Supplementary material to "Longitudinal mediation analysis based on Mendelian randomization" by

Xuezhi Zhu[1], Hong Zhang[1*]

[1]Department of Statistics anf Finance, School of Management, University of Science and Technology of China, Hefei, Anhui, China

Appendix A Proofs

Appendix A.1 Proof of Theorem 1

Proof. We have previously defined the LMEs as:

$$\begin{aligned}\mu_{\text{LTE}} =& E\left[Y_k^{\bar{a}+\bar{1},\bar{b}(\bar{a}+\bar{1})} - Y_k^{\bar{a},\bar{b}(\bar{a})}\right]\\ \mu_{\text{LDE}} =& E\left[Y_k^{\bar{a}+\bar{1},\bar{b}(\bar{a})} - Y_k^{\bar{a},\bar{b}(\bar{a})}\right]\\ \mu_{\text{LIE}} =& E\left[Y_k^{\bar{a}+\bar{1},\bar{b}(\bar{a}+\bar{1})} - Y_k^{\bar{a}+\bar{1},\bar{b}(\bar{a})}\right]\end{aligned} \tag{S.1}$$

The structural model of exposure, mediator and outcome is

$$\begin{aligned} E(A_t^{g_a,g_{ab}}) &= \theta_0(t) + \theta_1(t)g_a + \theta_2(t)g_{ab},\\ E(B_t^{g_a,g'_{ab},\bar{a}}) &= \mu_0(t) + \mu_1(t)g_b + \mu_2(t)g'_{ab} + \int_0^t \left(\mu_3^t(s)a(s)\right) ds,\\ E(Y_t^{\bar{a},\bar{b}(\bar{a})}) &= \gamma_0(t) + \int_0^t \left(\gamma_1^t(s)a(s) + \gamma_2^t(s)b(s)\right) ds,\end{aligned} \tag{S.2}$$

where $\theta_0(t) = E(A_t^{g_a=0,g_{ab}=0})$, $\mu_0(t) = E(B_t^{g_a=0,g'_{ab}=0,\bar{a}=0})$, $\gamma_0(t) = E(Y_t^{\bar{a}=0,\bar{b}(\bar{a})=0})$. And $\theta_1(t)$, $\theta_2(t)$ denote the effects of G_A or G_{AB} on exposure at t moment, $\mu_1(t)$ and $\mu_2(t)$ the effects of G_B or G_{AB} on mediator at t moment, $\mu_3^t(s)$ the effect of exposure at s moment on mediator at t moment, $\gamma_1^t(s)$ and $\gamma_2^t(s)$ the effects of exposure or mediator at s moment on outcome at t moment.

Under Assumption 4 and Assumption 5 in section 2.3, if exposure and mediator at time points k_0 and k can be observed, then:

$$
\begin{aligned}
E(A_{k_0}^{g_a,g_{ab}}) =&\theta_0(k_0) + \theta_1(k_0)g_a + \theta_2(k_0)g_{ab}, \\
E(A_{k}^{g_a,g_{ab}}) =&\theta_0(k) + \lambda_{k_0}^{k}\left(\theta_1(k_0)g_a + \theta_2(k_0)g_{ab}\right), \\
E(B_{k_0}^{g_a,g'_{ab},\bar{a}}) =&\mu_0(k_0) + \mu_1(k_0)g_b + \mu_2(k_0)g'_{ab} + \mu_3^{k_0}(k_0)a(k_0), \\
E(B_{k}^{g_a,g'_{ab},\bar{a}}) =&\mu_0(k) + \phi_{k_0}^{k}\left(\mu_1(k_0)g_b + \mu_2(k_0)g'_{ab}\right) + \mu_3^{k}(k_0)a(k_0) \\
&+ \mu_3^{k}(k)a(k), \qquad\qquad (S.3)\\
E(Y_{k}^{\bar{a},\bar{b}(\bar{a})}) =&\gamma_0(k) + \gamma_1^{k}(k)a(k) + \gamma_2^{k}(k)b(k) \\
=&\gamma_0(k) + \gamma_1^{k}(k)\left[\theta_0(k) + \lambda_{k_0}^{k}\left(\theta_1(k_0)g_a + \theta_2(k_0)g_{ab}\right)\right] \\
&+ \gamma_2^{k}(k)\left[\mu_0(k) + \phi_{k_0}^{k}\left(\mu_1(k_0)g_b + \mu_2(k_0)g'_{ab}\right) + \mu_3^{k}(k_0)a(k_0)\right. \\
&\left.+\mu_3^{k}(k)a(k)\right],
\end{aligned}
$$

