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SENSITIVITY ANALYSIS FOR UNMEASURED CONFOUNDING IN COARSE STRUCTURAL NESTED MEAN MODELS

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Abstract

Coarse Structural Nested Mean Models (SNMMs, Robins (2000)) and G-estimation can be used to estimate the causal effect of a time-varying treatment from longitudinal observational studies. However, they rely on an untestable assumption of no unmeasured confounding. In the presence of unmeasured confounders, the unobserved potential outcomes are not missing at random, and standard G-estimation leads to biased effect estimates. To remedy this, we investigate the sensitivity of G-estimators of coarse SNMMs to unmeasured confounding, assuming a nonidentifiable bias function which quantifies the impact of unmeasured confounding on the average potential outcome. We present adjusted G-estimators of coarse SNMM parameters and prove their consistency, under the bias modeling for unmeasured confounding. We apply this to a sensitivity analysis for the effect of the ART initiation time on the mean CD4 count at year 2 after infection in HIV-positive patients, based on the prospective Acute and Early Disease Research Program.

Keywords

Censoring; confounding by indication; estimating equations; HIV/AIDS research; non-ignorable; sequential randomization

1. Introduction

Randomized control trials have been regarded as the gold standard for treatment comparison; however, they may not be feasible due to ethical issues, cost restrictions, implementation difficulty, etcetera. In such cases, observational studies can be useful. Since individuals are not randomly assigned to treatments, the observed association between treatment and outcome may be due to confounders that predict both treatment assignment and outcome. Therefore, it is important to control for all the confounders in order to obtain a valid causal conclusion about the treatment effect.

We consider the potential outcomes framework (Rubin (1974); Robins et al. (1992)). This has been commonly adopted in the causal inference literature. For illustration, consider a single-time-point setting where we have pre-treatment variables L, a binary treatment A with

0 indicating the control treatment and 1 indicating the active treatment, and lastly an outcome at the end of the study, Y. In this setting, each patient has two potential outcomes: $Y^{(0)}$, the outcome that would be realized if the patient received the control treatment, and $Y^{(1)}$, the outcome that would be realized if the patient received the active treatment. We assume that the observed outcome is equal to the potential outcome under the actual treatment, $Y = Y^{(A)}$ (the consistency assumption, Rubin (1974)). Therefore, causal inference can be conceptualized as a missing data problem in which only one potential outcome is observed for each patient. Rubin (1974) described the condition for estimating average causal effects in this setting, which assumes that there is no unmeasured confounders,

$$Y^{(a)} \coprod A \mid L, \quad (1.1)$$

for $a = 0, 1$. Under (1.1), the potential outcomes are missing at random (Rubin (1976)) and selection bias can be removed by adjusting for the measured covariates. However, if there are unmeasured confounders, potential outcomes are not missing at random conditional on the measured covariates, which renders the effect estimates unidentifiable.

For observational studies with a time-varying treatment, Robins (1986; 1987) established the conditions for estimating causal effects, and proposed two classes of models: Marginal Structural Models (MSMs, Robins (2000)) and SNMMs (Robins (1994, 2000); Lok et al. (2004); Lok, Hérnan and Robins (2007)), which adjust for selection bias due to measured time-varying confounders. In a recent assessment of the dependence of the effect of ART on its initiation time, Lok and DeGruttola (2012) developed a new class of coarse SNMMs and applied it to the observational AIEDRP (Acute Infection and Early Disease Research Program) database. The validity of G-estimation of the SNMMs analyses relies on two key assumptions: (i) the treatment effect model is well-specified, and (ii) there are no unmeasured treatment-outcome confounders. In practice, both assumptions are rather strong and can be violated. Yang and Lok (2016) developed a goodness-of-fit test procedure to assess the model fit (assumption (i)). This paper addresses sensitivity to unmeasured confounding (assumption (ii)).

The existing literature on sensitivity analyses to unmeasured confounders is large, including Schlesselman (1978), Lin, Psaty and Kronmal (1998), Greenland (2003, 2005), McCandless, Gustafson and Levy (2007), Cornfield et al. (2009), and Rosenbaum (2009). Cornfield et al. (2009) used sensitivity analyses formally to assess the association between smoking and lung cancer; Rosenbaum (2009) has done extensive modeling of how unmeasured confounders affect the treatment assignment and outcome; and McCandless, Gustafson and Levy (2007) proposed a Bayesian approach to conducting sensitivity analyses where the prior distribution models beliefs about unknown and unmeasured confounding. Many existing methods are limited to simple settings, e.g., most of these works consider settings with a single time-point treatment, or rely on external sources of information on the unmeasured confounders. In a longitudinal setting with time-dependent treatments, the literature is scarce. The exceptions include Robins, Rotnitzky and Scharfstein (2000) and Brumback et al. (2004). Brumback et al. (2004) implemented a sensitivity analysis to unmeasured confounding of inverse-probability-of-treatment-weighting estimators for

MSMs. SNMMs have more desirable features than MSMs (Robins (2000)). For example, SNMMs do not require the positivity assumption which assumes the probability of all patients receiving each treatment regimen is positivity, which may be questionable in practice; SNMMs can handle continuous-valued treatments, but MSMs cannot; SNMMs are able to model time-varying interaction between covariates and treatment in the outcome model. Despite these advantages, their applications in practice are still limited (Vansteelandt and Joffe (2014)). We aim to provide a suitable methodology to deal with unmeasured confounding for SNMMs.

As in the single-time-point setting, in the presence of unmeasured confounders, the unobserved potential outcomes are not missing at random, and standard G-estimation lead to biased effect estimates. We investigate the sensitivity of G-estimation of coarse SNMMs to unmeasured confounding, assuming a nonidentifiable bias function quantifying the impact of unmeasured confounding on the average potential outcome. We propose adjusted G-estimators of coarse SNMMs parameters, and prove their consistency under the bias modeling for unmeasured confounding. In Section 2, we present a motivating data set and the coarse SNMMs analysis. In Section 3, we present the sensitivity analysis for coarse SNMMs in a time-varying treatment setting. In Section 4, we present the inverse-probability-of-censoring-weighting technique to accommodate patients loss to follow up. In Section 5, we apply the proposed method to the motivating data set. Section 6 concludes.

