Web Appendices for "Assessing mediation in cross-sectional stepped wedge cluster randomized trials"

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1 Web Appendix A: Mediation measures for four data types in stepped wedge design

1.1 Web Appendix A1: Mediation measures for a contunuous outcome and continuous mediator

In this case, the outcome model and the mediator model are a pair of linear mixed models

$$\begin{aligned}
Y_{ijk} &= \beta_{0j} + \theta A_{ij} + \beta_M M_{ijk} + \boldsymbol{\beta}_X^T \mathbf{X}_{ijk} + \alpha_i + \epsilon_{ijk}, \quad &(A.1)\\
M_{ijk} &= \gamma_{0j} + \eta A_{ij} + \boldsymbol{\gamma}_X^T \mathbf{X}_{ijk} + \tau_i + e_{ijk}, \quad &(A.2)
\end{aligned}$$

where, $\epsilon_{ijk} \sim N(0, \sigma_\epsilon^2)$ and $e_{ijk} \sim N(0, \sigma_e^2)$ are independent residual error terms in the outcome model and mediator model, respectively. By the definitions of mediation effect measures in (4) of the main text, we obtain from models (A.1) and (A.2) that

$$\begin{aligned}
\text{NIE}(j|\mathbf{x}) &= E\big[\beta_{0j} + \theta + \beta_M(\gamma_{0j} + \eta + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \epsilon_{ijk}\big]\\
&\quad -E\big[\beta_{0j} + \theta + \beta_M(\gamma_{0j} + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \epsilon_{ijk}\big] = \beta_M\eta,\\
\text{NDE}(j|\mathbf{x}) &= E\big[\beta_{0j} + \theta + \beta_M(\gamma_{0j} + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \epsilon_{ijk}\big]\\
&\quad -E\big[\beta_{0j} + \beta_M(\gamma_{0j} + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \epsilon_{ijk}\big] = \theta.
\end{aligned}$$

1.2 Web Appendix A2: Mediation measures for a contunuous outcome and binary mediator

In this scenario, the outcome model of Y_{ijk} remains the same as model (A.1), but we model the binary mediator using the following logistic generalized linear mixed model, that is,

$$\text{logit}\left(P(M_{ijk} = 1|A_{ij}, \mathbf{X}_{ijk}, \tau_i)\right) = \gamma_{0j} + \eta A_{ij} + \boldsymbol{\gamma}_X^T \mathbf{X}_{ijk} + \tau_i,$$

where $\text{logit}(x) = \log\left(\frac{x}{1-x}\right)$ is the link function for h. By the definitions of NIE and NDE in (4) of the main text, for calendar time index j, we obtain

$$\begin{aligned}
\text{NIE}(j|\mathbf{x}) &= E\left[\beta_{0j} + \theta + \beta_M M_{ijk}(1) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha_i + \epsilon_{ijk}\right] - E\left[\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha_i + \epsilon_{ijk}\right] \\
&= \beta_M [P(M_{ijk}(1) = 1|\mathbf{X}_{ijk} = \mathbf{x}) - P(M_{ijk}(0) = 1|\mathbf{X}_{ijk} = \mathbf{x})] \\
&= \beta_M\left[\kappa(1, j|\mathbf{x}) - \kappa(0, j|\mathbf{x})\right], \\
\text{NDE}(j|\mathbf{x}) &= E\left[\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha_i + \epsilon_{ijk}\right] - E\left[\beta_{0j} + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha_i + \epsilon_{ijk}\right] \\
&= \theta.
\end{aligned}$$

1.3 Web Appendix A3: Mediation measures for a binary outcome and continuous mediator

When the outcome is binary and mediator is continuous, the expectations of the counterfactual outcome in equation (4) of the main text, $E[Y_{ijk}(1, M_{ijk}(1))|\mathbf{X}_{ijk} = \mathbf{x}]$, $E[Y_{ijk}(1, M_{ijk}(0))|\mathbf{X}_{ijk} = \mathbf{x}]$ and $E[Y_{ijk}(0, M_{ijk}(0))|\mathbf{X}_{ijk} = \mathbf{x}]$ simplify to $P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$, $P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$ and $P(Y_{ijk}(0, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$, respectively. We then apply the same technique of Gaynor et al. (2019) to derive the expressions of $P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$, $P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$ and $P(Y_{ijk}(0, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$.

Of note, according to the mediator model (7) of the main text, $e_{ijk} \sim N(0, \sigma_e^2)$ and $\tau_i \sim N(0, \sigma_\tau^2)$, then we have

$$\begin{aligned}
& P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}) \\
= & \int P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha) f(\alpha_i = \alpha|\mathbf{X}_{ijk} = \mathbf{x}) d\alpha \\
= & \int \frac{\exp(\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha)}{1 + \exp(\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha)} \cdot \frac{1}{\sqrt{2}\sigma_\alpha} \exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right) d\alpha.
\end{aligned}$$

Rewrite $P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha)$ as

$$\begin{aligned}
& P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha) \\
= & \int P(Y_{ijk} = 1|A_{ij} = 1, M_{ijk}(0) = m, \mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha) f(M_{ijk}(0) = m|A_{ij} = 0, \mathbf{X}_{ijk} = \mathbf{x}) dm \\
= & \int \frac{\exp(\beta_{0j} + \theta + \beta_M m + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha)}{1 + \exp(\beta_{0j} + \theta + \beta_M m + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2 + \sigma_e^2)}} \exp\left(-\frac{(m - \gamma_{0j} - \boldsymbol{\gamma}_X^T \mathbf{x})^2}{2(\sigma_\tau^2 + \sigma_e^2)}\right) dm.
\end{aligned}$$

Thus, we have

$$\begin{aligned}
& P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}) \\
= & \int P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha) f(\alpha_i = \alpha|\mathbf{X}_{ijk} = \mathbf{x}) d\alpha \\
= & \int \left[\int P(Y_{ijk} = 1|A_{ij} = 1, M_{ijk}(0) = m, \mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha) f(M_{ijk}(0) = m|A_{ij} = 0, \mathbf{X}_{ijk} = \mathbf{x}) dm\right] \\
& \times f(\alpha_i = \alpha|\mathbf{X}_{ijk} = \mathbf{x}) d\alpha \\
= & \int \left[\int \frac{\exp(\beta_{0j} + \theta + \beta_M m + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha)}{1 + \exp(\beta_{0j} + \theta + \beta_M m + \beta_X^T \mathbf{x} + \alpha)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2 + \sigma_e^2)}} \cdot \exp\left(-\frac{(m - \gamma_{0j} - \boldsymbol{\gamma}_X^T \mathbf{x})^2}{2(\sigma_\tau^2 + \sigma_e^2)}\right) dm\right] \\
& \times \frac{1}{\sqrt{2}\sigma_\alpha} \exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right) d\alpha.
\end{aligned}$$

If we define $\mu(a, a^*, j|\mathbf{x}) = P(Y_{ijk}(a, M_{ijk}(a^*)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$ for $a, a^* \in \{0, 1\}$, then, we have

$$\begin{aligned}
\text{logit}[P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] &= \log\left[\frac{P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})}{1 - P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})}\right] \\
&= \log\left[\frac{\mu(1, 1, j|\mathbf{x})}{1 - \mu(1, 1, j|\mathbf{x})}\right].
\end{aligned}$$

Similarly, we have

$$\begin{aligned}
\text{logit}[P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] &= \log\left[\frac{\mu(1, 0, j|\mathbf{x})}{1 - \mu(1, 0, j|\mathbf{x})}\right], \\
\text{logit}[P(Y_{ijk}(0, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] &= \log\left[\frac{\mu(0, 0, j|\mathbf{x})}{1 - \mu(0, 0, j|\mathbf{x})}\right].
\end{aligned}$$

Therefore, the period-specific NIE and NDE are

$$\begin{aligned}
\text{NIE}(j|\mathbf{x}) &= \text{logit}[P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] - \text{logit}[P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] \\
&= \log\left[\frac{\mu(1, 1, j|\mathbf{x})}{1 - \mu(1, 1, j|\mathbf{x})}\right] - \log\left[\frac{\mu(1, 0, j|\mathbf{x})}{1 - \mu(1, 0, j|\mathbf{x})}\right], \\
\text{NDE}(j|\mathbf{x}) &= \text{logit}[P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] - \text{logit}[P(Y_{ijk}(0, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] \\
&= \log\left[\frac{\mu(1, 0, j|\mathbf{x})}{1 - \mu(1, 0, j|\mathbf{x})}\right] - \log\left[\frac{\mu(0, 0, j|\mathbf{x})}{1 - \mu(0, 0, j|\mathbf{x})}\right].
\end{aligned}$$

1.4 Web Appendix A4: Mediation measures for a binary outcome and binary mediator

As given in Gaynor et al. (2019) and Cheng et al. (2021), $P(Y_{ijk}(1)=1|M_{ijk}(1),\mathbf{X}_{ijk}=\mathbf{x})$, $P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})$ and $P(Y_{ijk}(0)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})$ can be shown as

$$\begin{aligned}
& P(Y_{ijk}(1)=1|M_{ijk}(1),\mathbf{X}_{ijk}=\mathbf{x}) \\
= \;& \sum_{m=0}^{1} P(Y_{ijk}(1)=1|M_{ijk}(1)=m,\mathbf{X}_{ijk}=\mathbf{x})P(M_{ijk}(1)=m|\mathbf{X}_{ijk}=\mathbf{x}) \\
= \;& \sum_{m=0}^{1}\Big[\int P(Y_{ijk}(1)=1|M_{ijk}(1)=m,\alpha_i=\alpha,\mathbf{X}_{ijk}=\mathbf{x})f(\alpha_i=\alpha|M_{ijk}(1)=m,\mathbf{X}_{ijk}=\mathbf{x})d\alpha \\
& \times\int P(M_{ijk}(1)=m|\tau_i=\tau,\mathbf{X}_{ijk}=\mathbf{x})f(\tau_i=\tau|\mathbf{X}_{ijk}=\mathbf{x})d\tau\Big] \\
= \;& \Big[\int \frac{e^{\beta_{0j}+\theta+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\theta+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big)d\alpha\Big]\times\int\frac{1}{1+e^{\gamma_{0j}+\eta+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}\frac{1}{\sqrt{2}\sigma_\tau}\exp\Big(-\frac{\tau^2}{2\sigma_\tau^2}\Big)d\tau \\
& +\Big[\int \frac{e^{\beta_{0j}+\theta+\beta_M+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\theta+\beta_M+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big)d\alpha\Big]\times\int\frac{e^{\gamma_{0j}+\eta+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}{1+e^{\gamma_{0j}+\eta+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}\frac{1}{\sqrt{2}\sigma_\tau}\exp\Big(-\frac{\tau^2}{2\sigma_\tau^2}\Big)d\tau, \\
& P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x}) \\
= \;& \sum_{m=0}^{1} P(Y_{ijk}(1)=1|M_{ijk}(0)=m,\mathbf{X}_{ijk}=\mathbf{x})P(M_{ijk}(0)=m|\mathbf{X}_{ijk}=\mathbf{x}) \\
= \;& \sum_{m=0}^{1}\Big[\int P(Y_{ijk}(1)=1|M_{ijk}(0)=m,\alpha_i=\alpha,\mathbf{X}_{ijk}=\mathbf{x})f(\alpha_i=\alpha|M_{ijk}(0)=m,\mathbf{X}_{ijk}=\mathbf{x})d\alpha \\
& \times\int P(M_{ijk}(0)=m|\tau_i=\tau,\mathbf{X}_{ijk}=\mathbf{x})f(\tau_i=\tau|\mathbf{X}_{ijk}=\mathbf{x})d\tau\Big] \\
= \;& \Big[\int \frac{e^{\beta_{0j}+\theta+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\theta+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big)d\alpha\Big]\times\int\frac{1}{1+e^{\gamma_{0j}+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}\cdot\frac{1}{\sqrt{2}\sigma_\tau}\exp\Big(-\frac{\tau^2}{2\sigma_\tau^2}\Big)d\tau \\
& +\Big[\int \frac{e^{\beta_{0j}+\theta+\beta_M+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\theta+\beta_M+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big)d\alpha\Big]\times\int\frac{e^{\gamma_{0j}+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}{1+e^{\gamma_{0j}+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}\frac{1}{\sqrt{2}\sigma_\tau}\exp\Big(-\frac{\tau^2}{2\sigma_\tau^2}\Big)d\tau,
\end{aligned}$$

$$\begin{aligned}
& P(Y_{ijk}(0)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x}) \\
= \;& \sum_{m=0}^{1} P(Y_{ijk}(0)=1|M_{ijk}(0)=m,\mathbf{X}_{ijk}=\mathbf{x})P(M_{ijk}(0)=m|\mathbf{X}_{ijk}=\mathbf{x}) \\
= \;& \sum_{m=0}^{1}\Big[\int P(Y_{ijk}(0)|M_{ijk}(0)=m,\alpha_i=\alpha,\mathbf{X}_{ijk}=\mathbf{x})f(\alpha_i=\alpha|M_{ijk}(0)=m,\mathbf{X}_{ijk}=\mathbf{x})d\alpha \\
& \times\int P(M_{ijk}(0)=m|\tau_i=\tau,\mathbf{X}_{ijk}=\mathbf{x})f(\tau_i=\tau|\mathbf{X}_{ijk}=\mathbf{x})d\tau\Big] \\
= \;& \Big[\int \frac{e^{\beta_{0j}+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big)d\alpha\Big]\times\int\frac{1}{1+e^{\gamma_{0j}+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}\frac{1}{\sqrt{2}\sigma_\tau}\exp\Big(-\frac{\tau^2}{2\sigma_\tau^2}\Big)d\tau \\
& +\Big[\int \frac{e^{\beta_{0j}+\beta_M+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\beta_M+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big)d\alpha\Big]\times\int\frac{e^{\gamma_{0j}+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}{1+e^{\gamma_{0j}+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}\frac{1}{\sqrt{2}\sigma_\tau}\exp\Big(-\frac{\tau^2}{2\sigma_\tau^2}\Big)d\tau.
\end{aligned}$$

For $a, a^* \in \{0,1\}$, if we define

$$\lambda(a,a^*,j|\mathbf{x}) \quad = \quad \int \frac{e^{\beta_{0j}+\theta a+\beta_M a^*+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}}{1+e^{\beta_{0j}+\theta a+\beta_M a^*+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha}} \cdot \frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha,$$

and use $\kappa(a,j|\mathbf{x}) = \int \frac{e^{\gamma_{0j}+\eta a+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}}{1+e^{\gamma_{0j}+\eta a+\boldsymbol{\gamma}_X^T\mathbf{X}+\tau}} \cdot \frac{1}{\sqrt{2}\sigma_\tau}\exp\left(-\frac{\tau^2}{2\sigma_\tau^2}\right)d\tau$ defined in Section 3.3 of the main text, then, the probabilities $P(Y_{ijk}(1)=1|M_{ijk}(1),\mathbf{X}_{ijk}=\mathbf{x})$, $P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})$ and $P(Y_{ijk}(0)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})$ can be simplified as

$$\begin{aligned}
P(Y_{ijk}(1)=1|M_{ijk}(1),\mathbf{X}_{ijk}=\mathbf{x}) &= \lambda(1,0,j|\mathbf{x})[1-\kappa(1,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(1,j|\mathbf{x}),\\
P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x}) &= \lambda(1,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(0,j|\mathbf{x}),\\
P(Y_{ijk}(0)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x}) &= \lambda(0,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(0,1,j|\mathbf{x})\kappa(0,j|\mathbf{x}).
\end{aligned}$$

Therefore, the period-specific NIE and NDE are

$$\begin{aligned}
\text{NIE}(j|\mathbf{x}) &= \log\left\{\frac{P(Y_{ijk}(1)=1|M_{ijk}(1),\mathbf{X}_{ijk}=\mathbf{x})/\big[1-P(Y_{ijk}(1)=1|M_{ijk}(1),\mathbf{X}_{ijk}=\mathbf{x})\big]}{P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})/\big[1-P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})\big]}\right\}\\
&= \log\left\{\frac{\lambda(1,0,j|\mathbf{x})[1-\kappa(1,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(1,j|\mathbf{x})}{1-[\lambda(1,0,j|\mathbf{x})[1-\kappa(1,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(1,j|\mathbf{x})]}\right\}\\
&\quad -\log\left\{\frac{\lambda(1,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(0,j|\mathbf{x})}{1-[\lambda(1,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(0,j|\mathbf{x})]}\right\},\\
\text{NDE}(j|\mathbf{x}) &= \log\left\{\frac{P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})/\big[1-P(Y_{ijk}(1)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})\big]}{P(Y_{ijk}(0)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})/\big[1-P(Y_{ijk}(0)=1|M_{ijk}(0),\mathbf{X}_{ijk}=\mathbf{x})\big]}\right\}\\
&= \log\left\{\frac{\lambda(1,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(0,j|\mathbf{x})}{1-[\lambda(1,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(1,1,j|\mathbf{x})\kappa(0,j|\mathbf{x})]}\right\}\\
&\quad -\log\left\{\frac{\lambda(0,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(0,1,j|\mathbf{x})\kappa(0,j|\mathbf{x})}{1-[\lambda(0,0,j|\mathbf{x})[1-\kappa(0,j|\mathbf{x})]+\lambda(0,1,j|\mathbf{x})\kappa(0,j|\mathbf{x})]}\right\}.
\end{aligned}$$

2 Web Appendix B: Double STA method to approximate the double integral

The period-specific NIE and NDE for a binary outcome and continuous mediator in stepped wedge design involve a double integral, that is

$$\begin{aligned}
\mu(a,a^*,j|\mathbf{x}) \quad = \quad & \int\left[\int \frac{\exp(\beta_{0j}+\theta a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha)}{1+\exp(\beta_{0j}+\theta a+\beta_M m+\beta_X^T\mathbf{x}+\alpha)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2+\sigma_e^2)}}\right.\\
& \left.\cdot\exp\left(-\frac{(m-\gamma_{0j}-\eta a^*-\boldsymbol{\gamma}_X^T\mathbf{x})^2}{2(\sigma_\tau^2+\sigma_e^2)}\right)dm\right] \times \frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha,
\end{aligned}$$

where $a, a^* \in \{0,1\}$.