where $\lambda_{k_0}^{k}$ denotes the effect of exposure at k_0 time point on exposure at k time point, $\phi_{k_0}^{k}$ the effect of mediator at k_0 time point on mediator at k time point.

Considering the definition (S.1), we have

$$
\begin{aligned}
\mu_{\mathrm{LTE}} =&\gamma_1^{k}(k) + \gamma_2^{k}(k)(\mu_3^{k}(k_0) + \mu_3^{k}(k)), \\
\mu_{\mathrm{LDE}} =&\gamma_1^{k}(k), \qquad\qquad (S.4)\\
\mu_{\mathrm{LIE}} =&\gamma_2^{k}(k)(\mu_3^{k}(k_0) + \mu_3^{k}(k)).
\end{aligned}
$$

Then under the longitudinal mediation model (1), $\gamma_1^{k}(k) = \gamma_{a1}$, $\gamma_1^{k}(k) = \gamma_{b1}$, $\mu_3^{k}(k_0) = \beta_{a00}\beta_{b01}+\beta_{a01}$, and $\mu_3^{k}(k) = \beta_{a11}$. Therefore, we have $\mu_{\mathrm{LTE}} = \gamma_{a1}+\gamma_{b1}\left(\beta_{a00}\beta_{b01} + \beta_{a01} + \beta_{a11}\right)$, $\mu_{\mathrm{LDE}} = \gamma_{a1}$, and $\mu_{\mathrm{LIE}} = \gamma_{b1}\left(\beta_{a00}\beta_{b01} + \beta_{a01} + \beta_{a11}\right)$, which means that LMEs are identifiable under the longitudinal mediation model (1). $\square$

Appendix A.2 Proof of Theorem 2

Proof. We consider the estimation of μ_{LDE} first and rewrite the related model as follow:

$$
Y = \beta_1 A_1 + \beta_2 B_1 + \varepsilon, \qquad (S.5)
$$

where the outcome variable Y is linearly correlated with covariates of interest A_1 and B_1, and the instrumental variables are G_A, G_{AB} and G_B.

Let G_{Ai}, G_{ABi}, G_{Bi}, A_{0i}, B_{0i}, A_{1i}, B_{1i} and Y_i are the observation of ith individual $(i = 1, \ldots, n)$. Representing the data in matrix form we have:

$\boldsymbol{x_{11}} = (A_{01}, \ldots, A_{0n})'_{n\times 1}$, $\boldsymbol{x_{12}} = (B_{01}, \ldots, B_{0n})'_{n\times 1}$,

$\boldsymbol{x_{21}} = (A_{11}, \ldots, A_{1n})'_{n\times 1}$, $\boldsymbol{x_{22}} = (B_{11}, \ldots, B_{1n})'_{n\times 1}$,

$\boldsymbol{z_1} = (G_{A_1}, \ldots, G_{A_n})'_{n\times 1}$, $\boldsymbol{z_2} = (G_{AB_1}, \ldots, G_{AB_n})'_{n\times 1}$, $\boldsymbol{z_3} = (G_{B_1}, \ldots, G_{B_n})'_{n\times 1}$,

$\boldsymbol{Y} = (Y_1, \ldots, Y_n)'_{n\times 1}$.

