)=0\end{array}\right)\Pr(Y(k+1)=0)\\ +\mathrm{E}\left(\begin{array}{l}Y(k+1)\\ \prod_{t=k}^{k+1}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}|Y(k+1)=1\end{array}\right)\Pr(Y(k+1)=1)\\ \\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k-1)=\bar{m}(k-1),Y(k)=0\right.\end{array}\right].$$

from the SNMM (2) and the law of iterative expectancy. Recursively,

$$\begin{aligned}&\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y(K+1)\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}|Y(K)=0\end{array}\right)\\ \times\Pr(Y(K)=0\,|Y(K-1)=0)\\ +\sum_{s=k}^{K-1}\left[\mathrm{E}\left(\begin{array}{l}Y(s+1)\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}|Y(s+1)=1\end{array}\right)\right.\\ \left.\times\Pr(Y(s+1)=1\,|Y(s)=0)\right]\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k-1)=\bar{m}(k-1),Y(k)=0\right.\end{array}\right]\\ &=\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y(K+1)\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}|Y(K)=0\end{array}\right)\\ \times\Pr(Y(K)=0\,|Y(K-1)=0)\\ +\sum_{s=k}^{K-1}\left[\mathrm{E}\left(\begin{array}{l}Y(K+1)\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}|Y(s+1)=1\end{array}\right)\right.\\ \left.\times\Pr(Y(s+1)=1\,|Y(s)=0)\right]\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k-1)=\bar{m}(k-1),Y(k)=0\right.\end{array}\right]\\ &=\mathrm{E}\left[\begin{array}{l}Y(K+1)\prod_{t=s}^{k}\exp\left\{-\delta_t\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k-1)=\bar{m}(k-1),Y(k)=0\right.\end{array}\right]\end{aligned}$$

Therefore, $H_k(\theta)=Y(K+1)\times\exp\left(\sum_{t=k}^{K}\left\{-\delta_k\left[\bar{M}(t),\bar{A}(t-1),\bar{L}(t);\theta\right]\right\}\right)$, at the extreme right-hand side of the equation, is conditionally equal in expectation to the counterfactual outcome in which the effect of $M(t)$ after visit k is nullified, and result (5) is shown. Because of conditions $\bar{A}(k-1)=g_A(k-1)$ and $\bar{M}(k-1)=g_M(k-1)$ in the aforementioned equation, $M(k)$ is mean-independent of $H_k(\theta)$ conditional on the history of measured variables $(\bar{M}(k-1),\bar{A}(A-1),\bar{L}(k))$ by conditional exchangeability (4); hence, we can derive the g-estimating function (7).

Next, result (6) can be obtained by the direct effect SNMM (1) and conditional exchangeability (3) in the same way used to obtain result (5). From the SNMM (1),

$$\begin{aligned}&\mathrm{E}\left[\begin{array}{l}Y_{g_A=\{\bar{a}(k-1),\underline{0}(k)\},g_M=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1)\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\right.\end{array}\right]\\ &=\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left\{Y_{g_A=\{\bar{a}(k-1),\underline{0}(k)\},g_M=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1)\right|A(k)\}\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\right.\end{array}\right]\\ &=\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left\{\begin{array}{l}Y_{g_A=\{\bar{a}(k-1),A(k),\underline{0}(k+1)\},g_M=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1)\\ \times\exp\left\{-\gamma_k[\bar{A}(k),\bar{M}(k),\underline{m}(k+1)=\underline{0}(k+1),\bar{L}(k);\psi]\right\}\end{array}\right|A(k)\right\}\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\right.\end{array}\right]\end{aligned}$$