Of note, the inner integral of the above double integral is a logistic-normal integral, which can be regarded as the expectation of $q(m|\mathbf{x},\alpha)$ with respect to random variable m, that is,

$$\begin{aligned}
& \int \frac{\exp(\beta_{0j}+\theta a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha)}{1+\exp(\beta_{0j}+\theta a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2+\sigma_e^2)}}\exp\left(-\frac{(m-\gamma_{0j}-\eta a^*-\boldsymbol{\gamma}_X^T\mathbf{x})^2}{2(\sigma_\tau^2+\sigma_e^2)}\right)dm\\
= \quad & E_m\left\{q(m|\mathbf{x},\alpha)\right\},
\end{aligned}$$

where $q(m|\mathbf{x},\alpha)=\frac{\exp(\beta_{0j}+\theta a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha)}{1+\exp(\beta_{0j}+\theta a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{X}+\alpha)}$, $E_m\{\bullet\}$ is defined with respect to the normal distribution of mediator marginalized over the mediator random effect, that is, a normal density with mean $\overline{m}=\gamma_{0j}+\eta a^*+\boldsymbol{\gamma}_X^T\mathbf{x}$ and variance $\sigma_\tau^2+\sigma_e^2$.

Inspired by the Taylor expansion technique used in the approximate maximum likelihood estimation proposed by Cao and Wong (2021) to correct for measurement error in covariates for logistic regression, here, we apply the same technique to approximate the logistic-normal integral $E_m\left\{q(m|\mathbf{x},\alpha)\right\}$. For example, when using the second-order Taylor approximation (STA) technique to approximate the $q(m|\mathbf{x},\alpha)$ around $m=\overline{m}$, we have

$$q(m|\mathbf{x},\alpha) \quad = \quad q(\overline{m}|\mathbf{x},\alpha)+q'(m|\mathbf{x},\alpha)|_{m=\overline{m}}(m-\overline{m})+\frac{1}{2!}q''(m|\mathbf{x},\alpha)|_{m=\overline{m}}(m-\overline{m})^2+\ldots$$

Since all odd central moments of a normal distribution are equal to 0, then keeping the second-order Taylor expansion results of $q(m|\mathbf{x},\alpha)$, we have

$$\begin{aligned}
E_m\left\{q(m|\mathbf{x},\alpha)\right\} &= E[q(\overline{m}|\mathbf{x},\alpha)+q'(m|\mathbf{x},\alpha)|_{m=\overline{m}}(m-\overline{m})+\frac{1}{2!}q''(m|\mathbf{x},\alpha)|_{m=\overline{m}}(m-\overline{m})^2+\ldots] \\
&= q(\overline{m}|\mathbf{x},\alpha)+\frac{1}{2!}q''(m|\mathbf{x},\alpha)|_{m=\overline{m}}Var(m)+\mathcal{O}\left(\frac{1}{8}\beta_M^4(\sigma_\tau^2+\sigma_e^2)^2\right) \qquad \text{(A.3)} \\
&\approx q(\overline{m}|\mathbf{x},\alpha)+q(\overline{m}|\mathbf{x},\alpha)\left[1-q(\overline{m}|\mathbf{x},\alpha)\right]\left[1-2q(\overline{m}|\mathbf{x},\alpha)\right]\frac{1}{2}\beta_M^2(\sigma_\tau^2+\sigma_e^2),
\end{aligned}$$

where $q''(m|\mathbf{x},\alpha)=\frac{\partial^2 q(m|\mathbf{X},\alpha)}{\partial m^2}$ and $Var(m)=\sigma_\tau^2+\sigma_e^2$. Note that for (A.3), the next non-zero term is $\frac{1}{4!}\frac{\partial^4 q(m|\mathbf{X},\alpha)}{\partial m^2}|_{m=\overline{m}}\cdot E(m-\overline{m})^4=g(q(\overline{m}|\mathbf{x},\alpha))\frac{1}{4!}\beta_M^4E(m-\overline{m})^4$, where $g(x)=x-15x^2+50x^3-60x^4+24x^5$. By the property of the central moment of a normal distribution with mean μ and variance σ^2, we know $\mu_r=E(X-\mu)^r=(r-1)!!\sigma^r$ when r is even and $\mu_r=0$ when r is odd. Thus, we have $E(m-\overline{m})^4=3(\sigma_\tau^2+\sigma_e^2)^2$ and $\frac{1}{4!}\beta_M^4E(m-\overline{m})^4=\frac{1}{8}\beta_M^4(\sigma_\tau^2+\sigma_e^2)^2$. Note that it is easy to show that $g(q(\overline{m}|\mathbf{x},\alpha))$ is bounded, we obtain the $\mathcal{O}(\cdot)$ result in (A.3).

Therefore, the double integral reduces to a single integral as

$$\begin{aligned}
\mu(a,a^*,j|\mathbf{x}) &\approx \int\left\{q(\overline{m}|\mathbf{x},\alpha)+\left[q(\overline{m}|\mathbf{x},\alpha)-3q(\overline{m}|\mathbf{x},\alpha)^2+2q(\overline{m}|\mathbf{x},\alpha)^3\right]\frac{1}{2}\beta_M^2(\sigma_\tau^2+\sigma_e^2)\right\} \\
&\quad\times\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha. \qquad \text{(A.4)}
\end{aligned}$$

In the single integral (A.4), we treat approximation result of $E_m q(m|\mathbf{x},\alpha)$ as a function of α conditional on $\overline{m}$ and $\mathbf{x}$ (denoted as $s(\alpha|\overline{m},\mathbf{x})$), that is,

$$s(\alpha|\overline{m},\mathbf{x})=q(\overline{m}|\mathbf{x},\alpha)+\left[q(\overline{m}|\mathbf{x},\alpha)-3q(\overline{m}|\mathbf{x},\alpha)^2+2q(\overline{m}|\mathbf{x},\alpha)^3\right]\frac{1}{2}\beta_M^2(\sigma_\tau^2+\sigma_e^2).$$

Therefore, the integral (A.4) is equal to $E_\alpha\left\{s(\alpha|\overline{m},\mathbf{x})\right\}$, and $E_\alpha\{\bullet\}$ is defined with respect to the normal distribution of random effect variable α, that is, a normal density with mean 0 and variance σ_α^2. Then, we apply an additional second-order Taylor expansion for $s(\alpha|\overline{m},\mathbf{x})$ around $\alpha=0$. Typically, we can apply STA technique for each term of $s(\alpha|\overline{m},\mathbf{x})$ and obtain corresponding approximation results. For example, treating $q(\overline{m}|\mathbf{x},\alpha)$ as a function of α and take Taylor expansion for $q(\overline{m}|\mathbf{x},\alpha)$ at $\alpha=0$, by using the same arguments as (A.3), we have

$$A_1 \quad = \quad \int q(\overline{m}|\mathbf{x},\alpha)\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha\approx q(\overline{m}|\mathbf{x},0)+\left[q(\overline{m}|\mathbf{x},0)-3q(\overline{m}|\mathbf{x},0)^2+2q(\overline{m}|\mathbf{x},0)^3\right]\frac{1}{2}\sigma_\alpha^2.$$

Similarly, we can also treat $q(\overline{m}|\mathbf{x},\alpha)^2$ and $q(\overline{m}|\mathbf{x},\alpha)^3$ as a function of α, and obtain the following approximation results by STA technique

$$
\begin{aligned}
A_2 &= \int q(\overline{m}|\mathbf{x},\alpha)^2 \frac{1}{\sqrt{2}\sigma_\alpha} \exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big) d\alpha \approx q(\overline{m}|\mathbf{x},0)^2 + \big[4q(\overline{m}|\mathbf{x},0)^2 - 10q(\overline{m}|\mathbf{x},0)^3 + 6q(\overline{m}|\mathbf{x},0)^4\big] \frac{1}{2}\sigma_\alpha^2, \\
A_3 &= \int q(\overline{m}|\mathbf{x},\alpha)^3 \frac{1}{\sqrt{2}\sigma_\alpha} \exp\Big(-\frac{\alpha^2}{2\sigma_\alpha^2}\Big) d\alpha \approx q(\overline{m}|\mathbf{x},0)^3 + \big[9q(\overline{m}|\mathbf{x},0)^3 - 21q(\overline{m}|\mathbf{x},0)^4 + 12q(\overline{m}|\mathbf{x},0)^5\big] \frac{1}{2}\sigma_\alpha^2.
\end{aligned}
$$

Thus, based on double STA method, equation (A.4) is given by the following closed-form representation

$$
\mu(a,a^*,j|\mathbf{x}) \approx A_1 + (A_1 - 3A_2 + 2A_3)\frac{1}{2}\beta_M^2(\sigma_\tau^2+\sigma_e^2). \tag{A.5}
$$

Since the coefficient of α is 1 in each term of $s(\alpha|\overline{m},\mathbf{x})$, by using similar arguments to show $\mathcal{O}(\cdot)$ in (A.3), the accuracy of approximate formula A_k ($k=1,2,3$) depends on $\mathcal{O}(\frac{1}{8}\sigma_\alpha^4)$. Therefore, the accuracy of formula (A.5) depends on both $\mathcal{O}\left(\frac{1}{8}\beta_M^4(\sigma_\tau^2+\sigma_e^2)^2\right)$ and $\mathcal{O}(\frac{1}{8}\sigma_\alpha^4)$, and the approximate formula (A.5) is particularly accurate when both the values of the term $\frac{1}{8}\beta_M^4(\sigma_\tau^2+\sigma_e^2)^2$ and $\frac{1}{8}\sigma_\alpha^4$ are relative small.

3 Web Appendix C: Mediation analysis under nested exchangeable random-effects structure

3.1 Under an instantaneous and constant treatment effect structure

3.1.1 Data type 1-A continuous outcome and a continuous mediator (Y_cM_c)

In this scenario, the outcome model and the mediator model are a pair of linear mixed models

$$
\begin{aligned}
Y_{ijk} &= \beta_{0j} + \theta A_{ij} + \beta_M M_{ijk} + \boldsymbol{\beta}_X^T \mathbf{X}_{ijk} + \alpha_i + \phi_{ij} + \epsilon_{ijk}, && \text{(A.6)} \\
M_{ijk} &= \gamma_{0j} + \eta A_{ij} + \boldsymbol{\gamma}_X^T \mathbf{X}_{ijk} + \tau_i + \psi_{ij} + e_{ijk}, && \text{(A.7)}
\end{aligned}
$$

where $\alpha_i \sim N(0,\sigma_\alpha^2)$, $\phi_{ij} \sim N(0,\sigma_\phi^2)$, $\tau_i \sim N(0,\sigma_\tau^2)$ and $\psi_{ij} \sim N(0,\sigma_\psi^2)$. Furthermore, these four random intercepts are mutually independent. In addition, $\epsilon_{ijk} \sim N(0,\sigma_\epsilon^2)$ and $e_{ijk} \sim N(0,\sigma_e^2)$ are independent residual error terms in the outcome model and mediator model, respectively.

By the definitions of mediation effect measures in (4) of the main text, we obtain from models (A.6) and (A.7) that

$$
\begin{aligned}
\text{NIE}(j|\mathbf{x}) &= E\big[\beta_{0j} + \theta + \beta_M(\gamma_{0j} + \eta + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + \psi_{ij} + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \phi_{ij} + \epsilon_{ijk}\big] \\
&\quad - E\big[\beta_{0j} + \theta + \beta_M(\gamma_{0j} + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + \psi_{ij} + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \psi_{ij} + \epsilon_{ijk}\big] = \beta_M\eta, \\
\text{NDE}(j|\mathbf{x}) &= E\big[\beta_{0j} + \theta + \beta_M(\gamma_{0j} + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + \psi_{ij} + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \psi_{ij} + \epsilon_{ijk}\big] \\
&\quad - E\big[\beta_{0j} + \beta_M(\gamma_{0j} + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau_i + \psi_{ij} + e_{ijk}) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \psi_{ij} + \epsilon_{ijk}\big] = \theta.
\end{aligned}
$$

3.1.2 Data type 2-A continuous outcome and a binary mediator (Y_cM_b)

In this scenario, the outcome model of Y_{ijk} remains the same as model (A.6), but we model the binary mediator using the following logistic generalized linear mixed model, that is,

$$
\text{logit}\left(P(M_{ijk}=1|A_{ij},\mathbf{X}_{ijk},\tau_i)\right) = \gamma_{0j} + \eta A_{ij} + \boldsymbol{\gamma}_X^T\mathbf{X}_{ijk} + \tau_i + \psi_{ij}, \tag{A.8}
$$

where $\mathrm{logit}(x) = \log\big(\frac{x}{1-x}\big)$ is the link function for h. By the definitions of NIE and NDE in (4) of the main text, for calendar time index j, we obtain

$$\begin{aligned}
\mathrm{NIE}(j|\mathbf{x}) &= E\big[\beta_{0j} + \theta + \beta_M M_{ijk}(1) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \phi_{ij} + \epsilon_{ijk}\big] - E\big[\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \phi_{ij} + \epsilon_{ijk}\big] \\
&= \beta_M[P(M_{ijk}(1) = 1|\mathbf{X}_{ijk} = \mathbf{x}) - P(M_{ijk}(0) = 1|\mathbf{X}_{ijk} = \mathbf{x})] \\
&= \beta_M\big[\kappa^*(1, j|\mathbf{x}) - \kappa^*(0, j|\mathbf{x})\big], \\
\mathrm{NDE}(j|\mathbf{x}) &= E\big[\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \phi_{ij} + \epsilon_{ijk}\big] - E\big[\beta_{0j} + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha_i + \phi_{ij} + \epsilon_{ijk}\big] = \theta,
\end{aligned}$$

where

$$\begin{aligned}
\kappa^*(a, j|\mathbf{x}) &= P(M_{ijk}(a) = 1|\mathbf{X}_{ijk} = \mathbf{x}) \\
&= \int\int P(M_{ijk}(a) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \tau_i = \tau, \psi_{ij} = \psi) f(\tau_i = \tau, \psi_{ij} = \psi|\mathbf{X}_{ijk} = \mathbf{x}) d\tau d\psi \\
&= \int\int P(M_{ijk}(a) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \tau_i = \tau, \psi_{ij} = \psi) f(\tau_i = \tau) f(\psi_{ij} = \psi) d\tau d\psi \\
&= \int\left[\int \frac{\exp(\gamma_{0j} + \eta a + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau + \psi)}{1 + \exp(\gamma_{0j} + \eta a + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau + \psi)} \frac{1}{\sqrt{2}\sigma_\tau} \exp\left(-\frac{\tau^2}{2\sigma_\tau^2}\right) d\tau\right] \times \frac{1}{\sqrt{2}\sigma_\psi} \exp\left(-\frac{\psi^2}{2\sigma_\psi^2}\right) d\psi
\end{aligned} \quad (A.9)$$

To compute (A.9), we can also apply the double STA method (see Web Appendix B in details) and approximate $\kappa^*(a, j|\mathbf{x})$ as

$$\kappa^*(a, j|\mathbf{x}) \approx B_1 + (B_1 - 3B_2 + 2B_3)\,\frac{1}{2}\sigma_\tau^2, \quad (A.10)$$

where

$$\begin{aligned}
B_1 &= \int m^*(\psi|\mathbf{x}) \frac{1}{\sqrt{2}\sigma_\psi} \exp\left(-\frac{\psi^2}{2\sigma_\psi^2}\right) d\psi \approx m^*(0|\mathbf{x}) + \big[m^*(0|\mathbf{x}) - 3m^*(0|\mathbf{x})^2 + 2m^*(0|\mathbf{x})^3\big]\,\frac{1}{2}\sigma_\psi^2, \\
B_2 &= \int m^*(\psi|\mathbf{x})^2 \frac{1}{\sqrt{2}\sigma_\psi} \exp\left(-\frac{\psi^2}{2\sigma_\psi^2}\right) d\psi \approx m^*(0|\mathbf{x})^2 + \big[4m^*(0|\mathbf{x})^2 - 10m^*(0|\mathbf{x})^3 + 6m^*(0|\mathbf{x})^4\big]\,\frac{1}{2}\sigma_\psi^2, \\
B_3 &= \int m^*(\psi|\mathbf{x})^3 \frac{1}{\sqrt{2}\sigma_\psi} \exp\left(-\frac{\psi^2}{2\sigma_\psi^2}\right) d\psi \approx m^*(0|\mathbf{x})^3 + \big[9m^*(0|\mathbf{x})^3 - 21m^*(0|\mathbf{x})^4 + 12m^*(0|\mathbf{x})^5\big]\,\frac{1}{2}\sigma_\psi^2, \\
m^*(\psi|\mathbf{x}) &= \frac{\exp(\gamma_{0j} + \eta a + \boldsymbol{\gamma}_X^T\mathbf{x} + \psi)}{1 + \exp(\gamma_{0j} + \eta a + \boldsymbol{\gamma}_X^T\mathbf{x} + \psi)} = m(0|\mathbf{x}, \psi), \\
m(\tau|\mathbf{x}, \psi) &= \frac{\exp(\gamma_{0j} + \eta a + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau + \psi)}{1 + \exp(\gamma_{0j} + \eta a + \boldsymbol{\gamma}_X^T\mathbf{x} + \tau + \psi)}.
\end{aligned}$$

3.1.3 Data type 3-A binary outcome and a continuous mediator (Y_bM_c)

Under this scenario, the mediator model remains the same as model (A.7), but we assume the binary outcome to follow a logistic generalized linear mixed model as:

$$\mathrm{logit}\left(P(Y_{ijk} = 1|A_{ij}, M_{ijk}, \mathbf{X}_{ijk}, \alpha_i)\right) = \beta_{0j} + \theta A_{ij} + \beta_M M_{ijk} + \boldsymbol{\beta}_X^T\mathbf{X}_{ijk} + \alpha_i + \phi_{ij}. \quad (A.11)$$