Let $\boldsymbol{X} = (\boldsymbol{x_{21}}, \boldsymbol{x_{22}})_{n\times 2}$, $\boldsymbol{Z} = (\boldsymbol{z_1}, \boldsymbol{z_2}, \boldsymbol{z_3})_{n\times 3}$, $\boldsymbol{\beta} = (\beta_1, \beta_2)'$, $\boldsymbol{y} = \boldsymbol{Y}$, then the model S.5 can be expressed as:

$$\begin{aligned} \boldsymbol{y} &= \boldsymbol{X}\boldsymbol{\beta} + \boldsymbol{\varepsilon}, \\ \boldsymbol{X} &= \boldsymbol{Z}\boldsymbol{\Gamma} + \boldsymbol{V}, \end{aligned} \tag{S.6}$$

where $E(\varepsilon^2 \mid \boldsymbol{Z}) = \sigma^2 = \mathrm{Var}(\varepsilon)$, $\mathrm{Cov}(\boldsymbol{X}, \varepsilon) \neq 0$, $\mathrm{Cov}(\boldsymbol{Z}, \varepsilon) = 0$.

According to 2SLS, $\boldsymbol{\beta}$ has the following estimate:

$$\begin{aligned} \hat{\boldsymbol{\beta}}_{IV} &= \left(\hat{\boldsymbol{X}}'\hat{\boldsymbol{X}}\right)^{-1}\hat{\boldsymbol{X}}'\boldsymbol{y} \\ &= \left(\boldsymbol{X}'\boldsymbol{Z}(\boldsymbol{Z}'\boldsymbol{Z})^{-1}\boldsymbol{Z}'\boldsymbol{X}\right)^{-1}\boldsymbol{X}'\boldsymbol{Z}(\boldsymbol{Z}'\boldsymbol{Z})^{-1}\boldsymbol{Z}'\boldsymbol{y}, \end{aligned} \tag{S.7}$$

the mean and variance of $\hat{\boldsymbol{\beta}}_{IV}$ are

$$\begin{aligned} E(\hat{\boldsymbol{\beta}}_{IV}) &= \boldsymbol{\beta} + E\left[\left(\hat{\boldsymbol{X}}'\hat{\boldsymbol{X}}\right)^{-1}\hat{\boldsymbol{X}}'\boldsymbol{\varepsilon}\right] \\ &= \boldsymbol{\beta} + E\left[\left(\boldsymbol{X}'\boldsymbol{Z}(\boldsymbol{Z}'\boldsymbol{Z})^{-1}\boldsymbol{Z}'\boldsymbol{X}\right)^{-1}\boldsymbol{X}'\boldsymbol{Z}(\boldsymbol{Z}'\boldsymbol{Z})^{-1}\boldsymbol{Z}'\boldsymbol{\varepsilon}\right], \\ \mathrm{Var}(\hat{\boldsymbol{\beta}}_{IV}) &= \sigma^2(\hat{\boldsymbol{X}}'\hat{\boldsymbol{X}})^{-1}, \end{aligned} \tag{S.8}$$

where $\hat{\boldsymbol{X}} = \boldsymbol{Z}\left[(\boldsymbol{Z}'\boldsymbol{Z})^{-1}\boldsymbol{Z}'\boldsymbol{X}\right]$.

Obviously, $\hat{\boldsymbol{\beta}}_{IV}$ is not a unbiased estimate of $\boldsymbol{\beta}$ (because the correlation between $\boldsymbol{X}$ and $\boldsymbol{\varepsilon}$). However, $\hat{\boldsymbol{\beta}}_{IV}$ is asymptotically unbiased in the large sample case, that is

$$\hat{\boldsymbol{\beta}}_{IV} \xrightarrow{P} \boldsymbol{\beta},$$

also

$$\sqrt{n}(\hat{\boldsymbol{\beta}}_{IV} - \boldsymbol{\beta}) \xrightarrow{D} \mathcal{N}\{0, \Sigma_{IV}\},$$

where Σ_{IV} denote the asymptotic variance of $\hat{\boldsymbol{\beta}}_{IV}$. [28] gives both a model-based and a sandwich estimate of Σ_{IV}, which is

$$\hat{\Sigma}_{IV} = (\hat{\boldsymbol{X}}'\hat{\boldsymbol{X}})^{-1}\hat{\boldsymbol{X}}'(\boldsymbol{y}-\boldsymbol{X}\boldsymbol{\beta})(\boldsymbol{y}-\boldsymbol{X}\boldsymbol{\beta})'\hat{\boldsymbol{X}}(\hat{\boldsymbol{X}}'\hat{\boldsymbol{X}})^{-1}, \tag{S.9}$$

So $\hat{\boldsymbol{\beta}}_{IV}$ is a consistent estimate of $\boldsymbol{\beta}$.