Then, we apply the iterative condition on $Y(k+1)$ in the expectation,

$$\mathrm{E}\left[\mathrm{E}\left\{\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y_{g_A=\{\bar{a}(k-1),\underline{A}(k),\underline{0}(k+1)\},g_M=\{\bar{m}(k),\underline{0}(k+1)\}}(K+1)\\ \times\exp\left\{-\gamma_k[\bar{A}(k),\bar{M}(k),\underline{m}(k+1)=\underline{0}(k+1),\bar{L}(k);\psi]\right\}\\ |\Pr[Y(k+1)=0]\end{array}\right)\\ \times\Pr[Y(k+1)=0]\\ +\mathrm{E}\left(\begin{array}{l}Y(k+1)\\ \times\exp\left\{-\gamma_k\left[\bar{A}(k),\bar{M}(k),\underline{m}(k+1)=\underline{0}(k+1),\bar{L}(k);\psi\right]\right\}\\ |\Pr[Y(k+1)=1]\end{array}\right)\\ \times\Pr[Y(k+1)=1]\end{array}\middle|\begin{array}{l}\\ \\ A(k)\end{array}\right\}\middle|\begin{array}{l}\\ \\ \bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\end{array}\right]$$

$$=\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y_{g_A=\{\bar{a}(k-1),A(k),A(k+1),\underline{0}(k+2)\},g_M=\{\bar{m}(k),M(k+1),\underline{0}(k+2)\}}(K+1)\\ \times\prod_{t=k}^{k+1}\exp\left\{-\gamma_t\left[\bar{A}(t),\bar{M}(t),\underline{m}(t+1)=\underline{0}(t+1),\bar{L}(t);\psi\right]\right\}\\ \times\exp\left\{-\delta_{k+1}\left[\bar{M}(k+1),\bar{A}(k),\bar{L}(k+1);\theta\right]\right\}\\ |\Pr[Y(k+1)=0]\end{array}\right)\Pr\left(Y(k+1)=0\right)\\ +\mathrm{E}\left(\begin{array}{l}Y(k+1)\\ \times\prod_{t=k}^{k+1}\exp\left\{-\gamma_t\left[\bar{A}(t),\bar{M}(t),\underline{m}(t+1)=\underline{0}(t+1),\bar{L}(t);\psi\right]\right\}\\ \times\exp\left\{-\delta_{k+1}\left[\bar{M}(k+1),\bar{A}(k),\bar{L}(k+1);\theta\right]\right\}\\ |\Pr[Y(k+1)=1]\end{array}\right)\Pr\left(Y(k+1)=1\right)\\ \\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\right.\end{array}\right]$$

where the value 0 is imputed for the missing values of $A(k+1)$ and $M(k+1)$ if the patient's observed outcome $Y(k+1)$ is 1. Recursively,

$$\mathrm{E}\left[\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y(K+1)\\ \times\prod_{t=k}^{K}\exp\left\{-\gamma_t\left[\bar{A}(t),\bar{M}(t),\underline{m}(t+1)=\underline{0}(t+1),\bar{L}(t);\psi\right]\right\}\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_{t+1}\left[\bar{M}(t+1),\bar{A}(t),\bar{L}(t+1);\theta\right]\right\}|Y(K)=0\end{array}\right)\\ \times\Pr\left(Y(K)=0\,|Y(K-1)=0\right)\\ +\sum_{s=k}^{K-1}\left[\begin{array}{l}\mathrm{E}\left(\begin{array}{l}Y(s+1)\\ \times\prod_{t=k}^{K}\exp\left\{-\gamma_t\left[\bar{A}(t),\bar{M}(t),\underline{m}(t+1)=\underline{0}(t+1),\bar{L}(t);\psi\right]\right\}\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_{t+1}\left[\bar{M}(t+1),\bar{A}(t),\bar{L}(t+1);\theta\right]\right\}|Y(s+1)=1\end{array}\right)\\ \times\Pr\left(Y(s+1)=1\,|Y(s)=0\right)\end{array}\right]\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\right.\end{array}\right]$$