According to the (A.7), $e_{ijk} \sim N(0, \sigma_e^2)$, $\tau_i \sim N(0, \sigma_\tau^2)$ and $\psi_{ij} \sim N(0, \sigma_\psi^2)$, then by using similar arguments in Web Appendix A3, we have

$$\begin{aligned}
& P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}) \\
= & \int\int P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi) f(\alpha_i = \alpha, \phi_{ij} = \phi|\mathbf{X}_{ijk} = \mathbf{x}) d\alpha d\phi \\
= & \int\int P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi) f(\alpha_i = \alpha) f(\phi_{ij} = \phi) d\alpha d\phi \\
= & \int\Bigg[\int \frac{\exp(\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha + \phi)}{1 + \exp(\beta_{0j} + \theta + \beta_M M_{ijk}(0) + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha + \phi)} \cdot \frac{1}{\sqrt{2}\sigma_\alpha} \exp\Bigg(-\frac{\alpha^2}{2\sigma_\alpha^2}\Bigg) d\alpha\Bigg] \times \frac{1}{\sqrt{2}\sigma_\phi} \exp\Bigg(-\frac{\phi^2}{2\sigma_\phi^2}\Bigg) d\phi.
\end{aligned}$$

In consideration of random effects and error terms included in M_{ijk}, we rewrite $P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi)$ as

$$\begin{aligned}
& P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi) \\
= & \int P(Y_{ijk} = 1|A_{ij} = 1, M_{ijk}(0) = m, \mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi) f(M_{ijk}(0) = m|A_{ij} = 0, \mathbf{X}_{ijk} = \mathbf{x}) dm \\
= & \int \frac{\exp(\beta_{0j} + \theta + \beta_M m + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha + \phi)}{1 + \exp(\beta_{0j} + \theta + \beta_M m + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha + \phi)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}} \exp\Bigg(-\frac{(m - \gamma_{0j} - \boldsymbol{\gamma}_X^T \mathbf{x})^2}{2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}\Bigg) dm.
\end{aligned}$$

Thus, we have

$$\begin{aligned}
& P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}) \\
= & \int\int P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi) f(\alpha_i = \alpha, \phi_{ij} = \phi|\mathbf{X}_{ijk} = \mathbf{x}) d\alpha d\phi \\
= & \int\int\Bigg[\int P(Y_{ijk} = 1|A_{ij} = 1, M_{ijk}(0) = m, \mathbf{X}_{ijk} = \mathbf{x}, \alpha_i = \alpha, \phi_{ij} = \phi) f(M_{ijk}(0) = m|A_{ij} = 0, \mathbf{X}_{ijk} = \mathbf{x}) dm\Bigg] \\
& \times f(\alpha_i = \alpha) f(\phi_{ij} = \phi) d\alpha d\phi \\
= & \int\Bigg[\int\Bigg[\int \frac{\exp(\beta_{0j} + \theta + \beta_M m + \boldsymbol{\beta}_X^T \mathbf{x} + \alpha + \phi)}{1 + \exp(\beta_{0j} + \theta + \beta_M m + \beta_X^T \mathbf{x} + \alpha + \phi)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}} \cdot \exp\Bigg(-\frac{(m - \gamma_{0j} - \boldsymbol{\gamma}_X^T \mathbf{x})^2}{2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}\Bigg) dm\Bigg] \\
& \times \frac{1}{\sqrt{2}\sigma_\alpha} \exp\Bigg(-\frac{\alpha^2}{2\sigma_\alpha^2}\Bigg) d\alpha\Bigg] \times \frac{1}{\sqrt{2}\sigma_\phi} \exp\Bigg(-\frac{\phi^2}{2\sigma_\phi^2}\Bigg) d\phi.
\end{aligned}$$

Define $\mu^*(a, a^*, j|\mathbf{x}) = P(Y_{ijk}(a, M_{ijk}(a^*)) = 1|\mathbf{X}_{ijk} = \mathbf{x})$ for $a, a^* \in \{0, 1\}$, then, we have

$$\begin{aligned}
\text{logit}[P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] &= \log\Bigg[\frac{P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})}{1 - P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})}\Bigg] \\
&= \log\Bigg[\frac{\mu^*(1, 1, j|\mathbf{x})}{1 - \mu^*(1, 1, j|\mathbf{x})}\Bigg].
\end{aligned}$$

Similarly, we have

$$\begin{aligned}
\text{logit}[P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] &= \log\Bigg[\frac{\mu^*(1, 0, j|\mathbf{x})}{1 - \mu^*(1, 0, j|\mathbf{x})}\Bigg], \\
\text{logit}[P(Y_{ijk}(0, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] &= \log\Bigg[\frac{\mu^*(0, 0, j|\mathbf{x})}{1 - \mu^*(0, 0, j|\mathbf{x})}\Bigg].
\end{aligned}$$

Therefore, the period-specific NIE and NDE are

$$\begin{aligned}
\mathrm{NIE}(j|\mathbf{x}) &= \mathrm{logit}[P(Y_{ijk}(1, M_{ijk}(1)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] - \mathrm{logit}[P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] \\
&= \log\left[\frac{\mu^*(1,1,j|\mathbf{x})}{1-\mu^*(1,1,j|\mathbf{x})}\right] - \log\left[\frac{\mu^*(1,0,j|\mathbf{x})}{1-\mu^*(1,0,j|\mathbf{x})}\right], \\
\mathrm{NDE}(j|\mathbf{x}) &= \mathrm{logit}[P(Y_{ijk}(1, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] - \mathrm{logit}[P(Y_{ijk}(0, M_{ijk}(0)) = 1|\mathbf{X}_{ijk} = \mathbf{x})] \\
&= \log\left[\frac{\mu^*(1,0,j|\mathbf{x})}{1-\mu^*(1,0,j|\mathbf{x})}\right] - \log\left[\frac{\mu^*(0,0,j|\mathbf{x})}{1-\mu^*(0,0,j|\mathbf{x})}\right].
\end{aligned}$$

Of note the above period-specific NIE and NDE involve a triple integral, that is

$$\begin{aligned}
&\mu^*(a, a^*, j|\mathbf{x}) \\
= &\int\left[\int\left[\int \frac{\exp(\beta_{0j} + \theta a + \beta_M m + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha + \phi)}{1 + \exp(\beta_{0j} + \theta a + \beta_M m + \beta_X^T\mathbf{x} + \alpha + \phi)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}} \cdot \exp\left(-\frac{(m - \gamma_{0j} - \eta a^* - \boldsymbol{\gamma}_X^T\mathbf{x})^2}{2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}\right)dm\right]\right. \\
&\left.\times\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha\right] \times \frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi. \qquad \text{(A.12)}
\end{aligned}$$

Here, we propose the triple STA method to approximate it, i.e., using the STA approximation three times. By using similar arguments in Web Appendix B, the inner double integral of $\mu^*(a, a^*, j|\mathbf{x})$ can be approximated as

$$\begin{aligned}
&\int\left[\int \frac{\exp(\beta_{0j} + \theta a + \beta_M m + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha + \phi)}{1 + \exp(\beta_{0j} + \theta a + \beta_M m + \beta_X^T\mathbf{x} + \alpha + \phi)} \cdot \frac{1}{\sqrt{2\pi(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}} \cdot \exp\left(-\frac{(m - \gamma_{0j} - \eta a^* - \boldsymbol{\gamma}_X^T\mathbf{x})^2}{2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)}\right)dm\right] \\
&\times\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha \approx A_1^* + (A_1^* - 3A_2^* + 2A_3^*)\,\frac{1}{2}\beta_M^2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2), \qquad \text{(A.13)}
\end{aligned}$$

where

$$\begin{aligned}
A_1^* &\approx q(\overline{m}|\mathbf{x},0,\phi) + \left[q(\overline{m}|\mathbf{x},0,\phi) - 3q(\overline{m}|\mathbf{x},0,\phi)^2 + 2q(\overline{m}|\mathbf{x},0,\phi)^3\right]\frac{1}{2}\sigma_\alpha^2, \\
A_2^* &\approx q(\overline{m}|\mathbf{x},0,\phi)^2 + \left[4q(\overline{m}|\mathbf{x},0,\phi)^2 - 10q(\overline{m}|\mathbf{x},0,\phi)^3 + 6q(\overline{m}|\mathbf{x},0,\phi)^4\right]\frac{1}{2}\sigma_\alpha^2, \\
A_3^* &\approx q(\overline{m}|\mathbf{x},0,\phi)^3 + \left[9q(\overline{m}|\mathbf{x},0,\phi)^3 - 21q(\overline{m}|\mathbf{x},0,\phi)^4 + 12q(\overline{m}|\mathbf{x},0,\phi)^5\right]\frac{1}{2}\sigma_\alpha^2, \\
q(m|\mathbf{x},\alpha,\phi) &= \frac{\exp(\beta_{0j} + \theta a + \beta_M m + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha + \phi)}{1 + \exp(\beta_{0j} + \theta a + \beta_M m + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha + \phi)},
\end{aligned}$$

and $\overline{m} = \gamma_{0j} + \eta a^* + \boldsymbol{\gamma}_X^T\mathbf{x}$. Note that we can rewrite $q(\overline{m}|\mathbf{x}, 0, \phi)$ as a function of ϕ, that is,

$$q^*(\phi|\mathbf{x},\overline{m}) = q(\overline{m}|\mathbf{x},0,\phi) = \frac{\exp(\beta_{0j} + \theta a + \beta_M\overline{m} + \boldsymbol{\beta}_X^T\mathbf{x} + \phi)}{1 + \exp(\beta_{0j} + \theta a + \beta_M\overline{m} + \boldsymbol{\beta}_X^T\mathbf{x} + \phi)}.$$

Then, after some algebra, the right hand side of (A.13), i.e., $A_1^* + (A_1^* - 3A_2^* + 2A_3^*)\,\frac{1}{2}\beta_M^2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)$, is equal to

$$\begin{aligned}
&q^*(\phi|\mathbf{x},\overline{m}) + [q^*(\phi|\mathbf{x},\overline{m}) - 3q^*(\phi|\mathbf{x},\overline{m})^2 + 2q^*(\phi|\mathbf{x},\overline{m})^3]\frac{1}{2}\left[\sigma_\alpha^2 + \beta_M^2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2)\right] \\
&+[q^*(\phi|\mathbf{x},\overline{m}) - 15q^*(\phi|\mathbf{x},\overline{m})^2 + 50q^*(\phi|\mathbf{x},\overline{m})^3 - 60q^*(\phi|\mathbf{x},\overline{m})^4 + 24q^*(\phi|\mathbf{x},\overline{m})^5]\frac{1}{4}\beta_M^2\sigma_\alpha^2(\sigma_\tau^2 + \sigma_\psi^2 + \sigma_e^2).
\end{aligned}$$

Therefore, the triple integral (A.12) reduces to a single integral as

$$\begin{aligned}\mu^*(a,a^*,j|\mathbf{x}) \;\approx\;& \int \{q^*(\phi|\mathbf{x},\overline{m}) + [q^*(\phi|\mathbf{x},\overline{m}) - 3q^*(\phi|\mathbf{x},\overline{m})^2 + 2q^*(\phi|\mathbf{x},\overline{m})^3]\frac{1}{2}\left[\sigma_\alpha^2 + \beta_M^2(\sigma_\tau^2+\sigma_\psi^2+\sigma_e^2)\right] + [q^*(\phi|\mathbf{x},\overline{m}) \\ & -15q^*(\phi|\mathbf{x},\overline{m})^2 + 50q^*(\phi|\mathbf{x},\overline{m})^3 - 60q^*(\phi|\mathbf{x},\overline{m})^4 + 24q^*(\phi|\mathbf{x},\overline{m})^5]\frac{1}{4}\beta_M^2\sigma_\alpha^2(\sigma_\tau^2+\sigma_\psi^2+\sigma_e^2)\} \\ & \times \frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi. \qquad \text{(A.14)}\end{aligned}$$

For each term in (A.14), once again, we apply an additional second-order Taylor expansion for that around $\phi = 0$ and approximate the distinct summand terms as

$$\begin{aligned}A_1^{**} &= \int q^*(\phi|\mathbf{x},\overline{m})\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi \approx q^*(0|\mathbf{x},\overline{m}) + \left[q^*(0|\mathbf{x},\overline{m}) - 3q^*(0|\mathbf{x},\overline{m})^2 + 2q^*(0|\mathbf{x},\overline{m})^3\right]\frac{1}{2}\sigma_\phi^2, \\ A_2^{**} &= \int q^*(\phi|\mathbf{x},\overline{m})^2\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi \approx q^*(0|\mathbf{x},\overline{m})^2 + \left[4q^*(0|\mathbf{x},\overline{m})^2 - 10q^*(0|\mathbf{x},\overline{m})^3 + 6q^*(0|\mathbf{x},\overline{m})^4\right]\frac{1}{2}\sigma_\phi^2, \\ A_3^{**} &= \int q^*(\phi|\mathbf{x},\overline{m})^3\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi \approx q^*(0|\mathbf{x},\overline{m})^3 + \left[9q^*(0|\mathbf{x},\overline{m})^3 - 21q^*(0|\mathbf{x},\overline{m})^4 + 12q^*(0|\mathbf{x},\overline{m})^5\right]\frac{1}{2}\sigma_\phi^2, \\ A_4^{**} &= \int q^*(\phi|\mathbf{x},\overline{m})^4\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi \approx q^*(0|\mathbf{x},\overline{m})^4 + \left[16q^*(0|\mathbf{x},\overline{m})^4 - 36q^*(0|\mathbf{x},\overline{m})^5 + 20q^*(0|\mathbf{x},\overline{m})^6\right]\frac{1}{2}\sigma_\phi^2, \\ A_5^{**} &= \int q^*(\phi|\mathbf{x},\overline{m})^5\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi \approx q^*(0|\mathbf{x},\overline{m})^5 + \left[25q^*(0|\mathbf{x},\overline{m})^5 - 55q^*(0|\mathbf{x},\overline{m})^6 + 30q^*(0|\mathbf{x},\overline{m})^7\right]\frac{1}{2}\sigma_\phi^2.\end{aligned}$$

Thus, based on triple STA method, equation (A.14) is given by the following closed-form representation

$$\begin{aligned}\mu^*(a,a^*,j|\mathbf{x}) \;\approx\;& A_1^{**} + (A_1^{**} - 3A_2^{**} + 2A_3^{**})\frac{1}{2}\left[\sigma_\alpha^2 + \beta_M^2(\sigma_\tau^2+\sigma_\psi^2+\sigma_e^2)\right] \\ & + (A_1^{**} - 15A_2^{**} + 50A_3^{**} - 60A_4^{**} + 24A_5^{**})\frac{1}{4}\beta_M^2\sigma_\alpha^2(\sigma_\tau^2+\sigma_\psi^2+\sigma_e^2). \qquad \text{(A.15)}\end{aligned}$$

3.1.4 Data type 4-A binary outcome and a binary mediator ($Y_b M_b$)

When the outcome model and the mediator model are specified in (A.11) and (A.8) as a pair of logistic generalized linear mixed models (such that both g and h are logistic link functions), respectively, by using similar technique in Web Appendix A4, we can show that the period-specific mediation effect measures are given by

$$\begin{aligned}\text{NIE}(j|\mathbf{x}) &= \log\left\{\frac{\lambda^*(1,0,j|\mathbf{x})[1-\kappa^*(1,j|\mathbf{x})] + \lambda^*(1,1,j|\mathbf{x})\kappa^*(1,j|\mathbf{x})}{1-[\lambda^*(1,0,j|\mathbf{x})[1-\kappa^*(1,j|\mathbf{x})] + \lambda^*(1,1,j|\mathbf{x})\kappa^*(1,j|\mathbf{x})]}\right\} \\ &\quad - \log\left\{\frac{\lambda^*(1,0,j|\mathbf{x})[1-\kappa^*(0,j|\mathbf{x})] + \lambda^*(1,1,j|\mathbf{x})\kappa^*(0,j|\mathbf{x})}{1-[\lambda^*(1,0,j|\mathbf{x})[1-\kappa^*(0,j|\mathbf{x})] + \lambda^*(1,1,j|\mathbf{x})\kappa^*(0,j|\mathbf{x})]}\right\}, \\ \text{NDE}(j|\mathbf{x}) &= \log\left\{\frac{\lambda^*(1,0,j|\mathbf{x})[1-\kappa^*(0,j|\mathbf{x})] + \lambda^*(1,1,j|\mathbf{x})\kappa^*(0,j|\mathbf{x})}{1-[\lambda^*(1,0,j|\mathbf{x})[1-\kappa^*(0,j|\mathbf{x})] + \lambda^*(1,1,j|\mathbf{x})\kappa^*(0,j|\mathbf{x})]}\right\} \\ &\quad - \log\left\{\frac{\lambda^*(0,0,j|\mathbf{x})[1-\kappa^*(0,j|\mathbf{x})] + \lambda^*(0,1,j|\mathbf{x})\kappa^*(0,j|\mathbf{x})}{1-[\lambda^*(0,0,j|\mathbf{x})[1-\kappa^*(0,j|\mathbf{x})] + \lambda^*(0,1,j|\mathbf{x})\kappa^*(0,j|\mathbf{x})]}\right\},\end{aligned}$$

where $\kappa^*(a,j|\mathbf{x})$ is defined in equation (A.9), and for $a, a^* \in \{0,1\}$, we have

$$\lambda^*(a,a^*,j|\mathbf{x}) = \int\left[\int \frac{\exp\left(\beta_{0j} + \theta a + \beta_M a^* + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha + \phi\right)}{1+\exp\left(\beta_{0j} + \theta a + \beta_M a^* + \boldsymbol{\beta}_X^T\mathbf{x} + \alpha + \phi\right)}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha\right]\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi \qquad \text{(A.16)}$$

By applying the double-STA method, we can approximate $\lambda^*(a, a^*, j|\mathbf{x})$ as

$$\lambda^*(a, a^*, j|\mathbf{x}) \quad \approx \quad C_1 + (C_1 - 3C_2 + 2C_3)\, \frac{1}{2}\sigma_\alpha^2, \tag{A.17}$$

where

$$\begin{aligned}
C_1 &= \int p(\phi|\mathbf{x}) \frac{1}{\sqrt{2}\sigma_\phi} \exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right) d\phi \approx p(0|\mathbf{x}) + \left[p(0|\mathbf{x}) - p(0|\mathbf{x})^2 + 2p(0|\mathbf{x})^3\right] \frac{1}{2}\sigma_\phi^2, \\
C_2 &= \int p(\phi|\mathbf{x})^2 \frac{1}{\sqrt{2}\sigma_\phi} \exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right) d\phi \approx p(0|\mathbf{x})^2 + \left[4p(0|\mathbf{x})^2 - 10p(0|\mathbf{x})^3 + 6p(0|\mathbf{x})^4\right] \frac{1}{2}\sigma_\phi^2, \\
C_3 &= \int p(\phi|\mathbf{x})^3 \frac{1}{\sqrt{2}\sigma_\phi} \exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right) d\phi \approx p(0|\mathbf{x})^3 + \left[9p(0|\mathbf{x})^3 - 21p(0|\mathbf{x})^4 + 12p(0|\mathbf{x})^5\right] \frac{1}{2}\sigma_\phi^2, \\
p(\phi|\mathbf{x}) &= \frac{\exp(\beta_{0j} + \theta a + \beta_M a^* + \boldsymbol{\beta}_X^T \mathbf{x} + \phi)}{1 + \exp(\beta_{0j} + \theta a + \beta_M a^* + \boldsymbol{\beta}_X^T \mathbf{x} + \phi)}.
\end{aligned}$$

3.1.5 Variance estimation

We can also use the same jackknife variance estimator defined in (13) of the main text to compute variance estimation, that is, for $\boldsymbol{\xi} \in \{\mathrm{NIE}, \mathrm{NDE}, \mathrm{TE}, \mathrm{MP}\}$, we have

$$\widehat{\mathrm{Var}}(\widehat{\boldsymbol{\xi}}) = \frac{I-1}{I} \sum_{i=1}^{I} (\widehat{\boldsymbol{\xi}}_{-i} - \overline{\boldsymbol{\xi}})^2,$$

where $\overline{\boldsymbol{\xi}} = \frac{1}{I}\sum_{i=1}^{I} \widehat{\boldsymbol{\xi}}_{-i}$, and $\widehat{\boldsymbol{\xi}}_{-i}$ is the delete-one-cluster estimator obtained by removing the observations in cluster i.