2. Coarse Structural Nested Mean Models

2.1. The AIEDRP dataset

ART (Antiretroviral Treatment) is a standard initial treatment for HIV-positive patients, and has considerably reduced the morbidity and mortality in them. However, there is no strong evidence to support when to start ART in patients in the acute and early stages of infection. For this investigation, we use the observational AIEDRP (Acute Infection and Early Disease Research Program), which consists of 1762 HIV-positive patients diagnosed during acute and early infection (Hecht et al (2006)). Dates of infection were estimated based on a stepwise algorithm using clinical and laboratory data (Hecht et al (2006); Smith et al. (2006)).

Lok and DeGruttola (2012) explored this data set and argued that the data show time-varying confounding by indication, and applied coarse SNMMs to estimate how the time between infection and ART initiation affects the effect of one year of ART on immune reconstitution as measured by CD4 count. They adjusted for selection bias due to observed time-varying confounders. Their analysis showed that ART is beneficial in acute and early infection, with a possibly increased beneficial effect of earlier ART initiation. Although several measured confounders were censored, including age, gender, race, injection drug use, CD4 count, and viral load, the adjusted effect estimate may be biased due to unmeasured confounders. For example, psychosocial factors (Villes et al. (2007)) and comorbidities (Abara et al. (2014)) are important confounders of the association between the ART initiation time and the CD4 count outcome. These confounders were not available.

We estimate the averaged causal relationship between the ART initiation time and the mean CD4 counts two years after infection. We adjust for both measured confounders and possibly unmeasured confounding. To do this, we use sensitivity analyses to estimate the potential impact of unmeasured confounders on the estimated causal parameters.

2.2. Data structure

Suppose all participants, in a random sample of size n, are followed monthly at months 0, …, $K+1$, where 0 is the estimated date of infection, and $K+1$ is the last month of interest (month 24 in our application). For each individual, we observe a treatment regimen (A_0, …, A_K) with A_k the treatment determined at month k, and a covariate process (L_0, …, L_{K+1}). $A_k = 1$ if the treatment is started at month k and 0 otherwise, and L_k is a set of observed covariates at month k, which is measured after A_{k-1} and before A_k. The data are represented as n i.i.d. realizations of $\left(L_0, A_0, L_1, A_1, \ldots, L_K, A_K, L_{K+1}\right) = \left(\bar{A}_K, \bar{L}_{K+1}\right)$, where we use overbars to denote the histories of time-dependent treatments and covariates. and for notational simplicity we drop the subscript i for patients. We denote the outcome of interest by Y and we have $Y = L_{K+1}$, the CD4 count measured at the end of the study. We assume that treatment is monotone in the sense that once the treatment is initiated, it never stops under follow-up. Thus, the treatment regimen is determined by the treatment initiation time m. Let T be the actual month of treatment initiation. If treatment was never initiated during the study period, let $T = \infty$.

2.3. The potential outcomes

Let $Y^{(\infty)}$ be the outcome CD4 count at month $K+1$ after infection had the patient never initiated treatment. This is a counterfactual outcome. It is only observed if the patient did not initiate the treatment. Let $Y^{(m)}$ be the CD4 count at month $K+1$ had the patient started treatment at month m. Under this potential outcome framework, we need the consistency assumption, which links the counterfactual data to the observed data, $Y = Y^{(T)}$.

2.4. Coarse SNMMs

Following Robins (2000) and Lok and DeGruttola (2012), we define the treatment effect model as conditional treatment contrasts, for $0 \le m \le K$,

$$\gamma_m\left(\bar{l}_m\right) = E\left(Y^{(m)} - Y^{(\infty)} \mid \bar{L}_m = \bar{l}_m, T = m\right).$$

We assume a parametric model for $\gamma, \gamma_{m,\psi}\left(\bar{l}_m\right) = \left(\psi_0 + \psi_1 m\right)\left(K + 1 - m\right)$, since arguably the average treatment effect is proportional to the treatment duration ($K+1-m$), and the coefficients can depend on the treatment initiation time m. If $\psi_0 + \psi_1 m > 0$ and $\psi_1 < 0$, the treatment is beneficial with increased gain if it was started earlier.

2.5. The conditional probabilities of treatment initiation

Unlike in randomized control trials, the treatment assignment mechanism is unknown in observational studies. We assume that we have a correctly specified parametric model for treatment initiation given the observed covariate history:

$$Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) = Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \alpha\right). \quad (2.1)$$

This could be a pooled logistic regression model. Since treatment is monotone, $Pr\left(A_m = 1 \mid \bar{L}_m, A_{m-1} = 1\right) = 1$.

2.6. G-estimation under no unmeasured confounding

The parameters in γ_ψ cannot be estimated by regression methods since the dependent variable involves the potential outcome. For parameter identification, we require the assumption of no unmeasured confounding (Robins et al. (1992); Robins (1998a,b); Robins (2000)): for $0 \leq m \leq K$,

$$A_m \coprod Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1}, \quad (2.2)$$

where $A \coprod B$ means "A is independent of B" (Dawid (1979)).

To facilitate estimation, take

$$H_\psi = Y - \gamma_{T,\psi}\left(\bar{L}_T\right), \quad (2.3)$$

which mimics the potential outcome $Y^{(\infty)}$ since by blipping o the average treatment effect from the observed outcome, we obtain a quantity that has the same conditional distribution as the outcome that would have been observed (Lok and DeGruttola (2012)):

$$E\left(H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) = E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right), \quad (2.4)$$

where by convention, $E\left(\cdot \mid \bar{L}_0, \bar{A}_{-1} = \bar{0}, A_0\right) = E\left(\cdot \mid \bar{L}_0, A_0\right)$. (2.2) does not require (2.4). Together, (2.2) and (2.4) imply that

$$E\left(H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) = E\left(H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right). \quad (2.5)$$

G-estimators solves unbiased estimating equations constructed based on (2.5) (Robins et al. (1992); Robins (1994, 2000); Lok and DeGruttola (2012)).

3. Evaluating the Impact of Unmeasured Confounding

Assumption (2.2) cannot be tested empirically from the data. If it fails, the treatment assignment is non-ignorable or, equivalently, there is selection bias on unmeasured confounders. For $0 \leq m \leq K$, define the selection bias function due to unmeasured confounders (Robins, Rotnitzky and Scharfstein (2000)) as

$$g\left(\bar{L}_m\right) = E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right).$$

If A_m is given not just based on $((\bar{L}_m, \bar{A}_{m-1}))$, this represents the average difference in the potential outcome $Y^{(\infty)}$ between those with $A_m = 1$ and those with $A_m = 0$ for the subgroup of patients with $\bar{L}_m$ and $\bar{A}_{m-1} = \bar{0}$. Thus, the selection bias function measures the impact of unmeasured confounders of A_m on the difference in the potential outcome between the treated and untreated patients at each month, given the past treatment and covariate history. Under the assumption of No Unmeasured Confounding, $g\left(\bar{L}_m\right) = 0$.