By similar means above, we can get estimates of some coefficients in model (1) as well as the combination of several coefficients after simple addition, subtraction, multiplication and division operations. More specifically, substituting different $\boldsymbol{y}$, $\boldsymbol{X}$ and corresponding instrumental variable $\boldsymbol{Z}$ into the equation (S.6) and then continue with the above steps. The substitution of $\boldsymbol{y}$, $\boldsymbol{X}$, $\boldsymbol{Z}$ and estimation results are shown in tab S.1 :

Table S.1: Composition of equation and corresponding estimates

$\boldsymbol{y}$	$\boldsymbol{X}$	$\boldsymbol{Z}$	estimate
$\boldsymbol{Y}$	$\boldsymbol{x_{21}}$	$\boldsymbol{z_1}$	$\hat{\theta}_3$
$\boldsymbol{Y}$	$\boldsymbol{x_{11}}$	$\boldsymbol{z_1}$	$\hat{\theta}_4$
$\boldsymbol{x_{12}}$	$\boldsymbol{x_{11}}$	$\boldsymbol{z_1}$	$\hat{\theta}_5$
$\boldsymbol{x_{22}}$	$(\boldsymbol{x_{11}}, \boldsymbol{x_{12}})$	$(\boldsymbol{z_1}, \boldsymbol{z_2}, \boldsymbol{z_3})$	$\hat{\theta}_6$,$\hat{\theta}_7$
$\boldsymbol{x_{21}}$	$\boldsymbol{x_{11}}$	$\boldsymbol{z_1}$	$\hat{\theta}_8$

$$\begin{aligned}
&\hat{\theta}_1 \xrightarrow{D} \mathcal{N}\left\{\gamma_{a1}, V_1\right\}, \\
&\hat{\theta}_2 \xrightarrow{D} \mathcal{N}\left\{\gamma_{b1}, V_2\right\}, \\
&\hat{\theta}_3 \xrightarrow{D} \mathcal{N}\left\{\gamma_{a1} + \gamma_{b1}(\frac{\beta_{a00}\beta_{b01} + \beta_{a01}}{\alpha_{a01}} + \beta_{a11}), V_3\right\}, \\
&\hat{\theta}_4 \xrightarrow{D} \mathcal{N}\left\{\gamma_{a1}\alpha_{a01} + \gamma_{b1}(\beta_{a00}\beta_{b01} + \beta_{a01} + \beta_{a11}\alpha_{a01}), V_4\right\}, \\
&\hat{\theta}_5 \xrightarrow{D} \mathcal{N}\left\{\beta_{a00}, V_5\right\}, \\
&\hat{\theta}_6 \xrightarrow{D} \mathcal{N}\left\{\alpha_{a01}\beta_{a11} + \beta_{a01}, V_6\right\}, \\
&\hat{\theta}_7 \xrightarrow{D} \mathcal{N}\left\{\beta_{b01}, V_7\right\}, \\
&\hat{\theta}_8 \xrightarrow{D} \mathcal{N}\left\{\alpha_{a01}, V_8\right\}.
\end{aligned} \tag{S.10}$$

The variances of those estimates have similar form to $\mathrm{Var}(\hat{\boldsymbol{\beta}}_{IV})$ in equation (S.8). Here

$\theta_1 \equiv \gamma_{a1}$, $\theta_2 \equiv \gamma_{b1}$, $\theta_3 \equiv \gamma_{a1} + \gamma_{b1}(\frac{\beta_{a00}\beta_{b01}+\beta_{a01}}{\alpha_{a01}} + \beta_{a11})$, $\theta_4 \equiv \gamma_{a1}\alpha_{a01} + \gamma_{b1}(\beta_{a00}\beta_{b01} + \beta_{a01} + \beta_{a11}\alpha_{a01}) \neq 0$, $\theta_5 \equiv \beta_{a00}$, $\theta_6 \equiv \alpha_{a01}\beta_{a11} + \beta_{a01}$, $\theta_7 \equiv \beta_{b01}$, $\theta_8 \equiv \alpha_{a01}$. Thus, combining with the expressions of LMEs, we have

$$
\begin{aligned}
\mu_{\text{LTE}} &= \theta_3 - \left(\frac{\theta_3}{\theta_4} - 1\right)(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\,\theta_2, \\
\mu_{\text{LDE}} &= \theta_1, \\
\mu_{\text{LIE}} &= \theta_3 - \left(\frac{\theta_3}{\theta_4} - 1\right)(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\,\theta_2 - \theta_1.
\end{aligned} \tag{S.11}
$$