$$=\mathrm{E}\left[\begin{array}{l}Y(K+1)\prod_{t=k}^{K}\exp\left\{-\gamma_t\left[\bar{A}(t),\bar{M}(t),\underline{m}(t+1)=\underline{0}(t+1),\bar{L}(t);\psi\right]\right\}\\ \times\prod_{t=k}^{K}\exp\left\{-\delta_{t+1}\left[\bar{M}(t+1),\bar{A}(t),\bar{L}(t+1);\theta\right]\right\}\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k-1)=\bar{m}(k-1),Y(k)=0\right.\end{array}\right]$$

$$=\mathrm{E}\left[\begin{array}{l}H_{k+1}(\theta)\prod_{t=k}^{K}\exp\left\{-\gamma_t\left[\bar{A}(t),\bar{M}(t),\underline{m}(t+1)=\underline{0}(t+1),\bar{L}(t);\psi\right]\right\}\\ \left|\bar{L}(k),\bar{A}(k-1)=\bar{a}(k-1),\bar{M}(k)=\bar{m}(k),Y(k)=0\right.\end{array}\right]$$

and result (6) is shown. Because $\bar{A}(k-1)=\bar{a}(k-1)=g_A(k-1)$ and $\bar{M}(k)=\bar{m}(k)=g_M(k)$ in the aforementioned equation, we can derive the g-estimating equation (8) by conditional exchangeability (3).

Appendix C: Sequential g-estimation in structural nested cumulative failure time models

Assume SNCFTMs $\gamma_{s,k}[\bar{a}(k),\bar{m},\bar{L}(k);\psi]$ and $\delta_{s,k}[\bar{m}(k),\bar{a}(k-1),\bar{L}(k);\theta]$ that model the outcome at s $(>k)$ instead of $K+1$ in the SNMMs (1) and (2). We can obtain g-estimates of parameters by solving the following estimating functions.

(1) Estimate θ in $\delta_{s,k}[\cdot]$ by $\sum_{i=1}^{n} U_{1i}(\theta) = 0$, where

$$U_{1i}(\theta) = \sum_{k=1}^{K} [1 - Y_i(k)] \sum_{s=k+1}^{K} \left\{ M_i(k) - \mu_k \left[\bar{L}_i(k), \bar{A}_i(k-1), \bar{M}_i(k-1); \hat{\alpha} \right] \right\} Q_{ik} H_{i,s,k}(\theta),$$

$$H_{i,s,k}(\theta) = Y_i(s) \exp \left\{ - \sum_{t=k}^{s-1} \delta_{s,t} \left[\bar{M}_i(t), \bar{A}_i(t-1), \bar{L}_i(t); \theta \right] \right\} \text{ for all } s \text{ and } k (s > k);$$

(2) Estimate ψ in $\gamma_{s,k}[\cdot]$ by $\sum_{i=1}^{n} U_{2i}(\psi, \hat{\theta}) = 0$, where

$$U_{2i}(\psi, \hat{\theta}) = \sum_{k=1}^{K} [1 - Y_i(k)] \sum_{s=k+1}^{K} \left\{ A_i(k) - \pi_k \left[\bar{A}_i(k-1), \bar{L}_i(k), \bar{M}_i(k); \hat{\beta} \right] \right\} Q^*_{ik} H^*_{i,s,k}(\psi, \hat{\theta})$$

$$H^*_{i,s,k}(\psi, \hat{\theta}) = H_{i,s,k+1}(\hat{\theta}) \exp \left\{ - \sum_{t=k}^{s-1} \gamma_{s,t} \left[\bar{A}_i(t), \bar{M}_i(t), \underline{m}(t+1) = \underline{0}(t+1), \bar{L}_i(t); \psi \right] \right\}$$

for all s and $k (s > k)$.