The observed data carry no information about selection bias on unmeasured confounders. Its presence, direction, and magnitude are important for modeling, but the data at hand cannot determine them. Therefore, the selection bias on unmeasured confounders should be pre-specified based on the modeler's belief, and its magnitude should be explored over a wide range in a sensitivity analysis. Let $g\left(\bar{L}_m; \eta\right)$ be a correct model of $g\left(\bar{L}_m\right)$, where η is regarded as the sensitivity parameter. We parametrize g so that $g\left(\bar{L}_m; 0\right) = 0$, $\eta = 0$ indicating the absence of unmeasured confounders. The functional form of the nuisance models can be selected on the basis of the observed data, as well as the literature and subject knowledge specific to the application setting. Later, we provide a more specific illustration in the context of our example.

Equation (2.5) is the key for estimation under the assumption of No Unmeasured Confounders. Since this assumption may not hold, (2.5) is not necessarily true. We would like to adjust the previously defined mimicking outcome H_ψ so that a similar relationship to (2.5) holds for the adjustments.

Definition 1 (Adjustments). *For* $0 \leq m \leq K$,

$$H^a_{m,(\psi,\eta)} = H_\psi - \sum_{k=m}^{K-1} Pr\left(1 - A_k \mid \bar{L}_k, \bar{A}_{k-1} = \bar{0}\right)\left(2A_k - 1\right)g\left(\bar{L}_k; \eta\right)1_{\bar{A}_{k-1} = \bar{0}}. \quad (3.1)$$

The superscript "a" stands for the adjustment. The proof of the following theorem is presented in the Appendix, showing that (3.1) replaces the role of (2.5) for estimation.

Theorem 1. *Under the Consistency assumption, if* γ_ψ *is a correctly specified model for the treatment effect* γ, $g\left(\bar{L}_m, A_m; \eta\right)$ *is a correctly specified selection bias function due to unmeasured confounding with pre-determined value for* η*; for* H^a_m *in* (3.1), *and* $0 \leq l \leq m \leq K$,

$$E\left(H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) = E\left(H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right). \quad (3.2)$$

Theorem 2 (Unbiased Estimating Equation Under Unmeasured Confounding). *Under the Consistency assumption, if* γ_ψ *is a correct model for the treatment effect* γ, $g(\bar{L}_m, \bar{A}_m; \eta)$ *is a correctly-specified selection bias function due to unmeasured confounding with pre-determined value for* η*; for* H^a_m *in* (3.1), *the estimating function*

$$U(\psi) = P_n G_{(\psi,\eta,q)}, \quad (3.3)$$

with

$$\begin{aligned} G_{(\psi,\eta,q)} = & \sum_{m=0}^{K} q(\bar{L}_m)\left\{H^a_{m,(\psi,\eta)} - E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\} \\ & \times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\} 1_{\bar{A}_{m-1} = \bar{0}}, \end{aligned} \quad (3.4)$$

is an unbiased estimating equation for any $q(\bar{L}_m)$.

The proof of Theorem 2 is given in the Appendix. It leads to a large number of unbiased estimating equations for ψ. To facilitate optimal estimation, we identify the optimal set of q, q^{opt}, that satisfies

$$E\left\{\frac{\partial G_{(\psi,\eta,q)}}{\partial \psi^T}\right\} = E\left\{G_{(\psi,\eta,q)} G^T_{(\psi,\eta,q^{\text{opt}})}\right\} \quad (3.5)$$

for any q. With this q^{opt}, the resulting estimator from (3.3) is most efficient among the class (Newey and McFadden (1994)).

Theorem 3 (Optimal estimation). *If for* $0 \le l \le m \le K$, $E\left\{H^a_{m,(\psi,\eta)} H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_m\right\}$ *does not depend on* A_m, *then*,

$$\begin{aligned} q^{\text{opt}}(\bar{L}_m)^T = & \left\{Var\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}^{-1} \\ & \times \left\{E\left(\frac{\partial}{\partial \psi^T} H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = 0,\ A_m = 1\right) - E\left(\frac{\partial}{\partial \psi^T} H_\psi \mid \bar{L}_m, \bar{A}_m = \bar{0}\right)\right\}, \end{aligned} \quad (3.6)$$

where H_ψ *is defined in* (2.3) *and* $H^a_{m,(\psi,\eta)}$ *is defined in* (3.1).

Proof of Theorem 3 is given in the Appendix. The assumption here is an organic extension of (3.2). It affects not the consistency of the estimator, but the effciency.

Remark 1. Estimating equations (3.3) with (3.6) are not well posed for estimation since they involve unknown population quantities through $E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)$, $E\left(\partial H_\psi \big/ \partial\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right)$, and $Var\left(H^q_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)$. If H_ψ is linear in $\psi, E\left(\partial H_\psi \big/ \partial\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(\partial H_\psi \big/ \partial\psi \mid \bar{L}_m, \bar{A}_m = \bar{0}\right)$ does not depend on ψ; however, one still needs the true unknown distribution to compute the conditional expectations. To obtain estimators with good efficiency properties we approximate the unknown functions with estimators of them under some working model. We propose the following algorithm: (i) obtain a consistent preliminary estimator of ψ, denote it by $\hat{\psi}_p$ (ii) approximate $E\left(\partial H_\psi \big/ \partial\psi \mid \bar{L}_m, \bar{A}_m\right)$ by regression models $E\left(\partial H_\psi \big/ \partial\psi \mid \bar{L}_m, \bar{A}_m; \hat{\xi}\right)$, where $\hat{\xi}$ is the estimated parameters in the regression models; (iii) approximate $E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)$ by regression outcome models $E\left(H^a_{m,\left(\hat{\psi}_p,\eta\right)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \hat{\xi}\right)$; and (iv) replace nuisance regression outcome models with estimators of them under the regression models, and solve the resulting estimating equation for ψ. The resulting estimator is locally optimal under these nuisance regression outcome models. The 95% bootstrap confidence intervals of $\hat{\psi}$ can be constructed using the 2.5% and 97.5% percentiles of 500 bootstrap realizations of $\hat{\psi}$.