Therefore, equation (2) in the main text is proved. Let

$$
\begin{aligned}
\Theta &= (\theta_1, \theta_2, \theta_3, \theta_4, \theta_5, \theta_6, \theta_7, \theta_8)', \\
\hat{\Theta} &= \left(\hat{\theta}_1, \hat{\theta}_2, \hat{\theta}_3, \hat{\theta}_4, \hat{\theta}_5, \hat{\theta}_6, \hat{\theta}_7, \hat{\theta}_8\right)',
\end{aligned} \tag{S.12}
$$

$\hat{\theta}_i$ is a consistent estimate of θ_i ($i = 1, \ldots, 8$), so $g(\hat{\Theta})$ is the consistent estimate of $g(\Theta)$ when $g(\cdot)$ is a real-valued continuous function.

Then we give the asymptotic distribution of three lifetime effects. According to Delta method, we have:

$$g(\hat{\Theta}) \approx g(\Theta) + \frac{\partial g(\Theta)}{\partial \Theta}. \tag{S.13}$$

The asymptotic normality of $g(\hat{\Theta})$ can be obtained as follow considering large sample theorem:

$$g(\hat{\Theta}) \xrightarrow{D} \mathcal{N}\left\{g(\Theta), \nabla g(\Theta)'\Sigma(\Theta)\nabla g(\Theta)\right\}. \tag{S.14}$$

Let LTE $= g_T(\Theta)$ and combine with expression (S.11), we have

$$g_T(\Theta) = \theta_3 - \left(\frac{\theta_3}{\theta_4} - 1\right)(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\,\theta_2.$$

Then

$$
\begin{aligned}
\nabla g_T(\Theta) = \Bigg(&0, -\left(\frac{\theta_3}{\theta_4} - 1\right)(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5), 1 - \frac{(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\theta_2}{\theta_4}, \\
&\frac{\theta_3(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\theta_2}{\theta_4^2}, -\theta_2\left(\frac{\theta_3}{\theta_4 - 1}\right)(\theta_7 - \theta_8), \\
&-\theta_2\left(\frac{\theta_3}{\theta_4} - 1\right), -\theta_2\theta_5\left(\frac{\theta_3}{\theta_4} - 1\right), \left(\frac{\theta_3}{\theta_4} - 1\right)\theta_5\theta_2\Bigg).
\end{aligned}
$$

Considering that some elements of $\Sigma(\Theta)$ have similar expression to equation (S.9), the estimate of $\Sigma(\Theta)$ can be expressed as $\hat{\Sigma}(\Theta)$. Thus the standard error of $g_T(\hat{\Theta})$ is

$$\sqrt{\nabla g_T(\Theta)'\hat{\Sigma}(\Theta)\nabla g_T(\Theta)}.$$

Similarly, let LDE $= g_D(\Theta)$, LIE $= g_I(\Theta)$ and we can have

$$\nabla g_D(\Theta) = (1, 0, 0, 0, 0, 0, 0, 0)\,,$$

$$\begin{aligned}\nabla g_I(\Theta) = \Bigg(&-1, -\left(\frac{\theta_3}{\theta_4} - 1\right)(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5), 1 - \frac{(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\theta_2}{\theta_4},\\ &\frac{\theta_3(\theta_5\theta_7 + \theta_6 - \theta_8\theta_5)\theta_2}{\theta_4^2}, -\theta_2\left(\frac{\theta_3}{\theta_4 - 1}\right)(\theta_7 - \theta_8),\\ &-\theta_2\left(\frac{\theta_3}{\theta_4} - 1\right), -\theta_2\theta_5\left(\frac{\theta_3}{\theta_4} - 1\right), \left(\frac{\theta_3}{\theta_4} - 1\right)\theta_5\theta_2\Bigg)\,.\end{aligned}$$