3.2 Under an exposure-time dependent treatment effect structure

3.2.1 Data type 1—A continuous outcome and a continuous mediator ($Y_c M_c$)

When both the outcome and mediator are continuous variables, we write the outcome model and the mediator model as the following pair of linear mixed models

$$Y_{ijk} \quad = \quad \beta_{0j} + \theta_{E_{ij}} A_{ij} + \beta_M M_{ijk} + \boldsymbol{\beta}_X^T \mathbf{X}_{ijk} + \alpha_i + \phi_{ij} + \epsilon_{ijk}, \tag{A.18}$$

$$M_{ijk} \quad = \quad \gamma_{0j} + \eta_{E_{ij}} A_{ij} + \boldsymbol{\gamma}_X^T \mathbf{X}_{ijk} + \tau_i + \psi_{ij} + e_{ijk}, \tag{A.19}$$

where $E_{ij} \in \{0, 1, \ldots, E\}$, the four random intercepts α_i, ϕ_{ij}, τ_i and ψ_{ij} are the same as in Section (3.1.1), $\epsilon_{ijk} \sim N(0, \sigma_\epsilon^2)$ and $e_{ijk} \sim N(0, \sigma_e^2)$ are independent residual error terms in the outcome model and mediator model, respectively. By the definitions of mediation effect measures in (15) of the main text, for $E_{ij} = e$, we obtain from models (A.18) and (A.19) that

$$\begin{aligned}
\mathrm{NIE}(j, e|\mathbf{x}) &= \beta_M \eta_e, \\
\mathrm{NDE}(j, e|\mathbf{x}) &= \theta_e, \qquad 1 \le e \le j-1 \ \text{ and } \ 2 \le j \le J.
\end{aligned}$$

Therefore, the exposure-time specific $\mathrm{NIE}(e|\mathbf{x})$ and $\mathrm{NDE}(e|\mathbf{x})$ are equal to $\beta_M \eta_e$ and θ_e respectively since both $\mathrm{NIE}(j, e|\mathbf{x})$ and $\mathrm{NDE}(j, e|\mathbf{x})$ are free of calendar time j and covariates, and the $\mathrm{MP}(e|\mathbf{x}) = \beta_M \eta_e / (\beta_M \eta_e + \theta_e)$. And according to definitions in (17) of the main text, the overall summary mediation effect measures across each exposure times are given

$$\text{NIE}(\mathbf{x}) = \frac{1}{J-1}\sum_{e=1}^{J-1}\beta_M\eta_e, \quad \text{NDE}(\mathbf{x}) = \frac{1}{J-1}\sum_{e=1}^{J-1}\theta_e, \quad \text{MP}(\mathbf{x}) = \frac{\beta_M\sum_{e=1}^{J-1}\eta_e}{\sum_{e=1}^{J-1}(\beta_M\eta_e+\theta_e)}.$$

3.2.2 Data type 2—A continuous outcome and a binary mediator (Y_cM_b)

When the outcome model of Y_{ijk} remains the same as model (A.18) and the mediator is binary, we apply the following logistic generalized linear mixed model to model the mediator, that is

$$\text{logit}\left(P(M_{ijk}=1|A_{ij},\mathbf{X}_{ijk},\tau_i)\right) = \gamma_{0j} + \eta_{E_{ij}}A_{ij} + \boldsymbol{\gamma}_X^T\mathbf{X}_{ijk} + \tau_i + \psi_{ij}. \tag{A.20}$$

Then, according to the definitions of (15) of the main text, under eligible calendar time index j at exposure time e, we obtain

$$\begin{aligned}\text{NIE}(j,e|\mathbf{x}) &= \beta_M\left[\kappa_e^*(1,j|\mathbf{x}) - \kappa_e^*(0,j|\mathbf{x})\right],\\ \text{NDE}(j,e|\mathbf{x}) &= \theta_e, \qquad 1\le e\le j-1 \ \text{ and } \ 2\le j\le J,\end{aligned}$$

where $\kappa_e^*(a,j|\mathbf{x})$ is given by the double integral over the random-effects distribution in the mediator model,

$$\kappa_e^*(a,j|\mathbf{x}) = \int\left[\int \frac{\exp(\gamma_{0j}+\eta_e a+\boldsymbol{\gamma}_X^T\mathbf{x}+\tau)}{1+\exp(\gamma_{0j}+\eta_e a+\boldsymbol{\gamma}_X^T\mathbf{x}+\tau)}\frac{1}{\sqrt{2}\sigma_\tau}\exp\left(-\frac{\tau^2}{2\sigma_\tau^2}\right)d\tau\right]\cdot\frac{1}{\sqrt{2}\sigma_\psi}\exp\left(-\frac{\psi^2}{2\sigma_\psi^2}\right)d\psi, \tag{A.21}$$

for $a\in\{0,1\}$, and which can be approximated similar to (A.10). Under this situation, by (16) of the main text, the exposure-time specific mediation effect measures are

$$\begin{aligned}\text{NIE}(e|\mathbf{x}) &= \frac{1}{J-e}\sum_{j=e+1}^{J}\beta_M\left[\kappa_e^*(1,j|\mathbf{x})-\kappa_e^*(0,j|\mathbf{x})\right], \quad \text{NDE}(e|\mathbf{x}) = \frac{1}{J-e}\sum_{j=e+1}^{J}\theta_e = \theta_e,\\ \text{MP}(e|\mathbf{x}) &= \frac{\sum_{j=e+1}^{J}\beta_M\left[\kappa_e^*(1,j|\mathbf{x})-\kappa_e^*(0,j|\mathbf{x})\right]}{\sum_{j=e+1}^{J}\left\{\beta_M\left[\kappa_e^*(1,j|\mathbf{x})-\kappa_e^*(0,j|\mathbf{x})\right]+\theta_e\right\}}, \qquad 1\le e\le J-1.\end{aligned}$$

3.2.3 Data type 3—A binary outcome and a continuous mediator (Y_bM_c)

Under this scenario, the mediator model is the same as that in (A.19). For the binary outcome, we apply a logistic generalized linear mixed model to model,

$$\text{logit}\left(P(Y_{ijk}=1|A_{ij},M_{ijk},\mathbf{X}_{ijk},\alpha_i)\right) = \beta_{0j} + \theta_{E_{ij}}A_{ij} + \beta_M M_{ijk} + \boldsymbol{\beta}_X^T\mathbf{X}_{ijk} + \alpha_i + \phi_{ij}. \tag{A.22}$$

By using the same technique in Web Appendix A3 and Section 3.1.3, the NIE and NDE during calendar time j at exposure time e defined in (15) of the main text are given by

$$\begin{aligned}\text{NIE}(j,e|\mathbf{x}) &= \log\left[\frac{\mu_e^*(1,1,j|\mathbf{x})}{1-\mu_e^*(1,1,j|\mathbf{x})}\right] - \log\left[\frac{\mu_e^*(1,0,j|\mathbf{x})}{1-\mu_e^*(1,0,j|\mathbf{x})}\right],\\ \text{NDE}(j,e|\mathbf{x}) &= \log\left[\frac{\mu_e^*(1,0,j|\mathbf{x})}{1-\mu_e^*(1,0,j|\mathbf{x})}\right] - \log\left[\frac{\mu_e^*(0,0,j|\mathbf{x})}{1-\mu_e^*(0,0,j|\mathbf{x})}\right], \qquad 1\le e\le j-1 \ \text{ and } \ 2\le j\le J,\end{aligned}$$

where for $a, a^* \in \{0,1\}$,

$$
\begin{aligned}
\mu_e^*(a,a^*,j) &= P(Y_{ijk}(e, M_{ijk}(e^*))=1|\mathbf{X}_{ijk}=\mathbf{x}) \\
&= \int\Bigg[\int\Bigg[\int \frac{\exp(\beta_{0j}+\theta_e a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha+\phi)}{1+\exp(\beta_{0j}+\theta_e a+\beta_M m+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha+\phi)}\frac{1}{\sqrt{2\pi(\sigma_\tau^2+\sigma_\psi^2+\sigma_e^2)}} \\
&\quad \times\exp\left(-\frac{(m-\gamma_{0j}-\eta_e a^*-\boldsymbol{\gamma}_X^T\mathbf{x})^2}{2(\sigma_\tau^2+\sigma_\psi^2+\sigma_e^2)}\right)dm\Bigg]\cdot\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha\Bigg]\cdot\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi,
\end{aligned} \tag{A.23}
$$

is a calendar time-specific triple integral, which can be approximated by triple STA method similar to (A.15). The exposure-time specific mediation effect measures NIE($e|\mathbf{x}$), NDE($e|\mathbf{x}$) and MP($e|\mathbf{x}$) can then be obtained based on (16) of the main text. After that, the overall summary mediation effect measures based on uniformly weighted exposure-time averages, i.e., NIE($\mathbf{x}$), NDE($\mathbf{x}$) and MP($\mathbf{x}$), can be obtained through (17) of the main text straightforward.

3.2.4 Data type 4—A binary outcome and a binary mediator (Y_bM_b)

When the outcome model and the mediator model are correctly specified in (A.22) and (A.20) as a pair of logistic generalized linear mixed models, respectively, both g and h are logistic link functions under this scenario. Then, by using the same technique in Web Appendix A4 for period-specific NIE($j|\mathbf{x}$) and NDE($j|\mathbf{x}$) under an instantaneous and constant treatment effect structure, we obtain the NIE and NDE during calendar time j at exposure time e as

$$
\begin{aligned}
\text{NIE}(j,e|\mathbf{x}) &= \log\left\{\frac{\lambda_e^*(1,0,j|\mathbf{x})[1-\kappa_e^*(1,j|\mathbf{x})]+\lambda_e^*(1,1,j|\mathbf{x})\kappa_e^*(1,j|\mathbf{x})}{1-[\lambda_e^*(1,0,j|\mathbf{x})[1-\kappa_e^*(1,j|\mathbf{x})]+\lambda_e^*(1,1,j|\mathbf{x})\kappa_e^*(1,j|\mathbf{x})]}\right\} \\
&\quad -\log\left\{\frac{\lambda_e^*(1,0,j|\mathbf{x})[1-\kappa_e^*(0,j|\mathbf{x})]+\lambda_e^*(1,1,j|\mathbf{x})\kappa_e^*(0,j|\mathbf{x})}{1-[\lambda_e^*(1,0,j|\mathbf{x})[1-\kappa_e^*(0,j|\mathbf{x})]+\lambda_e^*(1,1,j|\mathbf{x})\kappa_e^*(0,j|\mathbf{x})]}\right\}, \\
\text{NDE}(j,e|\mathbf{x}) &= \log\left\{\frac{\lambda_e^*(1,0,j|\mathbf{x})[1-\kappa_e^*(0,j|\mathbf{x})]+\lambda_e^*(1,1,j|\mathbf{x})\kappa_e^*(0,j|\mathbf{x})}{1-[\lambda_e^*(1,0,j|\mathbf{x})[1-\kappa_e^*(0,j|\mathbf{x})]+\lambda_e^*(1,1,j|\mathbf{x})\kappa_e^*(0,j|\mathbf{x})]}\right\} \\
&\quad -\log\left\{\frac{\lambda_e^*(0,0,j|\mathbf{x})[1-\kappa_e^*(0,j|\mathbf{x})]+\lambda_e^*(0,1,j|\mathbf{x})\kappa_e^*(0,j|\mathbf{x})}{1-[\lambda_e^*(0,0,j|\mathbf{x})[1-\kappa_e^*(0,j|\mathbf{x})]+\lambda_e^*(0,1,j|\mathbf{x})\kappa_e^*(0,j|\mathbf{x})]}\right\}, \qquad 1\le e\le j-1 \text{ and } 2\le j\le J,
\end{aligned}
$$

where $\kappa_e^*(a,j|\mathbf{x})(a\in\{0,1\})$ is defined in (A.21), and

$$
\begin{aligned}
&\lambda_e^*(a,a^*,j|\mathbf{x}) \\
&= \int\Bigg[\int \frac{\exp\left(\beta_{0j}+\theta_e a+\beta_M a^*+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha+\phi\right)}{1+\exp\left(\beta_{0j}+\theta_e a+\beta_M a^*+\boldsymbol{\beta}_X^T\mathbf{x}+\alpha+\phi\right)}\frac{1}{\sqrt{2}\sigma_\alpha}\exp\left(-\frac{\alpha^2}{2\sigma_\alpha^2}\right)d\alpha\Bigg]\frac{1}{\sqrt{2}\sigma_\phi}\exp\left(-\frac{\phi^2}{2\sigma_\phi^2}\right)d\phi
\end{aligned} \tag{A.24}
$$

for $a, a^* \in \{0,1\}$, which can be approximated similar to (A.17) through double STA method. Then, the exposure-time specific mediation effect measures can be directly obtained from (16) of the main text with $\omega(j,e)=\frac{1}{J-e}$, and the overall summary mediation effect measures NIE($\mathbf{x}$), NDE($\mathbf{x}$) and MP($\mathbf{x}$), can be obtained through (17) of the main text straightforward.

3.2.5 Variance estimation

As for the variance estimation, we can also use the same jackknife variance estimator defined in (13) of the main text to compute $\widehat{\text{Var}}(\widehat{\boldsymbol{\xi}})$ and $\widehat{\text{Var}}(\widehat{\boldsymbol{\xi}}(e|\mathbf{x}))$, where $\boldsymbol{\xi}(e|\mathbf{x})\in\{\text{NIE}(e|\mathbf{x}),\text{NDE}(e|\mathbf{x}),\text{TE}(e|\mathbf{x}),\text{MP}(e|\mathbf{x})\}$ for $e\in\{1,2,\ldots,J-1\}$.

For ease of reference, we summarize the period-specific NIE($j|\mathbf{x}$) and NDE($j|\mathbf{x}$) expressions, as well as $\boldsymbol{\xi}(e|\mathbf{x}) \in \{\text{NIE}(e|\mathbf{x}), \text{NDE}(e|\mathbf{x}), \text{TE}(e|\mathbf{x}), \text{MP}(e|\mathbf{x})\}$ for $e \in \{1, 2, \ldots, J-1\}$, under each data type in Table S1.

4 Web Appendix D: Simulation studies under an exposure-time dependent treatment effect

The simulation settings for evaluating mediation analysis assuming an exposure-time dependent treatment effect are similar to those in Section 5 of the main text, that is, three levels of sample size with $I \in \{15, 30, 60\}$, $N_{ij} = 20$ individuals per each cluster, $J = 4$ time points are considered in each calendar period. Besides, we set $\beta_{01} = \gamma_{01} = 0$, $\beta_{0(j+1)} - \beta_{0(j)} = 0.1 \times (0.5)^{j-1}$ and $\gamma_{0(j+1)} - \gamma_{0(j)} = 0.3 \times (0.5)^{j-1}$ for $j \geq 1$. For each data type and cluster, we consider the exposure A_{ij} as a binary variable and no confounders in both the outcome and the mediator models. A total of 1000 simulation replications are generated for each scenario to evaluate the finite-sample performance of the proposed mediation methods in cross-sectional SW-CRTs. We also report the percent bias of estimates (Bias(%)), Monte Carlo standard deviations of the 1000 estimates (MCSD), average estimated standard error based on jackknifing (AESE) and coverage probability (CP) of the 95% confidence intervals.