Remark 2 (Double robustness). In the estimating equations (3.3), the true treatment initiation model is unknown. We replace it with $Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \hat{\alpha}\right)$, where $\hat{\alpha}$ is the maximum likelihood estimator of α. The resulting estimator of ψ solves (3.3) with this replacement equivalent to the estimator of ψ solving (3.3) and the estimating equation for α. Although (3.3) depends on two sets of nuisance models, $E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \xi\right)$ and $Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \alpha\right)$, it does not require both specifications to be correct, which renders the estimator doubly robust. See the Appendix for the proof.

4. Censoring

Because of the time-dependent nature of longitudinal data, the data are often subject to censoring due to loss to follow up. When the censoring mechanism is informative in the sense that censoring may depend on time-varying covariates, e.g. sicker patients drop out of the study with higher probability than healthier patients, the patients remaining in the study are a biased sample of the full population.

Following Robins, Rotnitzky and Zhao (1995) and Lok and DeGruttola (2012), we use inverse probability of censoring weighting (IPCW) to accommodate patients lost to follow up. We assume that the censoring process is ignorable in the sense that censoring only depends on the past observed covariate history but not the future unobserved covariates and outcomes. Its heuristic idea is to redistribute the weight of censored patients among the "similar" remaining uncensored patients. Let C_m be the censoring indicator at month m: $C_m = 1$ if the patient is censored at month m and 0 otherwise. We assume a parametric model for the censoring process given the observed covariates history as

$Pr\left(C_{m+1}=0 \mid \bar{L}_m, \bar{A}_{m-1}, C_m=0\right)=Pr\left(C_{m+1}=0 \mid \bar{L}_m, \bar{A}_{m-1}, C_m=0;\beta\right)$, e.g. a pooled logistic regression model.

Define the IPCW version of estimating functions as

$$G^{\text{IPCW}}_{(\psi,\eta,q)}=\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{H^a_{m,(\psi,\eta)}-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\} \times\left\{A_m-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\hat{\alpha}\right)\right\} 1_{\bar{C}_{K+1}=\bar{0}} W_m,$$

with eqnarray $W_m=1\Big/\left\{\prod_{p=m+1}^{K+1} Pr\left(C_p=0 \mid \bar{L}_{p-1}, \bar{A}_{p-1}, \bar{C}_{p-1}=\bar{0};\hat{\beta}\right)\right\}$. Here, $P_n G^{\text{IPCW}}_{(\psi,\eta,q)}=0$ is an unbiased estimating equation if the censoring model is correct.

5. Application to Initiating ART in HIV-Positive Patients

We conducted a sensitivity analysis of estimating the effect of ART initiation time on mean CD4 count at year 2 after estimated date of infection in HIV-positive patients, based on the AIEDRP database described in Section .

We considered the true treatment effect model to be $\gamma_{m,\psi}\left(\bar{l}_m\right)=\left(\psi_1+\psi_2 m\right)\left(K+1-m\right)$. Yang and Lok (2016) showed that this model may be adequate using an overidentification restrictions test. In the estimation procedure, the treatment initiation model and the censoring model were fitted by pooled logistic regression models, and the nuisance regression outcome models were fitted by linear models, adjusting for a rich set of covariates based on the HIV literature and clinical knowledge (Lok and Griner (2014)).

In the sensitivity analysis, we considered three scenarios for specification of $g\left(\bar{L}_m;\eta\right)$: (i) η_0; (ii) $\eta_0+\eta_1\times m$; and (iii) $\eta_0+\eta_1\times CD4_m$. Table 1 shows the results of the sensitivity analysis. In scenario (i), $g\left(\bar{L}_m;\eta\right)=\eta_0$ with $\eta_0\in\{-100,-75,\ldots,75,100\}$. For interpretation, for example with $\eta_0<0$, the untreated individuals tend to be healthier than the treated at month m, uniformly across months, even after controlling for measured confounders. As the magnitude of η increases, $\hat{\psi}_1$ and $\hat{\psi}_2$ increase, which makes sense since the more the uncontrolled confounding is assumed, the further the adjusted estimator increases. Moreover, the confidence intervals of $\hat{\psi}_1$ and $\hat{\psi}_2$ are larger with larger η, which suggests that more unmeasured confounding would further obscure the treatment effect. In scenario (ii), $g\left(\bar{L}_m;\eta\right)=\eta_0+\eta_1\times m$, the effect of uncontrolled confounding changes linearly with m. We considered $\eta_0\in\{-100,-75,\ldots,75,100\}$ and $\eta_2\in\{-5,5\}$. For interpretation, consider for example $g\left(\bar{L}_m;\eta\right)=-100-5m$, the untreated individuals tend to be healthier than the treated at month m, and the effect of uncontrolled confounding increases with m. For $\eta_2=5$, as η_1 increases from −100 to 100, $\hat{\psi}_1$ and $\hat{\psi}_2$ decrease, and $\hat{\psi}_2$ remains negative but statistically insignificant. For $\eta_2=-5$, as η_1 increases from −100 to 100, $\hat{\psi}_1$ and $\hat{\psi}_2$ decrease, and $\hat{\psi}_2$

remains positive but statistically insignificant. In scenarios (iii), $g(\bar{L}_m;\eta) = \eta_0 + \eta_1 \times CD4_m$, the effect of uncontrolled confounding changes linearly with $CD4$, we considered $\eta_0 \in \{-100, -75, \ldots, 75, 100\}$ and $\eta_2 \in \{-0.02, 0.02\}$. As η_1 increases from −100 to 100, $\hat{\psi}_1$ and $\hat{\psi}_2$ decrease. $\hat{\psi}_2$ remains negative; however, the 95% bootstrap confidence interval of $\hat{\psi}_2$ remains statistically insignificant. In summary, we conducted a comprehensive sensitivity analysis for the AIEDRP study considering different forms of the selection bias function and different values of the coefficients. After accounting for possible uncontrolled confounding, treatment is beneficial under a wide range of plausible scenarios, and the effect of the initiation time is insignificant.

6. Discussion

We have introduced a new sensitivity analysis method that uses modified G-estimators to assess the effect of possible uncontrolled confounding in longitudinal observational studies. If strong prior information is available, appropriate functional forms for the selection bias function due to unmeasured confounding can be directly imposed. We suggest varying the coefficients over a set of plausible values, determined on the basis of observed data, literature, and subject matter knowledge. As with its application to HIV research, the new method can easily be adopted to provide valuable insight on the impact of uncontrolled confounding.