So the standard error of $g_D(\hat{\Theta})$ is

$$\sqrt{\nabla g_D(\Theta)'\hat{\Sigma}(\Theta)\nabla g_D(\Theta)},$$

the standard error of $g_I(\hat{\Theta})$ is

$$\sqrt{\nabla g_I(\Theta)'\hat{\Sigma}(\Theta)\nabla g_I(\Theta)}.$$

$\square$

Appendix B Figures

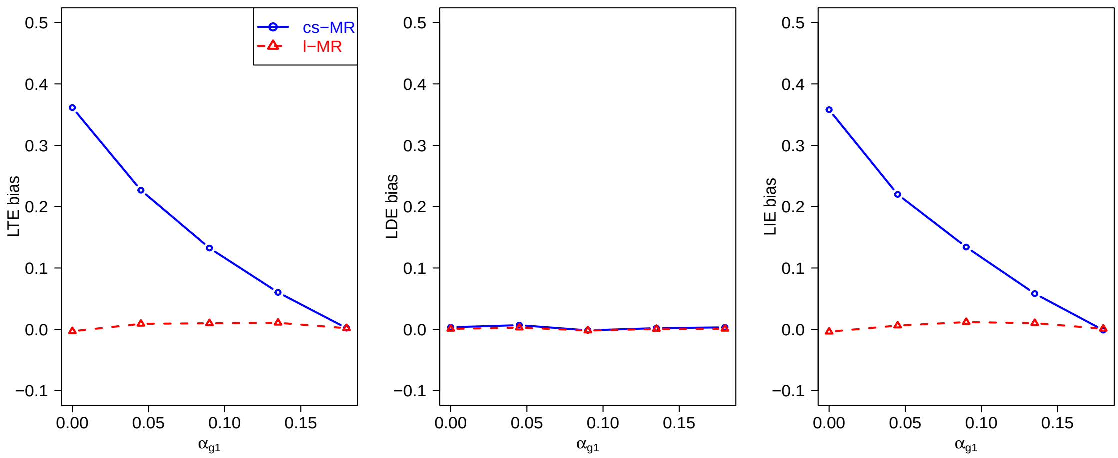

Figure S.1: Estimation biases under model (3) with Assumption 5 violated. Two of the four effects quantifying departure from Assumption 5 (i.e., α_{g1} and β_{g1}) were assumed to be the same and ranged from 0 to 0.18, and the other two effects (i.e., α_{g2} and β_{g2}) were assumed to be the same and ranged from 0 to 0.225. The three subfigures show the estimation biases of cs-MR (the traditional Mendelian randomization designed for cross-sectional data) and l-MR (our proposed method designed for longitudinal data) for LTE, LDE, and LIE, respectively.