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References

1. Pearl J. Direct and indirect effects. In *Proceedings of the Seventeenth Conference on Uncertainty in Artificial Intelligence*. Morgan Kaufmann: San Francisco, CA, 2001; 411–420.
2. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Jr., Stone NJ. Coordinating committee of the national cholesterol education program. Implications of recent clinical trials for the national cholesterol education program adult treatment panel III guidelines. *Circulation* 2004; **110**:227–239.
3. De Backer G, Ambrosioni E, Borch-Johnsen K, Brotons C, Cifkova R, Dallongeville J, Ebrahim S, Faergeman O, Graham I, Mancia G, Manger Cats V, Orth-Gomér K, Perk J, Pyörälä K, Rodicio JL, Sans S, Sansoy V, Sechtem U, Silber S, Thomsen T, Wood D. For the third joint task force of european and other societies on cardiovascular disease prevention in clinical practice. European guidelines on cardiovascular disease prevention in clinical practice: Third joint task force of european and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of eight societies and by invited experts). *European Heart Journal* 2003; **24**:1601–1610.
4. Robins JM, Greenland S. Identifiability and exchangeability for direct and indirect effects. *Epidemiology* 1992; **3**:143–155.
5. Cole SR, Hernán MA. Fallibility in estimating direct effects. *Epidemiology* 2002; **31**:163–165.
6. Petersen ML, Sinisi SE, van der Laan MJ. Estimation of direct causal effects. *Epidemiology* 2006; **17**:276–284.
7. Richiardi L, Bellocco R, Zugna D. Mediation analysis in epidemiology: methods, interpretation and bias. *International Journal of Epidemiology* 2013; **42**:1511–1519.
8. VanderWeele TJ, Vansteelandt S. Conceptual issues concerning mediation, interventions and composition. *Statistics and Its Interface* 2009; **2**:457–468.
9. Robins JM. The control of confounding by intermediate variables. *Statistics in Medicine* 1989; **8**:679–701.
10. Robins JM. Semantics of causal DAG models and the identification of direct and indirect effects. In *Highly Structured Stochastic Systems*, Hjort N, Green P, Richardson S (eds). Oxford University Press: Oxford, 2003; 70–81.
11. Robins JM. Association, causation, and marginal structural models. *Synthese* 1999; **121**:151–179.
12. Robins JM. Testing and estimation of direct effects by reparameterizing directed acyclic graphs with structural nested models. In *Computation, Causation, and Discovery*, Glymour C, Cooper GF (eds). AAAI Press/The MIT Press: Menlo Park, CA, Cambridge, MA, 1999; 349–405.
13. VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. *Epidemiology* 2009; **20**:18–26.
14. Rosenblum M, Jewell NP, van der Laan M, Shiboski S, van der Straten A, Padian N. Analysing direct effects in randomized trials with secondary interventions: an application to human immunodeficiency virus prevention trials. *Journal of Royal Statistical Society Series A* 2009; **172**:443–465.
15. Oba K, Sato T, Ogihara T, Saruta T, Nakao K. How to use marginal structural models in randomized trials to estimate the natural direct and indirect effects of therapies mediated by causal intermediates. *Clinical Trials* 2011; **8**:277–287.
16. Goetgeluk S, Vansteelandt S, Goetghebeur E. Estimation of controlled direct effects. *Journal of Royal Statistical Society Series B* 2008; **70**:1049–1066.
17. Vansteelandt S. Estimating direct effects in cohort and case-control studies. *Epidemiology* 2009; **20**:851–860.