An extensive literature has assumed that there is one binary unmeasured confounder U, and the association of U and Y has been considered as the sensitivity parameter (see e.g. Schlesselman (1978) and Rosenbaum and Rubin (1983)). The advantage of this approach is that the sensitivity parameter is easy to interpret; however, this approach can be restrictive, since in practice the unmeasured confounder can be of any type and may be multi-dimensional. Modeling the association of a multivariate U with Y is not straightforward. A major advantage of our approach is that it can be used to explore sensitivity to multiple unmeasured confounders simultaneously. The connection between the two approaches has not been established. In simple cases where there is one unmeasured confounder, modeling the relationship between the unmeasured confounder and the observed variables can provide insight for specifying the selection bias function and interpreting the sensitivity parameters. In the Appendix, we explore the connection between the two approaches in the context of our application to initiating ART in HIV-positive patients. In future work, we plan to evaluate and compare the performance of the two modeling approaches under various scenarios. We will also extend the work to longitudinal settings with repeated measurements, survival data, continuous treatments, and dynamic optimal treatments.

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Appendix

Appendix A. Proof of Theorem 1

First we show that

$$\begin{aligned} &E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &= Pr\left(1 - A_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\left(2A_m - 1\right)g\left(\bar{L}_m; \eta\right) \\ &= Pr\left(1 - A_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right)\right. \\ &\quad \left. - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, 1 - A_m\right)\right\}. \end{aligned} \tag{A.1}$$

To do so, we need to show (A.1) holds for both $A_m = 0$ and 1. Consider (A.1) for $A_m = 0$,

$$\begin{aligned} LHS &= E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right) - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &= E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right) \\ &\quad - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right) Pr\left(A_m = 0 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &\quad - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &= Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \times \left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right)\right. \\ &\quad \left. - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right)\right\} = RHS. \end{aligned}$$

Consider (A.1) for $A_m = 1$,

$$\begin{aligned} LHS &= E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &= E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) \\ &\quad - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right) Pr\left(A_m = 0 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &\quad - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \\ &= Pr\left(A_m = 0 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) \times \left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right)\right. \\ &\quad \left. - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right)\right\} = RHS. \end{aligned}$$

Therefore, (A.1) follows. For $k > m$, since

$$
\begin{aligned}
&E\left\{Pr\left(1-A_k \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\left(2A_k-1\right)1_{\bar{A}_{k-1}=\bar{0}}g\left(\bar{L}_k;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m=1\right\}=0,\\
&E\left\{Pr\left(1-A_k \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\left(2A_k-1\right)1_{\bar{A}_{k-1}=\bar{0}}g\left(\bar{L}_k;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m=0\right\}\\
&=E\Big[E\left\{Pr\left(1-A_k \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\left(2A_k-1\right) \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right\}\\
&\quad\times 1_{\bar{A}_{k-1}=\bar{0}}g\left(\bar{L}_k;\eta\right) \mid \bar{L}_m, \bar{A}_m=\bar{0}\Big]\\
&=E\Big[E\Big\{Pr\left(A_k=1 \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)Pr\left(A_k=0 \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\\
&\quad+Pr\left(A_k=0 \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)Pr\left(A_k=1 \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\\
&\quad\times\left(-1\right)\Big\}1_{\bar{A}_{k-1}=\bar{0}}g\left(\bar{L}_k;\eta\right) \mid \bar{L}_m, \bar{A}_m=\bar{0}\Big]=0,
\end{aligned}
$$

we have

$$
\begin{aligned}
&E\left\{Pr\left(1-A_k \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\left(2A_k-1\right)1_{\bar{A}_{k-1}=\bar{0}}g\left(\bar{L}_k;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m\right\}\\
&=E\left\{Pr\left(1-A_k \mid \bar{L}_k, \bar{A}_{k-1}=\bar{0}\right)\left(2A_k-1\right)1_{\bar{A}_{k-1}=\bar{0}}g\left(\bar{L}_k;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right\}=0.
\end{aligned}
\tag{A.2}
$$

For $l < m$, since

$$
\begin{aligned}
&E\left\{Pr\left(1-A_l \mid \bar{L}_l, \bar{A}_{l-1}=\bar{0}\right)\left(2A_l-1\right)1_{\bar{A}_{l-1}=\bar{0}}g\left(\bar{L}_l;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m\right\}\\
&=Pr\left(A_l=0 \mid \bar{L}_l, \bar{A}_{l-1}=\bar{0}\right)\left(-1\right)1_{\bar{A}_{l-1}=\bar{0}}g\left(\bar{L}_l;\eta\right),
\end{aligned}
$$

which does not depend on A_m, we have

$$
\begin{aligned}
&E\left\{Pr\left(1-A_l \mid \bar{L}_l, \bar{A}_{l-1}=\bar{0}\right)\left(2A_l-1\right)1_{\bar{A}_{l-1}=\bar{0}}g\left(\bar{L}_l;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m\right\}\\
&=E\left\{Pr\left(1-A_l \mid \bar{L}_l, \bar{A}_{l-1}=\bar{0}\right)\left(2A_l-1\right)1_{\bar{A}_{l-1}=\bar{0}}g\left(\bar{L}_l;\eta\right) \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right\}.
\end{aligned}
\tag{A.3}
$$

Now we consider, for $l \leq m$,

$$
\begin{aligned}
&E\left(H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) \\
&= E\left(H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) - Pr\left(1 - A_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\left(2A_m - 1\right)g\left(\bar{L}_m; \eta\right) \\
&\quad - E\left\{\sum_{k=m+1}^{K-1} Pr\left(1 - A_k \mid \bar{L}_k, \bar{A}_{k-1} = \bar{0}\right)\left(2A_k - 1\right)1_{\bar{A}_{k-1} = \bar{0}}g\left(\bar{L}_k; \eta\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right\} \\
&\quad - E\left\{\sum_{k=1}^{m-1} Pr\left(1 - A_k \mid \bar{L}_k, \bar{A}_{k-1} = \bar{0}\right)\left(2A_k - 1\right)1_{\bar{A}_{k-1} = \bar{0}}g\left(\bar{L}_k; \eta\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right\} \\
&= E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) \\
&\quad + E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) - 0 \\
&= E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) - E\left\{\sum_{k=l}^{m-1} Pr\left(1 - A_k \mid \bar{L}_k, \bar{A}_{k-1} = \bar{0}\right)\left(2A_k - 1\right)\right. \\
&\quad \left. \times \; 1_{\bar{A}_{k-1} = \bar{0}}g\left(\bar{L}_k; \eta\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right\},
\end{aligned}
$$

where by convention $\sum_{k=s}^{t} X = 0$ for $t < s$, the first equality follows from the definition of $H^a_{l,(\psi,\eta)}$, and the second equality follows from equations (2.4) and (A.1), (A.2), and (A.3). Therefore, $E\left(H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right)$ does not depend on A_m and (3.2) in Theorem 1 follows.