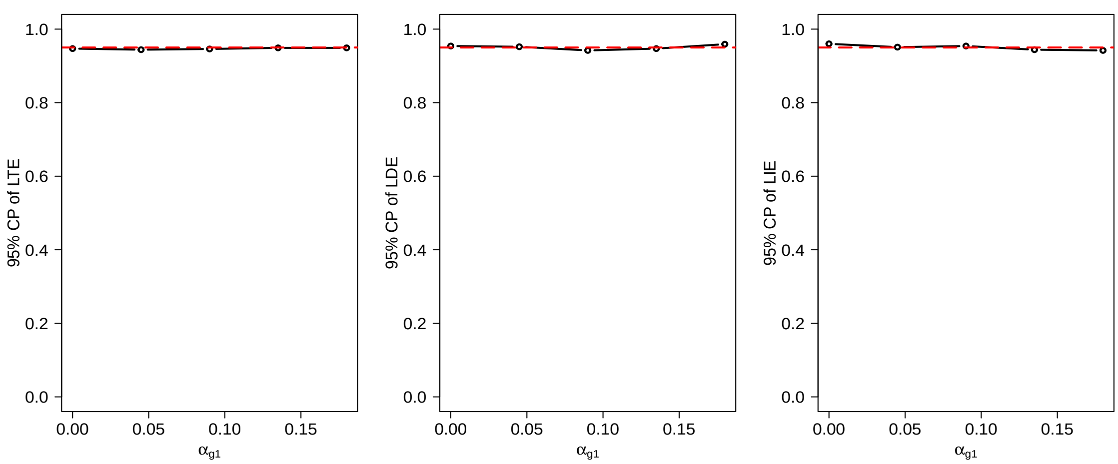

Figure S.2: Coverage probabilities (CPs) of 95% CIs of causal effects LTE, LDE, and LIE with Assumption 5 violated. Refer to the caption of Figure S.1 for simulation settings. The red dashed line represents the nominal level 0.95.

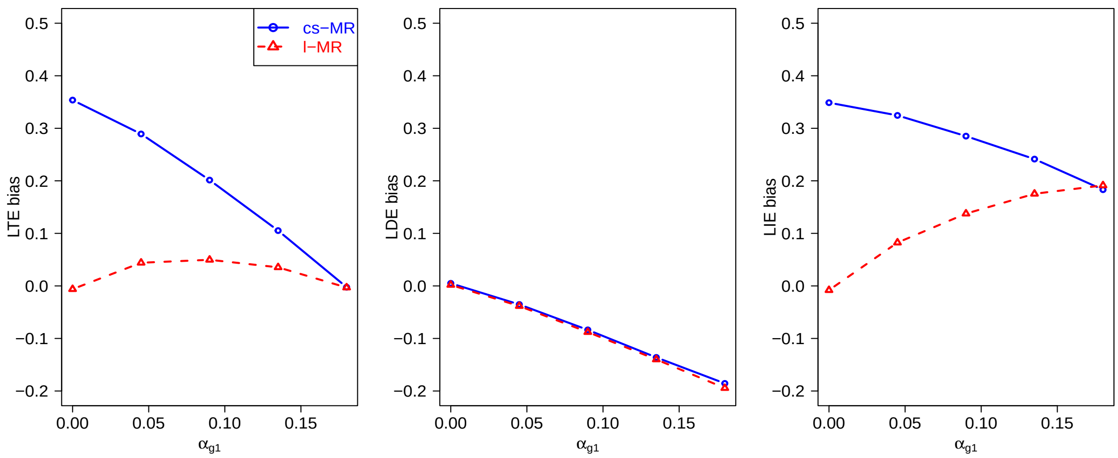

Figure S.3: Estimation biases under model (3) with both Assumption 4 and Assumption 5 violated. Four effects quantifying departure from Assumption 4 (i.e., γ_{a0}, γ_{b0}, γ_{b0}, and γ_{b0}) were assumed to be the same and ranged from 0 to 0.25. Two of the four effects quantifying departure from Assumption 5 (i.e., α_{g1} and β_{g1}) were assumed to be the same and ranged from 0 to 0.18, the other two effects (i.e., α_{g2} and β_{g2}) were assumed to be the same and ranged from 0 to 0.225. The three subfigures show the estimation biases of cs-MR (the traditional Mendelian randomization designed for cross-sectional data) and l-MR (our proposed method designed for longitudinal data) for LTE, LDE, and LIE, respectively.