For data type $Y_c M_c$ (i.e., a continuous outcome and a continuous mediator), to generate exposure-time dependent treatment effect, we fix MP(e) = 0.25 and vary TE at each exposure time e, that is, TE(e) $\in \{0.8, 1, 1.2\}$ under $e = 1$, 2 and 3, respectively. So by the relationships NIE(e) = TE(e)×MP(e) and NDE(e) = TE(e)×(1−MP(e)), both NIE(e) and NDE(e) also vary at each exposure time e. Then, the overall NIE, NDE, TE and MP are average of the exposure-time specific NIE(e), NDE(e), TE(e) and MP(e), respectively. Furthermore, we can obtain $\theta_e = (1 - \text{MP}(e)) \times \text{TE}(e)$ at each exposure time e. As for η_e, which is set to be 0.32, 0.40 and 0.48 at $e = 1$, 2 and 3, respectively. After such specifications, β_M can be determined by $\text{MP}(e) \times \text{TE}(e)/\eta_e$. Then, by using the same procedure and same other parameter settings described in Section 5.1 of the main text, we generate M_{ijk} and Y_{ijk} based on model (18) and (19) without $\mathbf{X}_{ijk}$ in the main text, respectively. The percent bias (%), MCSD, AESE and CP (%) for estimating the exposure-time specific mediation measures $\widehat{\text{NIE}}(e)$, $\widehat{\text{NDE}}(e)$, $\widehat{\text{TE}}(e)$ and $\widehat{\text{MP}}(e)$ as well as corresponding summary mediation measures are presented in Table S5.

For data type $Y_c M_b$ (i.e., a continuous outcome and a binary mediator), we still keep MP(e) = 0.25 at each exposure time, and let TE(e) = (0.8, 1, 1.2) and $\eta_e \in \{0.32, 0.40, 0.48\}$ at $e = 1$, 2 and 3, respectively. So θ_e is also the same as that in data type $Y_c M_c$, that is, $\theta_e \in \{0.60, 0.75, 0.90\}$ at $e = 1$, 2 and 3, respectively. Then, based on each period j, MP and TE at each exposure time e, β_M can be obtained by average of results $\text{MP}(j,e) \times \text{TE}(j,e)/\{\kappa_e(1,j|0) - \kappa_e(0,j|0)\}$. As for the remaining simulation parameters, which are set to be the same as those in data type $Y_c M_b$ in section 5.1 of the main text. Based on the logistic regression (20) without confounders $\mathbf{X}_{ijk}$, we first generate the mediator M_{ijk}. Then, we generate Y_{ijk} by using the same procedure as in data type $Y_c M_c$. The corresponding simulation results when the single integral is evaluated using both GHQ and STA methods are provided in Table S6.

For data type $Y_b M_c$ (i.e., a binary outcome and a continuous mediator). According to the results in (16) of the main text, for each exposure time e, it is difficult to solve the system of equations $\text{MP}(j,e) \times \text{TE}(j,e) = \mathcal{NIE}(\beta_{0j}, \theta_e, \beta_M, \gamma_{0j}, \eta_e)$ and $(1 - \text{MP}(j,e)) \times \text{TE}(j,e) = \mathcal{NDE}(\beta_{0j}, \theta_e, \beta_M, \gamma_{0j}, \eta_e)$ by fixing MP(j,e) and TE(j,e). Thus, we turn to an alternative approach, that is, we first set an initial value of MP (denoted as MP_0) to be 0.25, and TE (denoted as TE_0) to be a vector of $(0.8, 1, 1.2)$, $\eta_e \in \{0.32, 0.40, 0.48\}$. Then let $\theta_e = (1 - \mathrm{MP}_0) \times \mathrm{TE}_0$, and $\beta_M = \frac{1}{3}\sum_{e=1}^{3}\big(\mathrm{MP}_0 \times \mathrm{TE}_0/\eta_e\big)$. Based on the same parameter settings described in generating data type Y_bM_c in Section 5.1, we can generate mediator M_{ijk} and outcome Y_{ijk} by the same procedure therein. We then obtain the empirical true values of NIE(e), NDE(e), TE(e) and MP(e) at each exposure time based on (16) of the main text. The corresponding simulation results from double-STA method are presented in Table S7.

Due to the same reason as data type Y_bM_c, it is also difficult to obtain θ_e and β_M by solving the system of equations $\mathrm{MP}(j,e) \times \mathrm{TE}(j,e) = \mathcal{NIE}(\beta_{0j}, \theta_e, \beta_M, \gamma_{0j}, \eta_e)$ and $(1 - \mathrm{MP}(j,e)) \times \mathrm{TE}(j,e) = \mathcal{NDE}(\beta_{0j}, \theta_e, \beta_M, \gamma_{0j}, \eta_e)$ when we fix $\mathrm{MP}(j,e)$, $\mathrm{TE}(j,e)$ and η_e. So we use the same way as data type Y_bM_c to generate data and compute empirical mediation measures in data type Y_bM_b (i.e., a binary outcome and a binary mediator). Specifically, we keep the same MP_0, TE_0 and η_e as those in data type Y_bM_c but let $\beta_M = 5 \times \frac{1}{3}\sum_{e=1}^{3}\big(\mathrm{MP}_0 \times \mathrm{TE}_0/\eta_e\big)$. The other parameter settings are the same as those in data type Y_bM_b of Section 5.1. Empirical true values of NIE(e), NDE(e), TE(e) and MP(e) at each exposure time and their corresponding estimation results based on GHQ and STA methods are summarized in Table S8.

According to results in Table S5, the percent biases for all mediation measures are smaller than 1% except for $\widehat{\mathrm{MP}}(e)$ at $e = 1$ and $\widehat{\mathrm{NIE}}(e)$ at $e = 2$ when the number of cluster is 15. Their AESEs are in good agreement with MCSDs, and corresponding CPs are close to the nominal level. Similarly, it can be seen from Table S6 that all absolute percent bias of $\widehat{\mathrm{NIE}}$ are smaller than 5% except for that from GHQ at $e = 3$, and all absolute percent bias of $\widehat{\mathrm{NDE}}$ and $\widehat{\mathrm{TE}}$ are smaller than 2%. This indicates that both GHQ and STA methods lead to satisfactory estimators for NIE, NDE and TE. For $\widehat{\mathrm{MP}}$, as expected, its absolute percent bias increases with e since the effective sample size becomes smaller for a larger exposure time level due to fewer observed clusters received a longer treatment duration. Typically, its absolute percent bias can be as large as 32.72% (STA method at $e = 3$ when $I = 15$). However, when the number of cluster increases to 60, all absolute percent biases of $\widehat{\mathrm{MP}}$ are around 6%, and the percent bias is smaller than 10% at $e = 3$. Comparing results from GHQ with those from STA, the percent bias of each mediation measure is more or less the same except for that of $\widehat{\mathrm{MP}}$. When the number of cluster is small (e.g., 15), the absolute percent bias of $\widehat{\mathrm{MP}}$ from GHQ is smaller than that from STA. When the number of cluster is relative large (e.g., 60), the absolute percent bias of $\widehat{\mathrm{MP}}$ from STA are smaller than that from GHQ. In addition, the MCSD and AESE from both integral approximation methods are close, leading to nominal coverage of the resulting confidence intervals.

Results in Table S7 show that all absolute percent biases of $\widehat{\mathrm{NIE}}$, $\widehat{\mathrm{NDE}}$ and $\widehat{\mathrm{TE}}$ are small especially when the $I = 60$. The maximum absolute percent bias of $\widehat{\mathrm{MP}}$ is 20.62%, which occurs at $e = 3$ under $I = 15$, and when the number of cluster is 60, the average absolute percent bias of overall summary $\widehat{\mathrm{MP}}$ reduces to as small as 2.68%. The coverage probabilities under the Y_bM_c data type are all close to the nominal level. The performance of both GHQ and STA methods in Table S8 is generally similar to that in Table S6 across levels of sample size and exposure time levels.

5 Web Appendix E: A tutorial for the mediateSWCRT package

The `mediateSWCRT` package calculates the point and interval estimates for the NIE, NDE, TE and MP in a stepped wedge cluster randomized trials with a constant treatment effect or an exposure-time dependent treatment effect, as described in the main text. The source files for the `mediateSWCRT` is provided on GitHub platform https://github.com/Zhiqiangcao/mediateSWCRT.

First, use the following statements to install the `mediateSWCRT` package

```
library(devtools)
install_github("Zhiqiangcao/mediateSWCRT")
```

The main function of the "`mediateSWCRT`" package is mediate_swcrt(), which provides the mediation analysis results. It can be called with,

`mediate_swcrt(data,method,outcome,mediator,treatment,cluster,period,exposure, covariate.outcome,covariate.mediator,na.rm,a0,a1,binary.o,binary.m,time.dependent)`

This function has 15 arguments, that is:

- data: (Required) The name of the dataset.
- method: Two approximate methods are provided, one is GHQ (Gauss-Hermite Quadrature), the other is STA (second-order Taylor approximate). When both the outcome and mediator are continuous, the method choice is irrelevant; when the outcome is binary and mediator is continuous, we default to the STA method.
- outcome: (Required) Name of the outcome variable, which should be either a continuous or binary datatype.
- mediator: (Required) Name of the mediator variable, which should be either a continuous or binary datatype.
- treatment: (Required) Name of the treatment variable, which should be either a continuous or binary datatype. When there is a implementation period, then corresponding treatment status should be set to `-1`, which is mainly for convenience.
- cluster: (Required) Name of the cluster variable, which should be a factor.
- period: (Required) Name of the period variable, which should be a factor.
- exposure: Name of the exposure time variable, which should be a factor. For time-dependent model, this argument is required. For constant treatment effect model, if dataset has no exposure variable, then set it to NULL
- covariate.outcome: A vector of names showing the confounding variables used in the outcome model. The default value is NULL, which represents no confounding variables. We only accepted continuous and binary confounding variables, if one confounding variable is categorical, please set it to a series of binary variables in advance.
- covariate.mediator: A vector of names showing the confounding variables used in the mediator model. The default value is NULL, which represents no confounding variables. We only accepted continuous and binary confounding variables, if one confounding variable is categorical, please set it to a series of binary variables in advance.
- a0: The reference treatment level in defining TE and NIE. The default value is 0

- a1: The treatment level of interest in defining TE and NIE. The default value is 1
- binary.o: (Required) If the outcome is binary, set to 1. If the outcome is continuous, set to 0.
- binary.m: (Required) If the mediator is binary, set to 1. If the mediator is continuous, set to 0.
- time.dependent: (Required) If the treatment effect is time-dependent, set to TRUE. If the treatment effect is constant, set to FALSE.

We now illustrate the usage of the mediate_swcrt function. For conducting mediation analysis with a constant treatment effect, first, we use the gen_data_hhm() function in "`mediateSWCRT`" to simulate a dataset based on a SW-CRT.

```
library(mediateSWCRT)
I = 15
J = 4
n = 20
beta = cumsum(c(0,0.1,0.1/2,0.1/(2^2)))
gamma = cumsum(c(0,0.3,0.3/2,0.3/(2^2)))
sigma_tau = sigma_a = 0.334
sigma_em = sigma_ey = 1
set.seed(123456)
mydata1 = gen_data_hhm(I,J,n,beta,gamma,theta=0.75,beta_M=0.625,eta=0.4,sigma_a,
sigma_ey,sigma_tau,sigma_em,binary.o=0,binary.m=0)
covdata = data.frame("X1" = numeric(), "X2" = numeric())
set.seed(100)
for(i in 1:I){
  for(j in 1:J){
    x1_ijk = rnorm(n,mean=0.5)
    x2_ijk = rnorm(n,sd=0.1)
    covdata = rbind(covdata, data.frame(cbind(X1 = x1_ijk, X2 = x2_ijk)))
  }
}
mydata1 = data.frame(mydata1,covdata)
```

This dataset, named mydata1, has 15 clusters and 4 periods with 20 individuals per each cluster-period. It includes a continuous outcome Y and a continuous mediator M, binary treatment A and time since intervention E (i.e., exposure time). Besides, cluster-level random intercepts (i.e, α and τ) to account for correlated outcomes within clusters in outcome model and mediator model are also included. The above code is set to one scenario of simulated data type Y_cM_c in Section 5.1 of the main text in addition to two confounding variables ($X1$ and $X2$). mydata1 has 1200 observations, where the first 6 observations are shown as follows

```r
head(mydata1)
```

```
##   cluster period id E A c     alpha         tau            M         Y
## 1       1      1  1 0 0 1 0.2784669 -0.09219996 -0.447201794 0.0374583
## 2       1      1  2 0 0 1 0.2784669 -0.09219996 -0.004712532 0.4650614
## 3       1      1  3 0 0 1 0.2784669 -0.09219996  2.160055774 2.0910967
## 4       1      1  4 0 0 1 0.2784669 -0.09219996  0.742260173 0.3150164
## 5       1      1  5 0 0 1 0.2784669 -0.09219996  1.220215552 1.0576876
## 6       1      1  6 0 0 1 0.2784669 -0.09219996  2.410445452 2.4898744
##             X1          X2
## 1 -0.002192351 -0.04380900
## 2  0.631531165  0.07640606
## 3  0.421082910  0.02619613
## 4  1.386784809  0.07734046
## 5  0.616971271 -0.08143791
## 6  0.818630088 -0.04384506
```

Next, we conduct mediation analysis using mediate_swcrt(). In the first situation, we only adjust X1 in the outcome model and only adjust X2 in the mediator model. We calculate the NIE, NDE, TE and MP for binary treatment A in change from 0 to 1, as follows

```r
res1 = mediate_swcrt(data=mydata1,covariate.outcome = c("X1"),covariate.mediator = c("X2"))
```

Then, we obtain the following mediation analysis output

```r
print(res1)
```

```
## $point_est
##       NIE       NDE        TE        MP
## 0.1477560 0.6157318 0.7634878 0.1935276
##
## $var_est
##         NIE         NDE          TE          MP
## 0.003475700 0.007068884 0.008483027 0.004829385
##
## $sd_est
##        NIE        NDE         TE         MP
## 0.05895507 0.08407666 0.09210335 0.06949377
##
## $ci_est
##                                     NIE       NDE         TE          MP
```

```
## ci_lower_confidence_limit 0.02130994 0.4354053 0.5659458 0.04447831
## ci_upper_confidence_limit 0.27420203 0.7960583 0.9610298 0.34257695
```

In the second situation, we adjust covariates X1 and X2 in both outcome model and mediator model, then we can use the following code to calculate mediation measures

```
res2 = mediate_swcrt(data=mydata1,covariate.outcome = c("X1","X2"),
                     covariate.mediator = c("X1","X2"))
print(res2)

## $point_est
##       NIE       NDE        TE        MP
## 0.1478632 0.6150226 0.7628858 0.1938209
##
## $var_est
##         NIE         NDE          TE          MP
## 0.003484884 0.007271378 0.008357863 0.004939185
##
## $sd_est
##        NIE        NDE         TE         MP
## 0.05903291 0.08527237 0.09142135 0.07027934
##
## $ci_est
##                                  NIE       NDE        TE         MP
## ci_lower_confidence_limit 0.02125023 0.4321315 0.5668065 0.04308673
## ci_upper_confidence_limit 0.27447622 0.7979136 0.9589651 0.34455510
```

Third, if we don't want to include any covariate to calculate unadjusted mediation measures (this is only for illustration and in practice we still recommend mediation analysis with thoughtful control for confounding), we can also achieve this under the default settings of arguments covariate.outcome and covariate.mediator in mediate_swcrt(), that is,

```
res3 = mediate_swcrt(data=mydata1)
print(res3)

## $point_est
##       NIE       NDE        TE        MP
## 0.1478928 0.6154467 0.7633395 0.1937445
##
## $var_est
##         NIE         NDE          TE          MP
```

```
## 0.003452247 0.006852323 0.008262678 0.004789561
##
## $sd_est
##        NIE        NDE         TE         MP
## 0.05875582 0.08277876 0.09089928 0.06920665
##
## $ci_est
##                                  NIE       NDE        TE         MP
## ci_lower_confidence_limit 0.02187413 0.4379039 0.5683800 0.04531099
## ci_upper_confidence_limit 0.27391155 0.7929895 0.9582991 0.34217801
```

For conducting mediation analysis with an exposure-time dependent treatment effect by mediate_swcrt(), we use first the gen_data_etm() function in "`mediateSWCRT`" to simulate a dataset based on a SW-CRT.

```
I = 15
J = 4
n = 20
beta = cumsum(c(0,0.1,0.1/2,0.1/(2^2)))
gamma = cumsum(c(0,0.3,0.3/2,0.3/(2^2)))
eta_e = c(0.5,1.3,2.1)
theta_e = c(0.6,1,1.4)
sigma_a = 0.334
sigma_tau = 0.605
sigma_em = sigma_ey = 1
set.seed(123456)
mydata2 = gen_data_etm(I,J,n,beta,gamma,theta_e,beta_M=1.2,eta_e,sigma_a,
sigma_ey,sigma_tau,sigma_em,binary.o=0,binary.m=1)
covdata = data.frame("X1" = numeric(), "X2" = numeric())
set.seed(100)
for(i in 1:I){
   for(j in 1:J){
      x1_ijk = rnorm(n,mean=0.5)
      x2_ijk = rnorm(n,sd=0.5)
     covdata = rbind(covdata, data.frame(cbind(X1 = x1_ijk, X2 = x2_ijk)))
   }
 }
mydata2 = data.frame(mydata2,covdata)
```

The dataset mydata2 has a continuous outcome Y and a binary mediator M, other settings are similar to those in mydata1 in addition to its mediation measures are exposure-time dependent. Next, we apply both the STA and