Appendix B. Proof of Theorem 2

For each $0 \le m \le K - 1$,

$$
\begin{aligned}
&E\left[q\left(\bar{L}_m\right)\left\{H^a_{m,(\psi,\eta)} - E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}\right. \\
&\qquad \left. \times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}1_{\bar{A}_{m-1} = \bar{0}}\right] \\
&= E\left[q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) - E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}\right. \\
&\qquad \left. \times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}1_{\bar{A}_{m-1} = \bar{0}}\right] \\
&= E\left[q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) - E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}\right. \\
&\qquad \left. \times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}1_{\bar{A}_{m-1} = \bar{0}}\right] = 0,
\end{aligned}
$$

where the second equality follows from (3.2). Therefore, $E(G_{(\psi,\eta,q)}) = 0$, proving the result.

Appendix C. proof of double robustness

If $Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \theta\right)$ is correct,

$$
\begin{aligned}
&E\left\{G_{(\psi,\eta,q)}\right\}\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\right.\\
&\quad\left.\times\left\{A_m-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\right]\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\right.\\
&\quad\left.\times\left\{A_m-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\right]\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\right.\\
&\quad\left.\times\left\{E\left(A_m \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\right]\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\times\right.\\
&\quad\left.0\times 1_{\bar{A}_{m-1}=\bar{0}}\right]=0,
\end{aligned}
$$

where the second equality follows from (3.2) and the forth equality follows from the assumption that $Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)$ is correct. $E\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}$ is correct,

$$
\begin{aligned}
&E\left\{G_{(\psi,\eta,q)}\right\}\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\right.\\
&\quad\left.\times\left\{A_m-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\right]\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\right.\\
&\quad\left.\times\left\{A_m-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\right]\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\xi\right)\right\}\right.\\
&\quad\left.\times\left\{E\left(A_m \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\right]\\
&=E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\times 0\times\left\{E\left(A_m \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)-Pr\left(A_m=1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0};\theta\right)\right\}\right.\\
&\quad\left.\times 1_{\bar{A}_{m-1}=\bar{0}}\right]=0,
\end{aligned}
$$

where the second equality follows from (3.2) and the forth equality follows from the assumption that $E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \xi\right)\}$ is correct. Therefore, $G_{(\psi,\eta,q)}$ is an unbiased estimating function if either $Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \theta\right)$ is correct or $E\left(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}; \xi\right)\}$ is correct.

Appendix D. Proof of Theorem 3

The left hand side of (3.5) is

$$
\begin{aligned}
& E\left\{\frac{\partial}{\partial\psi} G_{(\psi,\eta,q)}\right\} \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{\frac{\partial}{\partial\psi} H_\psi - E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}\right. \\
&\quad \left.\times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\} 1_{\bar{A}_{m-1} = \bar{0}}\right] \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right) - E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}\right. \\
&\quad \left.\times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\} 1_{\bar{A}_{m-1} = \bar{0}}\right] \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_m = \bar{0}\right)\right\}\right. \\
&\quad \left.\times \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\}^2 1_{\bar{A}_{m-1} = \bar{0}}\right] \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)\left\{E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(\frac{\partial}{\partial\psi} H_\psi \mid \bar{L}_m, \bar{A}_m = \bar{0}\right)\right\}\right. \\
&\quad \left.\times \left\{1 - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right)\right\} Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\right) 1_{\bar{A}_{m-1} = \bar{0}}\right],
\end{aligned}
$$

where the last equality follows by applying $E(Y|A) = \{(E(Y|A = 1) - E(Y|A = 0)\}\{A - Pr(A = 1)\}$ to $E\left(\partial H_\psi \big/ \partial\psi \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\right)$. The right hand side of (3.5) is

$$
\begin{aligned}
& E\left\{G_{(\psi,\eta,q)}G^{T}_{\left(\psi,\eta,q^{\mathrm{opt}}\right)}\right\} \\
&= E\left[\sum_{m=0}^{K}\sum_{l=0}^{K} q\left(\bar{L}_m\right)\left\{H^{a}_{m,(\psi,\eta)} - E\left(H^{a}_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\}\right. \\
&\quad \times\left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\}1_{\bar{A}_{m-1}=\bar{0}} \\
&\quad \times q^{\mathrm{opt}}\left(\bar{L}_l\right)^{T}\left\{H^{a}_{l,(\psi,\eta)} - E\left(H^{a}_{l,(\psi,\eta)} \mid \bar{L}_l, \bar{A}_{l-1}=\bar{0}\right)\right\} \\
&\quad \left.\times\ \left\{A_l - Pr\left(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1}=\bar{0}\right)\right\}1_{\bar{A}_{l-1}=\bar{0}}\right] \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_m\right)^{T} Var\left(H^{a}_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}, A_m\right)^{2}\right. \\
&\quad \left.\times\ \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\}^{2}1_{\bar{A}_{m-1}=\bar{0}}\right] \qquad \text{(A.4)} \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_m\right)^{T} Var\left(H^{a}_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)^{2}\right. \\
&\quad \left.\times\ \left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\}^{2}1_{\bar{A}_{m-1}=\bar{0}}\right] \\
&= E\left(\sum_{m=0}^{K} q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_m\right)^{T} Var\left(H^{a}_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)^{2}\right. \\
&\quad \left.\times E\left[\left\{A_m - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\}^{2}1_{\bar{A}_{m-1}=\bar{0}} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right]\right) \\
&= E\left[\sum_{m=0}^{K} q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_m\right)^{T} Var\left(H^{a}_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)^{2}\ 1_{\bar{A}_{m-1}=\bar{0}}\right. \\
&\quad \left.\times\ \left\{1 - Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right\}Pr\left(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1}=\bar{0}\right)\right],
\end{aligned}
$$

where the expectations of the cross terms in the first equality are zero by the following argument. It suffices to show that for $m > l$,