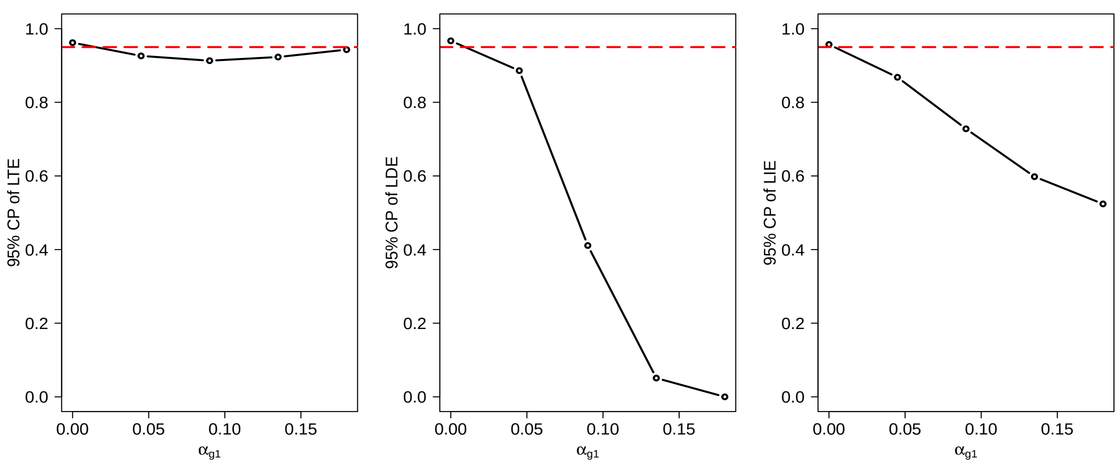

Figure S.4: Coverage probabilities (CPs) of 95% CIs of causal effects LTE, LDE, and LIE by l-MR with Assumption 4 and Assumption 5 violated. Refer to the caption of Figure S.3 for simulation settings. The red dashed line represents the nominal level 0.95.

Appendix C Tables

Table S.2: Performance of l-MR in the case of violating Assumption 5

	LTE[a]					LDE[b]					LIE[c]				
α_{g1} [d]	True[e]	Bias[f]	SE[g]	SEE[h]	CP[i]	True	Bias	SE	SEE	CP	TRUE	Bias	SE	SEE	CP
0.000	1.25	-0.003	0.126	0.129	0.947	0.25	0.001	0.065	0.066	0.954	1	-0.004	0.109	0.112	0.96
0.045	1.25	0.009	0.111	0.111	0.944	0.25	0.003	0.052	0.054	0.952	1	0.006	0.096	0.097	0.951
0.090	1.25	0.01	0.097	0.101	0.946	0.25	-0.002	0.047	0.046	0.942	1	0.012	0.085	0.088	0.954
0.135	1.25	0.011	0.089	0.091	0.949	0.25	0.001	0.04	0.039	0.947	1	0.01	0.08	0.079	0.944
0.180	1.25	0.002	0.082	0.083	0.949	0.25	0.001	0.035	0.035	0.959	1	0.001	0.074	0.073	0.942

[a]LTE, lifetime total effect; [b]LDE, lifetime direct effect; [c]LIE, lifetime indirect effect; [d]α_{g1}, the effect of genetic variants on the exposure and mediator after the initial time point.
[e]True, the true value of lifetime effect; [f]Bias, mean estimated lifetime effect minus the true value; [g]SE, standard error of estimated causal effects; [h]SEE, mean of estimated standard error; [i]CP, the coverage probability of 95% confidence intervals.

Table S.3: Performance of l-MR in the case of violating Assumption 4 and Assumption 5

	LTE[a]					LDE[b]					LIE[c]				
α_{g1} [d]	True[e]	Bias[f]	SE[g]	SEE[h]	CP[i]	True	Bias	SE	SEE	CP	TRUE	Bias	SE	SEE	CP
0	1.25	-0.006	0.123	0.129	0.962	0.25	0.002	0.063	0.066	0.967	1	-0.008	0.11	0.112	0.957
0.045	1.428	0.044	0.112	0.113	0.926	0.375	-0.038	0.048	0.049	0.886	1.053	0.082	0.103	0.106	0.868
0.09	1.606	0.05	0.105	0.107	0.913	0.5	-0.088	0.041	0.041	0.411	1.106	0.138	0.104	0.106	0.728
0.135	1.784	0.035	0.103	0.104	0.923	0.625	-0.14	0.038	0.037	0.051	1.159	0.175	0.108	0.107	0.598
0.18	1.962	-0.003	0.101	0.101	0.943	0.75	-0.194	0.035	0.036	0	1.212	0.191	0.107	0.107	0.524

[a]LTE, lifetime total effect; [b]LDE, lifetime direct effect; [c]LIE, lifetime indirect effect; [d]α_{g1}, the effect of genetic variants on the exposure and mediator after the initial time point.
[e]True, the true value of lifetime effect; [f]Bias, mean estimated lifetime effect minus the true value; [g]SE, standard error of estimated causal effects; [h]SEE, mean of estimated standard error; [i]CP, the coverage probability of 95% confidence intervals.