GHQ methods to calculate exposure-time specific mediation measures (i.e., NIE(e), NDE(e), TE(e) and MP(e)) and overall summary mediation measures adjusted by X1 and X2 in both the outcome model and mediator model.

```
# using the default STA method
res4 = mediate_swcrt(data=mydata2,covariate.outcome = c("X1","X2"),
covariate.mediator = c("X1","X2"),binary.m = 1, time.dependent = TRUE)
print(res4)
```

```
## $point_est
##                 NIE       NDE       TE        MP
## e=1     0.1375401 0.9156139 1.053154 0.1305983
## e=2     0.2605537 1.4359061 1.696460 0.1535867
## e=3     0.3164302 1.7672089 2.083639 0.1518642
## overall 0.2381746 1.3729097 1.611084 0.1478350
##
## $var_est
##                   NIE        NDE         TE          MP
## e=1     0.003492453 0.02701804 0.02178952 0.003919560
## e=2     0.006506597 0.05715173 0.04811671 0.002980591
## e=3     0.008826569 0.10189957 0.08674078 0.002860381
## overall 0.005032237 0.05401340 0.04271218 0.002818872
##
## $sd_est
##                  NIE       NDE        TE         MP
## e=1     0.05909698 0.1643717 0.1476127 0.06260639
## e=2     0.08066348 0.2390643 0.2193552 0.05459479
## e=3     0.09394982 0.3192171 0.2945179 0.05348253
## overall 0.07093826 0.2324078 0.2066692 0.05309305
##
## $ci_lower_confidence_limit
##                  NIE       NDE        TE           MP
## e=1     0.01078969 0.5630718 0.7365562 -0.003679073
## e=2     0.08754769 0.9231642 1.2259897  0.036492522
## e=3     0.11492784 1.0825563 1.4519611  0.037155576
## overall 0.08602721 0.8744444 1.1678229  0.033961736
##
## $ci_upper_confidence_limit
##                 NIE      NDE       TE        MP
## e=1     0.2642905 1.268156 1.369752 0.2648756
## e=2     0.4335596 1.948648 2.166930 0.2706809
```

```
## e=3     0.5179325 2.451862 2.715317 0.2665728
## overall 0.3903221 1.871375 2.054346 0.2617083
##
## $chisq_test
##    Test.stat      P.value
## 3.999916e+01 2.062021e-09
```

```r
# using the GHQ method
res5 = mediate_swcrt(data=mydata2,method = "GHQ",covariate.outcome = c("X1","X2"),
                      covariate.mediator = c("X1","X2"),binary.m = 1, time.dependent = TRUE)
print(res5)
```

```
## $point_est
##               NIE       NDE       TE        MP
## e=1     0.1375646 0.9156139 1.053179 0.1306185
## e=2     0.2598389 1.4359061 1.695745 0.1532299
## e=3     0.3152744 1.7672089 2.082483 0.1513935
## overall 0.2375593 1.3729097 1.610469 0.1475094
##
## $var_est
##                 NIE        NDE         TE          MP
## e=1     0.003508226 0.02701804 0.02177170 0.003934147
## e=2     0.006521287 0.05715173 0.04809624 0.002985575
## e=3     0.008821942 0.10189957 0.08679584 0.002855533
## overall 0.005048487 0.05401340 0.04271607 0.002823240
##
## $sd_est
##                NIE       NDE        TE         MP
## e=1     0.05923028 0.1643717 0.1475523 0.06272278
## e=2     0.08075449 0.2390643 0.2193086 0.05464041
## e=3     0.09392519 0.3192171 0.2946113 0.05343719
## overall 0.07105270 0.2324078 0.2066787 0.05313417
##
## $ci_lower_confidence_limit
##                NIE       NDE        TE           MP
## e=1     0.01052825 0.5630718 0.7367102 -0.003908505
## e=2     0.08663772 0.9231642 1.2253749  0.036037893
## e=3     0.11382487 1.0825563 1.4506048  0.036782095
## overall 0.08516638 0.8744444 1.1671873  0.033547929
##
```

```
## $ci_upper_confidence_limit
##               NIE      NDE       TE        MP
## e=1     0.2646009 1.268156 1.369647 0.2651455
## e=2     0.4330400 1.948648 2.166115 0.2704220
## e=3     0.5167239 2.451862 2.714362 0.2660048
## overall 0.3899522 1.871375 2.053751 0.2614708
##
## $chisq_test
##    Test.stat      P.value
## 3.988202e+01 2.186396e-09
```

In the output, except for the point and interval estimates for the NIE, NDE, TE and MP at each exposure time, as well as overall summary mediation measures, a chi-square test for testing equality of total effect conditional on confounders $\mathbf{x}^*$ over e, that is, H_0 : $\text{TE}(1|\mathbf{x}^*) = \text{TE}(2|\mathbf{x}^*) = \cdots = \text{TE}(J-1|\mathbf{x}^*)$ for $e = 1, 2, \ldots, J-1$, is also reported. The detailed information for conducting the chi-square test is described in Section 6 of the main text.

For SW-CRTs with the nested exchangeable random-effects structure, we can conduct corresponding mediation analysis by using the function mediate_swcrt_nem() in `mediateSWCRT`. Arguments of using mediate_swcrt_nem() are similar to those of mediate_swcrt(), and we thus use a simple example to illustrate the use of mediate_swcrt_nem().

```r
I = 15
J = 4
n = 20
beta = cumsum(c(0,0.1,0.1/2,0.1/(2^2)))
gamma = cumsum(c(0,0.3,0.3/2,0.3/(2^2)))
sigma_tau = sigma_a = 0.334
sigma_phi = sigma_psi = 0.6
sigma_em = sigma_ey = 0.8
#set.seed(123456)
mydata1 = gen_data_nem(I,J,n,beta,gamma,theta=0.75,beta_M=0.625,eta=0.4,sigma_a,
sigma_phi,sigma_ey,sigma_tau,sigma_psi,sigma_em,binary.o=0,binary.m=0)
covdata = data.frame("X1" = numeric(), "X2" = numeric())
set.seed(100)
for(i in 1:I){
  for(j in 1:J){
     x1_ijk = rnorm(n,mean=0.5)
     x2_ijk = rnorm(n,sd=0.1)
     covdata = rbind(covdata, data.frame(cbind(X1 = x1_ijk, X2 = x2_ijk)))
  }
}
```

```r
mydata1 = data.frame(mydata1,covdata)
res6 = mediate_swcrt_nem(data = mydata1,covariate.outcome = c("X1","X2"),
covariate.mediator = c("X1","X2"))
print(res6)

## $point_est
##       NIE       NDE        TE        MP
## 0.1821060 0.9438864 1.1259924 0.1617293
##
## $var_est
##        NIE        NDE         TE         MP
## 0.04079949 0.03482308 0.07695212 0.02242894
##
## $sd_est
##       NIE       NDE        TE        MP
## 0.2019888 0.1866094 0.2774025 0.1497630
##
## $ci_est
##                                  NIE      NDE        TE         MP
## ci_lower_confidence_limit -0.2511170 0.543649 0.5310233 -0.1594803
## ci_upper_confidence_limit  0.6153289 1.344124 1.7209615  0.4829389
```

When there is a implementation period in a SW-CRT, for example, the 99DOTS data analyzed in Section 6 of the main text and the corresponding schematic is provided in Figure S1, our package can also handle this scenario. It is noted that, under this situation, estimation expression of mediation measures under an instantaneous and constant treatment effect structure are not changed but the corresponding exposure-time specific NIE and NDE under time-dependent treatment effect in (16) of the main text should be changed as

$$\begin{aligned}
\text{NIE}(e|\mathbf{x}) &= \sum_{j=e+2}^{J} \omega(j,e)\text{NIE}(j,e|\mathbf{x}), \quad \text{NDE}(e|\mathbf{x}) = \sum_{j=e+2}^{J} \omega(j,e)\text{NDE}(j,e|\mathbf{x}), \\
\text{MP}(e|\mathbf{x}) &= \sum_{j=e+2}^{J} \left\{ \frac{\text{NIE}(j,e|\mathbf{x}) + \text{NDE}(j,e|\mathbf{x})}{\sum_{l=e+2}^{J} \text{NIE}(l,e|\mathbf{x}) + \text{NDE}(l,e|\mathbf{x})} \right\} \text{MP}(j,e|\mathbf{x}).
\end{aligned}$$

Next, we simulate a SW-CRT data with the same schematic provided in Figure S1, that is, the SW-CRT has $I = 18$ clusters with $J = 8$ periods, and the 18 clusters randomized in 6 groups with 3 clusters in each group. Each cluster-period cell has an equal number of $N_{ij} = 20$ individuals. Typically, for groups 1-6, we assume the implementation period is period 2,3,4,5,6,7,respectively. Furthermore, we recode the treatment status as -1 in the implementation period. Because for all the other clusters that are not in the implementation period, their treatment status still equals to 0 or 1. Setting treatment status=-1 is just to trigger our function to help automatically set outcome and mediator equaling to NA for those implementation cluster-periods. The detailed generation procedure of an incomplete designs with an implementation period is as followings:

```r
I = 21  #number of clusters
J = 8   #number of periods
n = 20  #sample size in each cluster-period cell
beta = cumsum(c(0,0.3,0.3/2,0.3/3,0.3/4,0.3/5,0.3/6,0.3/7))
gamma = cumsum(c(0,0.5,0.5/2,0.5/3,0.5/4,0.5/5,0.5/6,0.5/7))
eta_e = seq(0.3,2.7,by=0.4)
theta_e = seq(0.2,2,by=0.3)
sigma_em = sigma_ey = 1
sigma_a = sigma_tau = 0.334
set.seed(123456)
#simulate continuous outcome and continuous mediator type
mydata = gen_data_etm(I,J,n,beta,gamma,theta_e,beta_M=1,eta_e,sigma_a,sigma_ey,
                        sigma_tau,sigma_em,binary.o=0,binary.m=0)
#for cluster 1-3
group1 = mydata[mydata$cluster==1 | mydata$cluster==2 | mydata$cluster==3,]
index1 = group1$period==2 #implementation period indicator
group1$A[index1] = -1
#for this group, exposure time should be changed to
E1 = group1$period-2
E1[E1<=0] = 0
group1$E = E1

#for cluster 4-6
group2 = mydata[mydata$cluster==4 | mydata$cluster==5 | mydata$cluster==6,]
index2 = group2$period==3 #implementation period indicator
group2$A[index2] = -1
#for this group, exposure time should be changed to
E2 = group2$period-3
E2[E2<=0] = 0
group2$E = E2

#for cluster 7-9
group3 = mydata[mydata$cluster==7 | mydata$cluster==8 | mydata$cluster==9,]
index3 = group3$period==4 #implementation period indicator
group3$A[index3] = -1
#for this group, exposure time should be changed to
E3 = group3$period-4
E3[E3<=0] = 0
group3$E = E3
```

```r
#for cluster 10-12
group4 = mydata[mydata$cluster==10 | mydata$cluster==11 | mydata$cluster==12,]
index4 = group4$period==5 #implementation period indicator
group4$A[index4] = -1
#for this group, exposure time should be changed to
E4 = group4$period-5
E4[E4<=0] = 0
group4$E = E4

#for cluster 13-15
group5 = mydata[mydata$cluster==13 | mydata$cluster==14 | mydata$cluster==15,]
index5 = group5$period==6 #implementation period indicator
group5$A[index5] = -1
#for this group, exposure time should be changed to
E5 = group5$period-6
E5[E5<=0] = 0
group5$E = E5

#for cluster 16-18
group6 = mydata[mydata$cluster==16 | mydata$cluster==17 | mydata$cluster==18,]
index6 = group6$period==7 #implementation period indicator
group6$A[index6] = -1
#for this group, exposure time should be changed to
E6 = group6$period-7
E6[E6<=0] = 0
group6$E = E6

#To be consistent with Figure S1, we do not include clusters 19-21 since
#they have no implementation period.
mydata1 = rbind(group1,group2,group3,group4,group5,group6)

#generate potential covariates
covdata = data.frame("X1" = numeric(), "X2" = numeric())
set.seed(123456)
for(i in 1:(I-3)){
  for(j in 1:J){
    x1_ijk = rnorm(n,mean=0.5)
    x2_ijk = rnorm(n,sd=0.5)
```

```r
    covdata = rbind(covdata, data.frame(cbind(X1 = x1_ijk, X2 = x2_ijk)))
  }
}
mydata2 = data.frame(mydata1,covdata)
```

Then, we use our package to estimate corresponding mediation measures considering potential covariates.

```r
res7 = mediate_swcrt(data=mydata2,covariate.outcome = c("X1","X2"),
                     covariate.mediator = c("X1","X2"),binary.m = 0, binary.o = 0,
                     time.dependent = TRUE)
print(res7)
```

```
## $point_est
##               NIE       NDE       TE        MP
## e=1     0.5671342 0.5506566 1.117791 0.5073706
## e=2     0.8514633 0.7565160 1.607979 0.5295238
## e=3     1.2336336 1.2181922 2.451826 0.5031489
## e=4     1.6102868 1.4097565 3.020043 0.5331999
## e=5     1.9441613 1.7469559 3.691117 0.5267135
## e=6     2.4759679 2.1301160 4.606084 0.5375430
## overall 1.4471078 1.3020322 2.749140 0.5263856
##
## $var_est
##                 NIE        NDE         TE          MP
## e=1     0.006805756 0.01617593 0.02484870 0.004240931
## e=2     0.004902847 0.02124265 0.02832576 0.002564268
## e=3     0.007862852 0.03175638 0.04501573 0.001436276
## e=4     0.010078493 0.04825140 0.04931466 0.001992860
## e=5     0.034488670 0.06782966 0.06930353 0.002549701
## e=6     0.020470043 0.09363464 0.10231663 0.001628979
## overall 0.009433565 0.03479707 0.04267536 0.001602057
##
## $sd_est
##                NIE       NDE        TE         MP
## e=1     0.08249701 0.1271846 0.1576347 0.06512243
## e=2     0.07002033 0.1457486 0.1683026 0.05063860
## e=3     0.08867273 0.1782032 0.2121691 0.03789823
## e=4     0.10039170 0.2196620 0.2220690 0.04464146
## e=5     0.18571125 0.2604413 0.2632556 0.05049457
## e=6     0.14307356 0.3059978 0.3198697 0.04036061
```

```
## overall 0.09712654 0.1865397 0.2065801 0.04002571
##
## $ci_lower_confidence_limit
##               NIE       NDE        TE        MP
## e=1     0.3930807 0.2823205 0.7852106 0.3699743
## e=2     0.7037333 0.4490134 1.2528919 0.4226857
## e=3     1.0465505 0.8422163 2.0041881 0.4231907
## e=4     1.3984788 0.9463101 2.5515185 0.4390147
## e=5     1.5523448 1.1974728 3.1356964 0.4201793
## e=6     2.1741091 1.4845171 3.9312178 0.4523895
## overall 1.2421887 0.9084678 2.3132940 0.4419388
##
## $ci_upper_confidence_limit
##               NIE       NDE       TE        MP
## e=1     0.7411876 0.8189927 1.450371 0.6447669
## e=2     0.9991933 1.0640187 1.963067 0.6363619
## e=3     1.4207167 1.5941681 2.899464 0.5831072
## e=4     1.8220947 1.8732028 3.488568 0.6273852
## e=5     2.3359778 2.2964390 4.246538 0.6332477
## e=6     2.7778267 2.7757148 5.280950 0.6226964
## overall 1.6520269 1.6955966 3.184986 0.6108325
##
## $chisq_test
## Test.stat   P.value
##  303.6712    0.0000
```

References

1. Cao Z. and Wong M.Y. (2021). Approximate maximum likelihood estimation for logistic regression with covariate measurement error. *Biometrical Journal*, **63**(1):27–45.

2. Gaynor S.M., Schwartz J. and Lin X. (2019). Mediation analysis for common binary outcomes. *Statistics in Medicine*, **38**(4):512–529.

3. Cheng C., Spiegelman D., Li F. (2021). Estimating the natural indirect effect and the mediation proportion via the product method. *BMC Medical Research Methodology*, **21**(253):1–20.

6 Web Appendix F: Web Tables and Figures

Table S1: Summary of expressions of mediation measures, period-specific $\text{NIE}(j|\mathbf{x})$ and $\text{NDE}(j|\mathbf{x})$ as well as calendar-exposure-time specific $\text{NIE}(j,e|\mathbf{x})$ and $\text{NDE}(j,e|\mathbf{x})$ under four data types in SW-CRTs with nested exchangeable random-effects models. Under an instantaneous and constant treatment effect structure, the overall summary NIE and NDE measures can be obtained based on $\text{NIE}(j|\mathbf{x})$ and $\text{NDE}(j|\mathbf{x})$ by applying (5) of the main text. The definitions for $\kappa^*(a,j|\mathbf{x})$, $\mu^*(a,a^*,j|\mathbf{x})$ and $\lambda^*(a,a^*,j|\mathbf{x})$ for $a,a^* \in \{0,1\}$ are given in (A.9), (A.12) and (A.16), respectively. Under an exposure-time dependent treatment effect structure, the exposure-time specific $\text{NIE}(e|\mathbf{x})$ and $\text{NDE}(e|\mathbf{x})$ measures can be obtained based on $\text{NIE}(j,e|\mathbf{x})$ and $\text{NDE}(j,e|\mathbf{x})$ by applying (16) of the main text, and the overall summary NIE and NDE measures can be obtained by (17) of the main text directly. The definitions for $\kappa_e^*(a,j|\mathbf{x})$, $\mu_e^*(a,a^*,j|\mathbf{x})$ and $\lambda_e^*(a,a^*,j|\mathbf{x})$ for $a,a^* \in \{0,1\}$ are given in (A.21), (A.23) and (A.24), respectively.