$$
\begin{aligned}
E\ &\Big[q\big(\bar{L}_m\big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T E\Big(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)E\Big(H^a_{l,(\psi,\eta)} \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\\
&\times \big\{A_m - Pr\big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big)\big\}\\
&\times \Big\{A_l - Pr\Big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\Big\}1_{\bar{A}_{m-1} = \bar{0}}\Big]\\
= E\Big[&q\big(\bar{L}_m\big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T E\Big(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)E\Big(H^a_{l,(\psi,\eta)} \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\\
&\times \big\{E\big(A_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big) - Pr\big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big)\big\}\\
&\times 1_{\bar{A}_{m-1} = \bar{0}}\Big\{A_l - Pr\Big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\Big\}\Big] = 0,\\
&E\Big[q\Big(\bar{L}_m\Big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T H^a_{m,(\psi,\eta)}E\Big(H^a_{l,(\psi,\eta)} \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)1_{\bar{A}_{m-1} = \bar{0}}\\
&\times \big\{A_m - Pr\big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big)\big\}\big\{A_l - Pr\big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\big)\big\}\Big]\\
= E\Big[&q\big(\bar{L}_m\big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T E\Big(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)E\Big(H^a_{l,(\psi,\eta)} \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\\
&\times E\big(A_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big) - Pr\big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big)\big\}\\
&\times 1_{\bar{A}_{m-1} = \bar{0}}\Big\{A_l - Pr\Big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\Big\}\Big] = 0,\\
&E\Big[q\big(\bar{L}_m\big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T E\Big(\Big(H^q_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)H^a_{l,(\psi,\eta)}1_{\bar{A}_{m-1} = \bar{0}}\\
&\times \big\{A_m - Pr\big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big)\big\}\big\{A_l - Pr\big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\big)\big\}\Big]\\
= E\Big[&q\big(\bar{L}_m\big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T E\Big(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)E\Big\{H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m\Big\}\\
&\times \Big\{A_m - Pr\Big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)\Big\}1_{\bar{A}_{m-1} = \bar{0}}\Big\{A_l - Pr\Big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\Big\}\Big]\\
= E\Big[&q\big(\bar{L}_m\big)q^{\mathrm{opt}}\big(\bar{L}_l\big)^T E\Big(H^a_{m,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big)E\Big\{H^a_{l,(\psi,\eta)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\Big\}\\
&\times \big\{E\big(A_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big) - Pr\big(A_m = 1 \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}\big)\big\}\\
&\times 1_{\bar{A}_{m-1} = \bar{0}}\Big\{A_l - Pr\Big(A_l = 1 \mid \bar{L}_l, \bar{A}_{l-1} = \bar{0}\Big)\Big\}\Big] = 0,
\end{aligned}
$$

where the second equality follows from (3.2).

$$
\begin{aligned}
&E\left[q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_l\right)^T H^a_{m,(\psi,\eta)}H^a_{l,(\psi,\eta)}{}^1\bar{A}_{m-1}=\bar{0}\right.\\
&\left.\times\left\{A_m-Pr\left(A_m=1\mid\bar{L}_m,\bar{A}_{m-1}=\bar{0}\right)\right\}\left\{A_l-Pr\left(A_l=1\mid\bar{L}_l,\bar{A}_{l-1}=\bar{0}\right)\right\}\right]\\
=\;&E\left[q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_l\right)^T E\left\{H^a_{m,(\psi,\eta)}H^a_{l,(\psi,\eta)}\mid\bar{L}_m,\bar{A}_m\right\}1_{\bar{A}_{m-1}=\bar{0}}\right.\\
&\left.\times\left\{A_m-Pr\left(A_m=1\mid\bar{L}_m,\bar{A}_{m-1}=\bar{0}\right)\right\}\left\{A_l-Pr\left(A_l=1\mid\bar{L}_l,\bar{A}_{l-1}=\bar{0}\right)\right\}\right]\\
=\;&E\left[q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_l\right)^T E\left\{H^a_{m,(\psi,\eta)}H^a_{l,(\psi,\eta)}\mid\bar{L}_m,\bar{A}_{m-1}\right\}1_{\bar{A}_{m-1}=\bar{0}}\right.\\
&\left.\times\left\{A_m-Pr\left(A_m=1\mid\bar{L}_m,\bar{A}_{m-1}=\bar{0}\right)\right\}\left\{A_l-Pr\left(A_l=1\mid\bar{L}_l,\bar{A}_{l-1}=\bar{0}\right)\right\}\right]\\
=\;&E\left[q\left(\bar{L}_m\right)q^{\mathrm{opt}}\left(\bar{L}_l\right)^T E\left\{H^a_{m,(\psi,\eta)}H^a_{l,(\psi,\eta)}\mid\bar{L}_m,\bar{A}_{m-1}\right\}1_{\bar{A}_{m-1}=\bar{0}}\right.\\
&\times E\left[\left\{A_m-Pr\left(A_m=1\mid\bar{L}_m,\bar{A}_{m-1}=\bar{0}\right)\right\}1_{\bar{A}_{m-1}=\bar{0}}\mid\bar{L}_m,\bar{A}_{m-1}\right]\\
&\left.\times\left\{A_l-Pr\left(A_l=1\mid\bar{L}_l,\bar{A}_{l-1}=\bar{0}\right)\right\}\right]=0,
\end{aligned}
$$

where the third equality follows assuming $E\left\{H^a_{m,(\psi,\eta)}H^a_{l,(\psi,\eta)}\mid\bar{L}_m,\bar{A}_m\right\}=E\left\{H^a_{m,(\psi,\eta)}H^a_{l,(\psi,\eta)}\mid\bar{L}_m,\bar{A}_{m-1}\right\}$. Since (A.4) equals (A.4) for any q, the solution of q^{opt} is (3.6), proving Theorem 3.