18. Vansteelandt S. Estimation of controlled direct effects on a dichotomous outcome using logistic structural direct effect models. *Biometrika* 2010; **97**:921–934.
19. Robins JM, Hernán MA. Estimation of the causal effects of time-varying exposures. In *Longitudinal Data Analysis*, Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G (eds). Chapman and Hall/CRC Press: New York, 2008; 553–599.
20. Robins JM, Hernán MA, Siebert U. Effects of multiple interventions. In *Comparative Quantification of Health Risks: Global and Regional Burden of Disease Attributable to Selected Major Risk Factors*, Ezzati M, Lopez AD, Rodgers A, Murray CJL (eds). World Health Organization: Geneva, 2004; 2191–2230.
21. Taubman SL, Robins JM, Mittleman MA, Hernán MA. Intervening on risk factors for coronary heart disease: an application of the parametric g-formula. *International Journal of Epidemiology* 2009; **38**:1599–1611.
22. Young JG, Cain LE, Robins JM, O'Reilly EJ, Hernán MA. Comparative effectiveness of dynamic treatment regimes: an application of the parametric gformula. *Statistics in Biosciences* 2011; **3**:119–143.
23. Pearl J. *Causality: Models, Reasoning and Inference*, 2nd edition. Cambridge University Press: Cambridge, UK, 2009.
24. Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study Group. Design and baseline characteristics of a study of primary prevention of coronary events with pravastatin among Japanese with mildly elevated cholesterol levels. *Circulation Journal* 2004; **68**:860–867.
25. Nakamura H, Arakawa K, Itakura H, Kitabatake A, Goto Y, Toyota T, Nakaya N, Nishimoto S, Muranaka M, Yamamoto A, Mizuno K, Ohashi Y, MEGA Study Group. Primary prevention of cardiovascular disease with pravastatin in Japan (MEGA Study): a prospective randomized controlled trial. *Lancet* 2006; **368**:1155–1163.
26. Tanaka Y, Matsuyama Y, Ohashi Y. Estimation of treatment effect adjusting for treatment changes using the intensity score method: application to a large primary prevention study for coronary events (MEGA Study). *Statistics in Medicine* 2008; **27**:1718–1733.
27. Robins JM, Richardson TS. Alternative graphical causal models and the identification of direct effects. In *Causality and Psychopathology: Finding the Determinants of Disorders and Their Cures*, Shrout P, Keyes KM, Ornstein K (eds). Oxford University Press: New York, 2010; 103–158.
28. Robins JM. Structural nested failure time models. In *The Encyclopedia of Biostatistics*, Armitage P, Colton T (eds). John Wiley & Sons: Chichester, UK, 1998; 4372–4389.
29. Robins JM, Greenland S. Adjusting for differential rates of prophylaxis therapy for PCP in high- versus low-dose AZT treatment arms in an AIDS randomized trial. *Journal of the American Statistical Association* 1994; **89**:737–749.
30. Young JG, Hernán MA, Picciotto S, Robins JM. Relation between three classes of structural models for the effect of a time-varying exposure on survival. *Lifetime Data Analysis* 2010; **16**:71–84.
31. Picciotto S, Hernán MA, Page JH, Young JG, Robins JM. Structural nested cumulative failure time models to estimate the effects of interventions. *Journal of the American Statistical Association* 2012; **107**:886–900.
32. Robins JM. Causal inference from complex longitudinal data. In *Latent Variable Modeling and Applications to Causality*, Berkane M (ed.), Lecture Notes in Statistics (120). Springer Verlag: NY, 1998; 69–117.
33. Robins JM, Blevins D, Ritter G, Wulfsohn M. G-estimation of the effect of prophylaxis therapy for Pneumocystis carinii pneumonia on the survival of AIDS patients. *Epidemiology* 1992; **3**:319–336.
34. Robins JM. Correcting for non-compliance in randomized trials using structural nested mean models. *Communications in Statistics—Theory and Methods* 1994; **23**:2379–2412.
35. Yoshida M, Matsuyama Y, Ohashi Y, MEGA Study Group. Estimation of treatment effect adjusting for dependent censoring using the IPCW method: an application to a large primary prevention study for coronary events (MEGA Study). *Clinical Trials* 2007; **4**:318–328.
36. Tan Z. Nonparametric likelihood and doubly robust estimating equations for marginal and nested structural models. *Canadian Journal of Statistics* 2010; **38**:609–632.
37. Cain LE, Robins JM, Lanoy E, Logan R, Costagliola D, Hernán MA. When to start treatment? A systematic approach to the comparison of dynamic regimes using observational data. *International Journal of Biostatistics* 2010; **6**:Article 18. DOI: 10.2202/1557-4679.1212.

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