			Instantaneous and constant treatment effect structure			
Data type	Y	M	$\text{NIE}(j\|\mathbf{x})$	$\text{NDE}(j\|\mathbf{x})$	Depends on $\mathbf{x}$?	Depends on j?
Y_cM_c	Continuous	Continuous	$\beta_M\eta$	θ	$(\times,\ \times)$	$(\times,\ \times)$
Y_cM_b	Continuous	Binary	$\beta_M\left[\kappa^*(1,j\|\mathbf{x})-\kappa^*(0,j\|\mathbf{x})\right]$	θ	$(\checkmark,\ \times)$	$(\checkmark,\ \times)$
Y_bM_c	Binary	Continuous	$\text{logit}\left[\mu^*(1,1,j\|\mathbf{x})\right]-\text{logit}\left[\mu^*(1,0,j\|\mathbf{x})\right]$	$\text{logit}\left[\mu^*(1,0,j\|\mathbf{x})\right]-\text{logit}\left[\mu^*(0,0,j\|\mathbf{x})\right]$	$(\checkmark,\ \checkmark)$	$(\checkmark,\ \checkmark)$
Y_bM_b	Binary	Binary	$\text{logit}\left[\lambda^*(1,0,j\|\mathbf{x})[1-\kappa^*(1,j\|\mathbf{x})]+\lambda^*(1,1,j\|\mathbf{x})\kappa^*(1,j\|\mathbf{x})\right]$ $-\text{logit}\left[\lambda^*(1,0,j\|\mathbf{x})[1-\kappa^*(0,j\|\mathbf{x})]+\lambda^*(1,1,j\|\mathbf{x})\kappa^*(0,j\|\mathbf{x})\right]$	$\text{logit}\left[\lambda^*(1,0,j\|\mathbf{x})[1-\kappa^*(0,j\|\mathbf{x})]+\lambda^*(1,1,j\|\mathbf{x})\kappa^*(0,j\|\mathbf{x})\right]$ $-\text{logit}\left[\lambda^*(0,0,j\|\mathbf{x})[1-\kappa^*(0,j\|\mathbf{x})]+\lambda^*(0,1,j\|\mathbf{x})\kappa^*(0,j\|\mathbf{x})\right]$	$(\checkmark,\ \checkmark)$	$(\checkmark,\ \checkmark)$
			Exposure-time dependent treatment effect structure (for a given exposure time level e)			
Data type	Y	M	$\text{NIE}(j,e\|\mathbf{x})$	$\text{NDE}(j,e\|\mathbf{x})$	Depends on $\mathbf{x}$?	Depends on j?
Y_cM_c	Continuous	Continuous	$\beta_M\eta_e$	θ_e	$(\times,\ \times)$	$(\times,\ \times)$
Y_cM_b	Continuous	Binary	$\beta_M\left[\kappa_e^*(1,j\|\mathbf{x})-\kappa_e^*(0,j\|\mathbf{x})\right]$	θ_e	$(\checkmark,\ \times)$	$(\checkmark,\ \times)$
Y_bM_c	Binary	Continuous	$\text{logit}\left[\mu_e^*(1,1,j\|\mathbf{x})\right]-\text{logit}\left[\mu_e^*(1,0,j\|\mathbf{x})\right]$	$\text{logit}\left[\mu_e^*(1,0,j\|\mathbf{x})\right]-\text{logit}\left[\mu_e^*(0,0,j\|\mathbf{x})\right]$	$(\checkmark,\ \checkmark)$	$(\checkmark,\ \checkmark)$
Y_bM_b	Binary	Binary	$\text{logit}\left[\lambda_e^*(1,0,j\|\mathbf{x})[1-\kappa_e^*(1,j\|\mathbf{x})]+\lambda_e^*(1,1,j\|\mathbf{x})\kappa_e^*(1,j\|\mathbf{x})\right]$ $-\text{logit}\left[\lambda_e^*(1,0,j\|\mathbf{x})[1-\kappa_e^*(0,j\|\mathbf{x})]+\lambda_e^*(1,1,j\|\mathbf{x})\kappa_e^*(0,j\|\mathbf{x})\right]$	$\text{logit}\left[\lambda_e^*(1,0,j\|\mathbf{x})[1-\kappa_e^*(0,j\|\mathbf{x})]+\lambda_e^*(1,1,j\|\mathbf{x})\kappa_e^*(0,j\|\mathbf{x})\right]$ $-\text{logit}\left[\lambda_e^*(0,0,j\|\mathbf{x})[1-\kappa_e^*(0,j\|\mathbf{x})]+\lambda_e^*(0,1,j\|\mathbf{x})\kappa_e^*(0,j\|\mathbf{x})\right]$	$(\checkmark,\ \checkmark)$	$(\checkmark,\ \checkmark)$

Table S2: Simulation results for period-specific mediation measures (i.e., NIE(j), NDE(j), TE(j) and MP(j)) under continuous outcome and binary mediator (Y_cM_b) in SW-CRTs with an instantaneous and constant treatment effect structure under different number of clusters. GHQ: Gauss-Hermite Quadrature approach for single integral calculation; STA: second-order Taylor approximation method for single and double integral calculation.

			$I = 15$				$I = 30$				$I = 60$			
Method	Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)
GHQ	$j = 1$													
	NIE(j)	0.25	1.80	0.15	0.15	95.8	1.18	0.10	0.11	95.1	1.01	0.07	0.07	94.0
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	1.81	0.18	0.19	96.4	1.24	0.13	0.13	94.8	1.08	0.09	0.09	94.7
	MP(j)	0.25	-0.02	0.12	0.13	94.3	0.15	0.08	0.08	94.6	0.39	0.06	0.06	94.4
	$j = 2$													
	NIE(j)	0.25	0.79	0.14	0.15	96.4	0.18	0.10	0.10	95.5	-0.03	0.07	0.07	95.3
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	0.80	0.17	0.18	96.3	0.23	0.13	0.13	95.2	0.04	0.09	0.09	94.7
	MP(j)	0.25	-0.70	0.12	0.12	96.0	-0.56	0.08	0.08	95.5	-0.37	0.05	0.06	95.9
	$j = 3$													
	NIE(j)	0.25	0.16	0.14	0.15	95.8	-0.57	0.10	0.10	95.6	-0.82	0.07	0.07	95.3
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	0.18	0.17	0.18	96.9	-0.52	0.13	0.13	95.3	-0.75	0.09	0.09	94.7
	MP(j)	0.25	-1.17	0.12	0.12	95.9	-1.13	0.08	0.08	96.0	-0.97	0.05	0.06	95.7
	$j = 4$													
	NIE(j)	0.25	-0.04	0.14	0.15	95.5	-0.92	0.10	0.10	94.9	-1.24	0.07	0.07	95.1
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	-0.03	0.18	0.19	96.9	-0.87	0.13	0.13	95.3	-1.17	0.09	0.09	94.8
	MP(j)	0.25	-1.38	0.12	0.12	96.0	-1.43	0.08	0.08	95.8	-1.31	0.06	0.06	95.7
STA	$j = 1$													
	NIE(j)	0.25	1.50	0.14	0.15	96.0	0.87	0.10	0.11	95.3	0.67	0.07	0.07	94.7
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	1.52	0.18	0.19	96.3	0.92	0.13	0.13	94.8	0.74	0.09	0.09	94.8
	MP(j)	0.25	-0.22	0.12	0.12	94.6	-0.07	0.08	0.08	94.9	0.15	0.05	0.06	94.8
	$j = 2$													
	NIE(j)	0.25	0.59	0.14	0.15	96.3	-0.03	0.10	0.10	95.4	-0.25	0.07	0.07	95.2
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	0.60	0.17	0.18	96.4	0.02	0.13	0.13	95.1	-0.18	0.09	0.09	94.7
	MP(j)	0.25	-0.83	0.12	0.12	96.1	-0.71	0.08	0.08	95.6	-0.53	0.05	0.06	95.7
	$j = 3$													
	NIE(j)	0.25	0.02	0.14	0.15	95.8	-0.71	0.10	0.10	95.7	-0.96	0.07	0.07	95.3
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	0.03	0.17	0.18	96.8	-0.66	0.13	0.13	95.2	-0.89	0.09	0.09	94.7
	MP(j)	0.25	-1.26	0.11	0.12	96.2	-1.23	0.08	0.08	95.9	-1.07	0.05	0.06	95.8
	$j = 4$													
	NIE(j)	0.25	-0.18	0.14	0.15	95.5	-1.03	0.10	0.10	95.1	-1.35	0.07	0.07	95.2
	NDE(j)	0.75	0.01	0.10	0.11	95.4	0.05	0.08	0.08	94.2	0.07	0.05	0.05	96.0
	TE(j)	1.00	-0.16	0.18	0.19	96.9	-0.98	0.13	0.13	95.3	-1.28	0.09	0.09	94.8
	MP(j)	0.25	-1.46	0.12	0.12	96.1	-1.50	0.08	0.08	95.8	-1.39	0.06	0.06	95.7

Table S3: Simulation results for period-specific mediation measures (i.e., NIE(j), NDE(j), TE(j) and MP(j)) under binary outcome and continuous mediator ($Y_b M_c$) in SW-CRTs with an instantaneous and constant treatment effect structure under different number of clusters. These mediation measures results are obtained from STA: second-order Taylor approximation method for single and double integral calculation.

		$I = 15$				$I = 30$				$I = 60$			
Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)
$j = 1$													
NIE(j)	0.25	-0.23	0.07	0.07	95.6	-0.40	0.05	0.05	94.9	-0.55	0.03	0.03	95.8
NDE(j)	0.75	0.57	0.22	0.23	96.3	-1.28	0.15	0.15	94.7	-0.98	0.11	0.11	95.1
TE(j)	1.00	0.34	0.23	0.24	96.0	-1.68	0.16	0.16	95.0	-1.53	0.12	0.11	95.5
MP(j)	0.25	0.63	0.08	0.09	95.2	0.45	0.06	0.06	95.9	0.04	0.04	0.04	95.4
$j = 2$													
NIE(j)	0.25	0.34	0.07	0.07	95.8	0.17	0.05	0.05	95.3	0.01	0.03	0.04	96.1
NDE(j)	0.75	1.39	0.22	0.23	96.3	-0.55	0.15	0.16	95.1	-0.25	0.11	0.11	94.9
TE(j)	1.00	1.72	0.23	0.24	96.0	-0.38	0.16	0.16	94.9	-0.25	0.12	0.12	95.5
MP(j)	0.25	0.86	0.08	0.09	95.6	0.69	0.06	0.06	96.2	0.28	0.04	0.04	95.7
$j = 3$													
NIE(j)	0.25	0.63	0.07	0.07	95.5	0.48	0.05	0.05	95.6	0.31	0.03	0.04	96.3
NDE(j)	0.75	1.85	0.22	0.23	96.1	-0.04	0.15	0.16	95.1	0.26	0.11	0.11	94.8
TE(j)	1.00	2.47	0.23	0.24	96.1	0.44	0.16	0.16	95.0	0.58	0.12	0.11	94.8
MP(j)	0.25	0.94	0.09	0.09	95.4	0.79	0.06	0.06	96.1	0.38	0.04	0.04	96.0
$j = 4$													
NIE(j)	0.25	0.75	0.07	0.07	95.5	0.62	0.05	0.05	95.2	0.46	0.03	0.04	96.3
NDE(j)	0.75	2.06	0.21	0.22	96.7	0.23	0.15	0.15	94.8	0.54	0.11	0.11	94.8
TE(j)	1.00	2.80	0.22	0.23	96.6	0.86	0.16	0.16	94.9	1.00	0.11	0.11	94.5
MP(j)	0.25	0.96	0.09	0.09	95.4	0.83	0.06	0.06	96.1	0.42	0.04	0.04	95.9

Table S4: Simulation results for period-specific mediation measures (i.e., NIE(j), NDE(j), TE(j) and MP(j)) under binary outcome and binary mediator ($Y_b M_b$) in SW-CRTs with an instantaneous and constant treatment effect structure under different number of clusters. GHQ: Gauss-Hermite Quadrature approach for single integral calculation; STA: second-order Taylor approximation method for single and double integral calculation.

			$I = 15$				$I = 30$				$I = 60$			
Method	Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)
GHQ	$j = 1$													
	NIE(j)	0.25	-1.78	0.14	0.15	95.4	-1.94	0.10	0.10	94.6	-2.38	0.07	0.07	92.3
	NDE(j)	0.75	5.12	0.33	0.33	95.0	3.07	0.22	0.22	95.7	2.02	0.15	0.15	95.5
	TE(j)	1.00	3.34	0.35	0.35	95.8	1.12	0.23	0.24	95.9	-0.36	0.16	0.16	95.5
	MP(j)	0.25	-1.33	0.16	0.22	95.1	-1.75	0.10	0.10	93.2	-2.11	0.07	0.07	92.3
	$j = 2$													
	NIE(j)	0.25	-0.06	0.14	0.15	96.9	-0.10	0.10	0.10	95.3	-0.32	0.07	0.07	95.5
	NDE(j)	0.75	3.56	0.31	0.31	95.4	1.93	0.21	0.21	95.8	0.91	0.14	0.14	95.8
	TE(j)	1.00	3.50	0.34	0.35	96.5	1.83	0.23	0.23	95.3	0.59	0.16	0.16	95.0
	MP(j)	0.25	-0.00	0.16	0.28	97.6	-0.24	0.10	0.10	96.5	-0.36	0.07	0.07	95.4
	$j = 3$													
	NIE(j)	0.25	0.80	0.15	0.15	96.4	0.90	0.11	0.10	95.3	0.70	0.07	0.07	95.7
	NDE(j)	0.75	1.53	0.29	0.29	95.2	0.30	0.19	0.19	94.9	-0.53	0.13	0.13	95.9
	TE(j)	1.00	2.33	0.32	0.33	96.5	1.20	0.22	0.22	95.7	0.17	0.15	0.15	95.4
	MP(j)	0.25	0.81	0.16	0.22	98.4	0.74	0.10	0.10	96.6	0.69	0.07	0.07	96.1
	$j = 4$													
	NIE(j)	0.25	1.00	0.14	0.15	96.0	1.24	0.10	0.10	95.0	1.14	0.07	0.07	95.3
	NDE(j)	0.75	-0.53	0.25	0.25	95.6	-0.97	0.17	0.17	95.1	-1.40	0.12	0.12	95.8
	TE(j)	1.00	0.47	0.30	0.30	96.2	0.27	0.20	0.20	95.7	-0.26	0.14	0.14	95.8
	MP(j)	0.25	1.13	0.17	0.20	99.0	1.13	0.10	0.09	97.1	1.15	0.06	0.06	96.2
STA	$j = 1$													
	NIE(j)	0.25	-2.05	0.14	0.14	95.6	-2.23	0.10	0.10	94.5	-2.67	0.07	0.07	92.3
	NDE(j)	0.75	4.46	0.33	0.33	94.9	2.38	0.22	0.22	95.4	1.32	0.15	0.15	95.7
	TE(j)	1.00	2.41	0.35	0.35	95.7	0.15	0.23	0.24	95.3	-1.36	0.16	0.16	95.3
	MP(j)	0.25	-1.35	0.16	0.21	95.1	-1.80	0.10	0.10	93.1	-2.17	0.07	0.07	92.2
	$j = 2$													
	NIE(j)	0.25	-0.31	0.14	0.15	96.7	-0.36	0.10	0.10	95.3	-0.58	0.07	0.07	95.6
	NDE(j)	0.75	2.96	0.31	0.31	94.9	1.33	0.21	0.21	95.6	0.29	0.14	0.14	96.2
	TE(j)	1.00	2.65	0.34	0.35	96.5	0.96	0.23	0.23	95.2	-0.29	0.16	0.16	95.2
	MP(j)	0.25	-0.02	0.16	0.68	97.4	-0.28	0.10	0.10	96.2	-0.41	0.07	0.07	95.3
	$j = 3$													
	NIE(j)	0.25	0.58	0.14	0.15	96.5	0.68	0.10	0.10	95.3	0.48	0.07	0.07	95.8
	NDE(j)	0.75	0.89	0.29	0.29	95.1	-0.32	0.19	0.19	94.9	-1.15	0.13	0.13	96.1
	TE(j)	1.00	1.47	0.32	0.33	96.5	0.36	0.22	0.22	95.7	-0.67	0.15	0.15	95.2
	MP(j)	0.25	0.83	0.17	0.23	98.1	0.74	0.10	0.10	96.6	0.68	0.07	0.07	96.1
	$j = 4$													
	NIE(j)	0.25	0.80	0.14	0.15	96.2	1.05	0.10	0.10	95.1	0.94	0.07	0.07	95.3
	NDE(j)	0.75	-1.17	0.25	0.25	96.0	-1.59	0.17	0.17	94.9	-2.02	0.11	0.12	96.2
	TE(j)	1.00	-0.37	0.29	0.30	96.2	-0.54	0.20	0.20	95.3	-1.08	0.14	0.14	95.9
	MP(j)	0.25	1.14	0.17	0.20	99.0	1.14	0.10	0.09	97.0	1.17	0.06	0.06	96.3

Table S5: Simulation results for exposure-time specific and overall summary mediation measures under continuous outcome and continuous mediator (Y_cM_c) in SW-CRTs with an exposure-time dependent treatment effect under different number of clusters.

		$I = 15$				$I = 30$				$I = 60$			
Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)
$e = 1$													
NIE(e)	0.20	-0.99	0.07	0.07	95.3	-0.07	0.05	0.05	95.0	-0.37	0.04	0.04	94.9
NDE(e)	0.60	-0.19	0.12	0.12	96.5	-0.24	0.08	0.08	96.4	-0.15	0.05	0.06	96.0
TE(e)	0.80	-0.39	0.14	0.14	95.6	-0.20	0.09	0.10	95.4	-0.21	0.06	0.07	95.7
MP(e)	0.25	-1.18	0.08	0.08	96.9	-0.13	0.06	0.06	95.5	-0.29	0.04	0.04	95.4
$e = 2$													
NIE(e)	0.25	-1.42	0.10	0.11	96.9	-0.45	0.07	0.07	95.2	-0.15	0.05	0.05	94.4
NDE(e)	0.75	-0.38	0.17	0.17	95.5	-0.06	0.12	0.12	96.3	-0.19	0.08	0.08	95.2
TE(e)	1.00	-0.64	0.20	0.20	95.9	-0.16	0.14	0.14	95.9	-0.18	0.10	0.10	95.3
MP(e)	0.25	-0.90	0.09	0.10	97.5	-0.76	0.06	0.07	96.2	-0.14	0.04	0.04	95.6
$e = 3$													
NIE(e)	0.30	0.10	0.15	0.15	96.2	0.42	0.11	0.11	94.8	0.60	0.08	0.07	93.7
NDE(e)	0.90	-0.41	0.25	0.25	95.0	-0.75	0.16	0.17	95.4	-0.38	0.11	0.12	96.5
TE(e)	1.20	-0.28	0.29	0.29	95.5	-0.46	0.19	0.20	95.6	-0.13	0.14	0.14	95.7
MP(e)	0.25	0.00	0.12	0.13	97.2	0.43	0.08	0.08	96.1	0.40	0.05	0.05	95.2
overall summary													
NIE	0.25	-0.70	0.10	0.10	96.3	-0.00	0.07	0.07	94.7	0.09	0.05	0.05	94.0
NDE	0.75	-0.34	0.16	0.17	95.2	-0.38	0.11	0.11	96.5	-0.25	0.08	0.08	95.6
TE	1.00	-0.43	0.19	0.20	95.9	-0.29	0.13	0.13	95.5	-0.17	0.09	0.09	95.6
MP	0.25	-0.69	0.09	0.09	97.1	-0.15	0.06	0.06	95.5	-0.01	0.04	0.04	95.7

Table S6: Simulation results for exposure-time specific and overall summary mediation measures under continuous outcome and binary mediator ($Y_c M_b$) in SW-CRTs with an exposure-time dependent treatment effect under different number of clusters. GHQ: Gauss-Hermite Quadrature approach for single integral calculation; STA: second-order Taylor approximation for single and double integral calculation.