Appendix E. Exploring the connection between the two approaches to sensitivity analysis

The approach of Schlesselman (1978) and Rosenbaum and Rubin (1983) can be used to motivate the specification of the selection bias function. Assume that there is one unmeasured confounder U, and we have no unmeasured confounding if U is taken into account. For $0\le m\le K$,

$$A_m \coprod Y^{(\infty)}\mid\bar{L}_m,\bar{U}_m,\bar{A}_{m-1},$$

which implies that

$$E\left(Y^{(\infty)}\mid\bar{L}_m,\bar{U}_m,\bar{A}_{m-1}=\bar{0},A_m=1\right)=E\left(Y^{(\infty)}\mid\bar{L}_m,\bar{U}_m,\bar{A}_m=\bar{0}\right).$$

To motivate the selection bias function $g\left(\bar{L}_m\right)$ due to the unmeasured confounder U, assuming that we have $E\left(Y^{(\infty)}\mid\bar{L}_m,\bar{U}_m,\bar{A}_{m-1}=\bar{0}\right)=\beta_0+\beta_L^T L_m+\beta_U U_m+\psi\left(K-m\right)$, note that in this case,

$$
\begin{aligned}
g(\bar{L}_m) = {} & E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{A}_m = \bar{0}\right) \\
= {} & E\left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{U}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right\} \\
& - E\left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{U}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right\} \\
= {} & E\left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{U}_m, \bar{A}_{m-1} = \bar{0}\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right\} \\
& - E\left\{E\left(Y^{(\infty)} \mid \bar{L}_m, \bar{U}_m, \bar{A}_{m-1} = \bar{0}\right) \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right\} \\
= {} & \beta_U\left\{E\left(U_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(U_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right)\right\}.
\end{aligned}
$$

Considering U to be a variable like a measured confounder inspires the specification of $E\left(U_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(U_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right)$, and therefore of $g(\bar{L}_m)$. For example, in our application, it could be that $E\left(U_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 1\right) - E\left(U_m \mid \bar{L}_m, \bar{A}_{m-1} = \bar{0}, A_m = 0\right) = \alpha_0 + \alpha_1 CD4_m$, which corresponds to the third scenario for specification of $g(\bar{L}_m)$ in Section 5.

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Table 1

Results of the sensitivity analysis in AIEDRP: optimal estimates and 95% confidence intervals (CIs).

$g(\bar{L}_m;\eta)$	η_0	η_1	$\hat{\psi}_1$(CI)	$\hat{\psi}_2$(CI)
η_0	−100	0	43.33 (39.35, 47.39)	−0.305 (−1.973, 0.883)
	−75	0	38.33 (34.79, 43.08)	−0.340 (−1.635, 0.826)
	−50	0	36.42 (27.13, 39.11)	−0.396 (−1.771, 0.795)
	−25	0	31.06 (25.54, 33.46)	−0.411 (−1.856, 0.785)
	0	0	24.71 (21.37, 28.47)	−0.426 (−1.944, 0.654)
	25	0	20.64 (l6.37, 25.10)	−0.617 (−2.071, 1.190)
	50	0	16.30 (12.75, 20.78)	−0.727 (−2.131, 0.401)
	75	0	11.86 (7.82, 16.54)	−0.814 (−2.296, 0.519)
	100	0	7.43 (2.66, 11.29)	−0.891 (−2.277, 0.833)
$\eta_0 + \eta_1 m$	−100	5	42.72 (37.36, 49.17)	−1.243 (−3.763, 1.729)
	−75	5	38.42 (31.86, 42.71)	−1.408 (−3.317, 1.648)
	−50	5	35.51 (28.67, 38.00)	−1.481 (−3.642, 1.215)
	−25	5	29.17 (25.07, 33.89)	−1.512 (−3.381, 0.950)
	0	5	25.20 (18.87, 30.67)	−1.846 (−3.977, 0.932)
	25	5	21.34 (14.68, 27.25)	−2.157 (−4.272, 1.351)
	50	5	17.76 (12.17, 24.13)	−2.355 (−5.024, 0.768)
	75	5	12.40 (6.42, 19.78)	−2.419 (−6.199, 0.706)
	100	5	7.92 (1.57, 19.96)	−2.606 (−9.637, 0.587)
	−100	−5	42.03 (32.37, 53.61)	1.660 (−5.197, 6.836)
	−75	−5	37.82 (29.47, 47.70)	1.465 (−1.896, 6.007)
	−50	−5	33.63 (27.58, 42.98)	1.218 (−3.831, 3.908)
	−25	−5	29.36 (22.89, 37.24)	1.000 (−2.444, 4.158)
	0	−5	24.82 (19.11, 30.19)	0.806 (−1.333, 3.453)
	25	−5	20.61 (16.07, 26.51)	0.564 (−2.486, 2.538)
	50	−5	16.27 (12.76, 20.85)	0.432 (−1.861, 1.504)
	75	−5	11.91 (8.62, 16.03)	0.316 (−1.187, 1.454)
	100	−5	7.54 (3.45, 11.60)	0.202 (−1.249, 1.703)
$\eta_0 + \eta_1 CD4_m$	−100	0.02	41.23 (36.85, 45.51)	−0.341 (−1.950, 0.697)
	−75	0.02	36.54 (31.35, 40.42)	−0.375 (−2.115, 0.779)
	−50	0.02	31.97 (26.12, 36.99)	−0.429 (−2.751, 1.158)
	−25	0.02	27.65 (23.74, 30.96)	−0.544 (−2.253, 0.531)
	0	0.02	22.54 (18.74, 27.05)	−0.419 (−1.938, 0.845)
	25	0.02	18.54 (14.92, 21.90)	−0.629 (−1.659, 0.415)
	50	0.02	14.20 (8.61, 18.77)	−0.741 (−2.444, 1.452)
	75	0.02	9.76 (3.98, 13.87)	−0.833 (−2.046, 1.101)
	100	0.02	5.24 (0.55, 9.54)	−0.916 (−3.100, 0.630)
	−100	−0.02	45.71 (41.11, 49.71)	−0.283 (−1.301, 1.141)

$g(\bar{L}_m;\eta)$	η_0	η_1	$\hat{\psi}_1$(CI)	$\hat{\psi}_2$(CI)
	−75	−0.02	40.95 (37.06, 44.83)	−0.335 (−1.406, 0.683)
	−50	−0.02	36.35 (32.25, 39.68)	−0.415 (−1.633, 0.706)
	−25	−0.02	32.28 (28.20, 35.18)	−0.635 (−1.764, 0.526)
	0	−0.02	26.87 (23.62, 32.52)	−0.428 (−2.876, 0.617)
	25	−0.02	22.74 (19.55, 26.74)	−0.607 (−2.779, 0.284)
	50	−0.02	18.40 (14.34, 22.95)	−0.716 (−1.929, 0.628)
	75	−0.02	13.97 (9.93, 17.47)	−0.799 (−1.950, 0.497)
	100	−0.02	9.47 (3.99, 14.50)	−0.869 (−2.487, 1.033)