			$I = 15$				$I = 30$				$I = 60$			
Method	Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)
GHQ	$e = 1$													
	NIE(e)	0.20	2.40	0.15	0.16	95.5	-0.79	0.11	0.11	94.7	-1.70	0.08	0.08	94.6
	NDE(e)	0.60	0.21	0.11	0.12	96.1	0.14	0.08	0.08	94.8	0.04	0.06	0.06	95.6
	TE(e)	0.80	0.76	0.19	0.20	95.7	-0.10	0.14	0.14	95.0	-0.40	0.10	0.10	93.8
	MP(e)	0.25	-8.51	0.17	0.18	95.4	-5.89	0.11	0.11	96.1	-3.77	0.07	0.08	95.4
STA	$e = 1$													
	NIE(e)	0.20	-0.66	0.15	0.16	96.0	0.98	0.10	0.11	96.4	-1.33	0.08	0.07	94.6
	NDE(e)	0.60	-0.22	0.11	0.12	96.8	-0.08	0.08	0.08	95.7	0.42	0.05	0.06	95.8
	TE(e)	0.80	-0.33	0.20	0.20	95.8	0.18	0.13	0.14	95.9	-0.02	0.10	0.09	95.2
	MP(e)	0.25	-11.94	0.18	0.18	95.9	-3.25	0.10	0.11	96.5	-3.78	0.08	0.07	95.2
GHQ	$e = 2$													
	NIE(e)	0.25	3.42	0.21	0.22	96.3	-0.77	0.15	0.15	94.4	-4.45	0.11	0.11	94.3
	NDE(e)	0.75	1.13	0.17	0.17	94.6	0.23	0.11	0.12	95.8	-0.09	0.08	0.08	95.6
	TE(e)	1.00	1.71	0.27	0.28	94.8	-0.02	0.19	0.19	94.7	-1.18	0.14	0.14	95.6
	MP(e)	0.25	-12.94	0.23	0.27	96.1	-7.31	0.13	0.13	95.6	-6.40	0.09	0.09	95.4
STA	$e = 2$													
	NIE(e)	0.25	0.87	0.22	0.22	94.9	-0.93	0.15	0.15	95.8	-2.71	0.10	0.11	95.1
	NDE(e)	0.75	-0.08	0.16	0.17	96.0	0.06	0.11	0.12	95.9	0.36	0.08	0.08	95.1
	TE(e)	1.00	0.16	0.28	0.29	95.4	-0.19	0.19	0.19	96.0	-0.41	0.14	0.14	94.9
	MP(e)	0.25	-14.5	0.21	0.23	96.1	-6.78	0.13	0.13	96.7	-5.34	0.08	0.09	96.4
GHQ	$e = 3$													
	NIE(e)	0.30	-3.09	0.30	0.31	95.1	-4.91	0.21	0.21	94.3	-6.12	0.15	0.15	94.5
	NDE(e)	0.90	1.59	0.25	0.25	95.2	0.77	0.16	0.17	96.2	0.29	0.12	0.12	94.7
	TE(e)	1.20	0.42	0.40	0.41	95.6	-0.65	0.28	0.28	95.1	-1.32	0.21	0.20	94.1
	MP(e)	0.25	-28.68	0.81	4.29	96.4	-14.47	0.16	0.16	96.3	-9.31	0.10	0.11	96.8
STA	$e = 3$													
	NIE(e)	0.30	-2.10	0.32	0.32	94.8	-0.78	0.21	0.22	94.3	-3.70	0.15	0.15	93.9
	NDE(e)	0.90	0.52	0.24	0.25	95.5	0.06	0.17	0.17	94.9	0.50	0.12	0.12	96.5
	TE(e)	1.20	-0.14	0.41	0.42	94.7	-0.15	0.28	0.28	95.4	-0.55	0.20	0.20	94.4
	MP(e)	0.25	-32.72	1.01	0.76	95.3	-9.86	0.16	0.16	95.3	-7.79	0.11	0.10	95.8
GHQ	overall summary													
	NIE	0.25	0.55	0.20	0.21	95.4	-2.43	0.14	0.14	93.5	-4.38	0.10	0.10	94.7
	NDE	0.75	1.07	0.16	0.16	95.1	0.42	0.11	0.11	95.5	0.09	0.08	0.08	95.4
	TE	1.00	0.94	0.27	0.27	95.2	-0.29	0.19	0.19	94.6	-1.03	0.14	0.13	94.2
	MP	0.25	-16.71	0.31	1.54	95.9	-9.23	0.12	0.12	96.0	-6.49	0.08	0.08	96.2
STA	overall summary													
	NIE	0.25	-0.72	0.21	0.21	94.7	-0.36	0.14	0.15	95.3	-2.74	0.10	0.10	93.9
	NDE	0.75	0.12	0.16	0.17	95.9	0.02	0.11	0.11	96.1	0.43	0.08	0.08	95.9
	TE	1.00	-0.09	0.27	0.28	94.3	-0.07	0.18	0.19	95.5	-0.36	0.13	0.13	94.3
	MP	0.25	-19.72	0.38	0.37	95.7	-6.63	0.12	0.12	96.7	-5.63	0.08	0.08	95.9

Table S7: Simulation results for exposure-time specific and overall summary mediation measures under binary outcome and continuous mediator ($Y_b M_c$) in SW-CRTs with an exposure-time dependent treatment effect under different number of clusters. These mediation measures results are obtained from STA: second-order Taylor approximation method for single and double integral calculation.

		$I = 15$				$I = 30$				$I = 60$			
Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)
$e = 1$													
NIE(e)	0.17	1.50	0.06	0.07	96.0	1.11	0.04	0.05	95.4	-0.09	0.03	0.03	95.8
NDE(e)	0.51	1.43	0.22	0.23	95.8	-0.84	0.15	0.16	95.7	0.63	0.11	0.11	96.5
TE(e)	0.68	1.45	0.23	0.24	96.1	-0.35	0.16	0.16	94.9	0.45	0.12	0.11	95.8
MP(e)	0.25	-4.05	1.01	0.59	95.3	8.07	0.21	0.66	95.6	1.59	0.06	0.06	95.4
$e = 2$													
NIE(e)	0.22	3.06	0.10	0.10	96.2	0.89	0.06	0.07	96.7	-0.94	0.05	0.05	95.7
NDE(e)	0.64	4.29	0.33	0.34	95.5	-0.44	0.22	0.23	95.0	0.01	0.16	0.16	94.9
TE(e)	0.86	3.97	0.34	0.35	96.1	-0.10	0.23	0.24	95.7	-0.23	0.17	0.16	95.2
MP(e)	0.25	11.21	0.28	0.47	95.8	6.68	0.13	0.15	96.3	2.11	0.07	0.07	95.9
$e = 3$													
NIE(e)	0.27	3.42	0.14	0.14	95.0	1.74	0.09	0.10	96.1	-0.44	0.07	0.07	94.4
NDE(e)	0.77	2.95	0.49	0.51	94.9	0.06	0.34	0.34	94.8	0.83	0.25	0.24	94.1
TE(e)	1.04	3.07	0.52	0.53	95.3	0.49	0.36	0.36	95.2	0.51	0.26	0.25	93.2
MP(e)	0.26	20.62	1.47	11.19	96.5	9.35	0.24	0.51	96.2	4.32	0.09	0.09	94.7
overall summary													
NIE	0.22	2.80	0.09	0.10	95.8	1.29	0.06	0.06	96.5	-0.51	0.05	0.05	95.3
NDE	0.64	2.99	0.31	0.32	95.9	-0.35	0.21	0.22	95.5	0.51	0.15	0.15	94.0
TE	0.86	2.94	0.32	0.33	95.2	0.07	0.23	0.23	95.1	0.25	0.16	0.16	94.1
MP	0.25	9.32	0.62	4.01	96.4	8.03	0.14	0.43	96.9	2.68	0.06	0.06	94.9

Table S8: Simulation results for exposure-time specific and overall summary mediation measures under binary outcome and binary mediator ($Y_b M_b$) in SW-CRTs with an exposure-time dependent treatment effect under different number of clusters. GHQ: Gauss-Hermite Quadrature approach for single integral calculation; STA: second-order Taylor approximation method for single and double integral calculation.

			$I = 15$				$I = 30$				$I = 60$			
Method	Parameter	TRUE	Bias(%)	MCSD	AESE	CP(%)	Bias(%)	MCSD	AESE	CP(%)	RB(%)	MCSD	AESE	CP(%)
GHQ	$e = 1$													
	NIE(e)	0.18	-2.69	0.13	0.14	95.9	-0.26	0.10	0.10	94.7	-0.61	0.07	0.07	94.8
	NDE(e)	0.44	4.37	0.26	0.26	96.3	1.51	0.17	0.18	96.0	0.33	0.12	0.12	96.3
	TE(e)	0.62	2.32	0.29	0.30	94.6	0.99	0.19	0.20	95.3	0.06	0.14	0.14	95.1
	MP(e)	0.29	-6.17	0.99	2.42	98.8	0.91	0.19	0.21	98.1	0.33	0.11	0.11	96.8
STA	$e = 1$													
	NIE(e)	0.18	-2.65	0.13	0.14	96.0	-0.24	0.10	0.09	94.8	-0.61	0.07	0.07	95.0
	NDE(e)	0.43	4.48	0.25	0.26	96.2	1.56	0.17	0.17	96.1	0.35	0.12	0.12	96.5
	TE(e)	0.61	2.40	0.29	0.30	94.7	1.04	0.19	0.20	95.5	0.07	0.14	0.14	95.2
	MP(e)	0.29	-10.8	1.20	3.14	98.8	0.84	0.19	0.22	98.1	0.31	0.11	0.11	96.9
GHQ	$e = 2$													
	NIE(e)	0.23	-3.10	0.20	0.20	95.1	-0.50	0.14	0.14	95.3	0.30	0.10	0.10	95.3
	NDE(e)	0.55	2.65	0.38	0.39	96.1	1.81	0.26	0.26	95.3	2.00	0.18	0.18	95.7
	TE(e)	0.78	0.98	0.43	0.44	95.5	1.14	0.29	0.29	94.8	1.50	0.20	0.20	95.2
	MP(e)	0.29	-6.05	1.28	3.13	98.8	2.94	0.39	0.87	98.4	1.85	0.18	1.93	96.6
STA	$e = 2$													
	NIE(e)	0.23	-3.10	0.20	0.20	95.0	-0.49	0.14	0.14	95.4	0.30	0.10	0.10	95.4
	NDE(e)	0.55	2.78	0.37	0.38	96.1	1.89	0.26	0.26	95.8	2.03	0.18	0.18	95.7
	TE(e)	0.78	1.07	0.43	0.44	95.4	1.20	0.29	0.29	94.8	1.53	0.20	0.20	95.2
	MP(e)	0.29	-31.04	2.42	7.19	98.8	2.80	0.39	1.24	98.3	1.82	0.18	11.60	96.7
GHQ	$e = 3$													
	NIE(e)	0.27	-7.03	0.30	0.30	95.5	-2.49	0.20	0.20	95.2	-0.59	0.14	0.14	94.9
	NDE(e)	0.67	11.06	0.59	0.78	95.9	2.95	0.39	0.40	95.8	1.61	0.26	0.27	95.7
	TE(e)	0.95	5.84	0.67	0.86	96.1	1.38	0.44	0.45	95.9	0.97	0.30	0.31	94.7
	MP(e)	0.29	-74.92	6.97	6.74	98.4	-30.82	2.04	164.84	98.8	-2.54	0.40	0.39	98.6
STA	$e = 3$													
	NIE(e)	0.27	-7.05	0.30	0.30	95.4	-2.50	0.20	0.20	95.2	-0.59	0.14	0.14	95.0
	NDE(e)	0.67	11.31	0.59	0.78	96.1	3.06	0.39	0.40	95.9	1.66	0.26	0.27	95.6
	TE(e)	0.94	5.99	0.67	0.86	96.1	1.45	0.43	0.45	95.8	1.01	0.30	0.31	94.7
	MP(e)	0.29	-107.4	8.30	10.59	98.4	-30.6	2.03	11.21	98.8	-2.69	0.41	0.41	98.6
GHQ	overall summary													
	NIE	0.23	-4.58	0.19	0.19	96.1	-1.24	0.13	0.13	95.3	-0.30	0.09	0.09	95.2
	NDE	0.56	6.50	0.35	0.41	95.1	2.19	0.24	0.24	95.3	1.40	0.16	0.16	95.3
	TE	0.78	3.29	0.40	0.46	95.5	1.20	0.27	0.27	94.7	0.91	0.19	0.19	95.0
	MP	0.29	-28.98	2.43	3.72	98.9	-8.96	0.70	55.22	98.6	-0.12	0.18	0.79	97.7
STA	overall summary													
	NIE	0.23	-4.57	0.19	0.19	96.2	-1.24	0.13	0.13	95.3	-0.30	0.09	0.09	95.1
	NDE	0.55	6.68	0.35	0.41	95.2	2.28	0.23	0.24	95.3	1.44	0.16	0.16	95.3
	TE	0.78	3.41	0.40	0.46	95.5	1.26	0.27	0.27	94.7	0.94	0.19	0.19	95.1
	MP	0.29	-49.68	2.97	6.59	98.8	-8.96	0.70	4.14	98.7	-0.18	0.18	4.02	97.6

Table S9: Mediation analysis results in the 99DOTS-based SW-CRT based on the nested exchangeable random-effects model. The NIE, NDE, TE and MP are all defined on a log odds ratio scale, conditional on the median level of the covariates.

Treatment effect	Parameter	Estimate	S.E.	95% CI
Constant	NIE	1.047	0.342	(0.326,1.767)
	NDE	0.236	0.439	(-0.691,1.162)
	TE	1.282	0.526	(0.173,2.391)
	MP	0.816	0.287	(0.210,1.422)*
Time-dependent	$e = 1$			
	NIE(e)	0.982	0.403	(0.131,1.833)
	NDE(e)	0.132	0.572	(-1.076,1.340)
	TE(e)	1.114	0.654	(-0.265,2.492)
	MP(e)	0.881	0.456	(-0.081,1.844)*
	$e = 2$			
	NIE(e)	1.217	0.434	(0.302,2.133)
	NDE(e)	0.567	0.734	(-0.982,2.115)
	TE(e)	1.784	0.935	(-0.190,3.757)
	MP(e)	0.682	0.270	(0.112,1.252)*
	$e = 3$			
	NIE(e)	1.420	0.678	(-0.010,2.850)
	NDE(e)	-0.230	0.737	(-1.785,1.326)
	TE(e)	1.190	0.834	(-0.569,2.949)
	MP(e)	1.193	0.794	(-0.482,2.868)*
	$e = 4$			
	NIE(e)	0.578	0.724	(-0.950,2.105)
	NDE(e)	1.205	14.286	(-28.936,31.345)
	TE(e)	1.782	14.138	(-28.047,31.611)
	MP(e)	0.324	0.396	(-0.511,1.160)*
	$e = 5$			
	NIE(e)	1.643	0.804	(-0.054,3.339)
	NDE(e)	0.190	1.061	(-2.048,2.428)
	TE(e)	1.833	1.374	(-1.066,4.731)
	MP(e)	0.896	0.612	(-0.394,2.187)*
	$e = 6$			
	NIE(e)	-0.149	1.095	(-2.460,2.162)
	NDE(e)	-0.544	0.954	(-2.556,1.468)
	TE(e)	-0.692	1.663	(-4.200,2.815)
	MP(e)	0.215	1.206	(-2.330,2.760)*
	overall summary			
	NIE	0.948	0.414	(0.074,1.822)
	NDE	0.220	2.612	(-5.291,5.731)
	TE	1.168	2.583	(-4.280,6.617)
	MP	0.812	0.744	(-0.758,2.382)*

Note: S.E. denotes the standard error estimate calculated by jackknife. The notation * indicates that the lower boundary or upper boundary of CI for MP is non-informative since MP should be strictly bounded between 0 and 1. In practice, one can winzorize the interval to be within $[0, 1]$ for ease of interpretation.

	$j=1$	$j=2$	$j=3$	$j=4$	$j=5$	$j=6$	$j=7$	$j=8$
group 1	$E_{11}=0$	$E_{12}=0$	$E_{13}=1$	$E_{14}=2$	$E_{15}=3$	$E_{16}=4$	$E_{17}=5$	$E_{18}=6$
group 2	$E_{21}=0$	$E_{22}=0$	$E_{23}=0$	$E_{24}=1$	$E_{25}=2$	$E_{26}=3$	$E_{27}=4$	$E_{28}=5$
group 3	$E_{31}=0$	$E_{32}=0$	$E_{33}=0$	$E_{34}=0$	$E_{35}=1$	$E_{36}=2$	$E_{37}=3$	$E_{38}=4$
group 4	$E_{41}=0$	$E_{42}=0$	$E_{43}=0$	$E_{44}=0$	$E_{45}=0$	$E_{46}=1$	$E_{47}=2$	$E_{48}=3$
group 5	$E_{51}=0$	$E_{52}=0$	$E_{53}=0$	$E_{54}=0$	$E_{55}=0$	$E_{56}=0$	$E_{57}=1$	$E_{58}=2$
group 6	$E_{61}=0$	$E_{62}=0$	$E_{63}=0$	$E_{64}=0$	$E_{65}=0$	$E_{66}=0$	$E_{67}=0$	$E_{68}=1$

Figure S1: A schematic illustration of the 99DOTS stepped wedge design with 6 groups and $J = 8$ periods, with three randomized clusters included in each group. Each white cell indicates a control ($A_{ij} = 0$) cluster-period, each grey cell indicates a treatment ($A_{ij} = 1$) cluster-period and each blue cell indicates a cluster-implementation period (treatment is coded as -1, i.e., $A_{ij} = -1$). To explain the concept of exposure time, the value of E_{ij}—the duration of treatment—is included in each cluster-period.