

Appendix 1. Identification of randomly interventional analogue of mediation

parameter $r\Phi(a, a', a'', a''')$

Proof A

$$\begin{aligned}
r\Phi(a, a', a'', a''') &\equiv E[Y(a, G_1(a'), G_2(a'', G_1(a''')))] \\
&= \sum_{m_1} E[Y(a, m_1, G_2(a'', G_1(a''')))|G_1(a') = m_1] \Pr(G_1(a') = m_1) \text{ (add } G_1(a')) \\
&= \sum_{m_1} E[Y(a, m_1, G_2(a'', G_1(a''')))] \Pr(G_1(a') = m_1) \\
&\text{(} G_1(a') \text{ depends to all variables, including } G_1(a''')) \\
&= \sum_{m_1, m_2} E[Y(a, m_1, m_2)|G_2(a'', G_1(a''')) = m_2] \Pr(G_2(a'', G_1(a''')) = m_2) \\
&\Pr(G_1(a') = m_1) \\
&\text{(add } G_2(a'', G_1(a''')))) \\
&= \sum_{m_1, m_2} E[Y(a, m_1, m_2)] \Pr(G_2(a'', G_1(a''')) = m_2) \Pr(G_1(a') = m_1) \\
&\text{(} G_2(a'', G_1(a''')) \text{ depends to all variables)} \\
&= \sum_{m_1, m_2} E[Y(a, m_1, m_2)] \Pr(M_2(a'', G_1(a''')) = m_2) \Pr(M_1(a') = m_1) \\
&\text{(G and M have the same distribution)} \\
&= \sum_{m_1, m_2, m'_1} E[Y(a, m_1, m_2)] \Pr(M_2(a'', m'_1) = m_2|G_1(a''') = m'_1) \\
&\Pr(G_1(a''') = m'_1) \Pr(M_1(a') = m_1) \\
&\text{(add } G_1(a''')) \\
&= \sum_{m_1, m_2, m'_1} E[Y(a, m_1, m_2)] \Pr(M_2(a'', m'_1) = m_2) \Pr(G_1(a''') = m'_1) \Pr(M_1(a') = m_1) \\
&\text{(} G_1(a') \text{ depends to all variables)} \\
&= \sum_{m_1, m_2, m'_1} E[Y(a, m_1, m_2)] \Pr(M_2(a'', m'_1) = m_2) \Pr(M_1(a''') = m'_1) \Pr(M_1(a') = m_1) \\
&\text{(G and M have the same distribution)}
\end{aligned}$$

Proof B

All components in the last equation of proof a can be identified as the expression of g-formula. In order to do that, we need to make four no unmeasured confounding assumptions: (1) no unmeasured exposure-outcome confounding ($Y(a, m_1, m_2) \perp A|V$), (2) no unmeasured mediator-outcome confounding ($Y(a, m_1, m_2) \perp M_1|V, A, L_1$ and $Y(a, m_1, m_2) \perp M_2|V, A, L_1, M_1, L_2$), (3) no unmeasured exposure-mediator confounding ($(M_1(a), M_2(a, m_1)) \perp$

$A|V$), and (4) no unmeasured mediator-mediator confounding ($M_2(a, m_1) \perp M_1|V, A, L_1$).

Under the four assumptions, all components can be identified in forms of g-formula as follows.

$$E[Y(a, m_1, m_2)|v] = \sum_{l_1, l_2} E[Y|v, a, l_1, m_1, l_2, m_2] \Pr(l_1|v, a) \Pr(l_2|v, a, l_1, m_1)$$

$$\Pr(M_2(a, m_1) = m_2|v) = \sum_{l_1} \Pr(m_2|v, a, m_1, l_1) \Pr(l_1|v, a)$$

$$\Pr(M_1(a) = m_1|v) = \Pr(m_1|v, a)$$

Based on the above three expressions,

$$\begin{aligned} & \sum_{m_1, m_2, m'_1} E[Y(a, m_1, m_2)] \Pr(M_1(a') = m_1) \Pr(M_2(a'', m'_1) = m_2) \Pr(M_1(a''') = m'_1) \\ &= \sum_{v, m_1, m_2, m'_1} E[Y(a, m_1, m_2)|v] \Pr(M_1(a') = m_1|v) \Pr(M_2(a'', m'_1) = m_2|v) \\ & \Pr(M_1(a''') = m'_1|v) \Pr(v) \\ &= \sum_{v, m_1, m_2, l_1, l_2} E[Y|v, a, l_1, m_1, l_2, m_2] \Pr(l_1|v, a) \Pr(l_2|v, a, l_1, m_1) \Pr(m_1|v, a') \\ & \quad \sum_{l'_1, m'_1} \Pr(m_2|v, a'', m'_1, l'_1) \Pr(l'_1|v, a'') \Pr(m'_1|v, a''') \Pr(v) \end{aligned}$$

Appendix 2

Consider settings with one exposure (A), k mediators (M_1, M_2, \dots, M_k), and k sets of mediator-outcome confounder (L_1, L_2, \dots, L_k). For simplicity we assume that the exposure A was randomly assigned and there is no baseline confounder. Since the number of rPSEs is $2k$ and there is no close form for all rPSEs, here we use $k = 3$ as example to illustrate the methods.

When $k = 3$, the number of rPSEs is $23 = 8$, which are listed as follows:

$$\begin{aligned}
rPSE_{A \rightarrow Y} &= r\Phi(a_1, a_0, a_0, a_0, a_0, a_0, a_0, a_0) - r\Phi(a_0, a_0, a_0, a_0, a_0, a_0, a_0, a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow Y} &= r\Phi(a_1, a_1, a_0, a_0, a_0, a_0, a_0, a_0) - r\Phi(a_1, a_0, a_0, a_0, a_0, a_0, a_0, a_0) \\
rPSE_{A \rightarrow M_2 \rightarrow Y} &= r\Phi(a_1, a_1, a_1, a_0, a_0, a_0, a_0, a_0) - r\Phi(a_1, a_1, a_0, a_0, a_0, a_0, a_0, a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow M_2 \rightarrow Y} &= r\Phi(a_1, a_1, a_1, a_1, a_0, a_0, a_0, a_0) - r\Phi(a_1, a_1, a_1, a_0, a_0, a_0, a_0, a_0) \\
rPSE_{A \rightarrow M_3 \rightarrow Y} &= r\Phi(a_1, a_1, a_1, a_1, a_1, a_0, a_0, a_0) - r\Phi(a_1, a_1, a_1, a_1, a_0, a_0, a_0, a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow M_3 \rightarrow Y} &= r\Phi(a_1, a_1, a_1, a_1, a_1, a_1, a_0, a_0) - r\Phi(a_1, a_1, a_1, a_1, a_1, a_0, a_0, a_0) \\
rPSE_{A \rightarrow M_2 \rightarrow M_3 \rightarrow Y} &= r\Phi(a_1, a_1, a_1, a_1, a_1, a_1, a_1, a_0) - r\Phi(a_1, a_1, a_1, a_1, a_1, a_1, a_0, a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow M_2 \rightarrow M_3 \rightarrow Y} &= r\Phi(a_1, a_1, a_1, a_1, a_1, a_1, a_1, a_1) - r\Phi(a_1, a_1, a_1, a_1, a_1, a_1, a_1, a_0)
\end{aligned}$$

$r\Phi(a^{(1)}, a^{(2)}, a^{(3)}, a^{(4)}, a^{(5)}, a^{(6)}, a^{(7)}, a^{(8)})$ is defined as

$$E[Y(a^{(1)}, G_1(a^{(2)}), G_2(a^{(3)}, G_1(a^{(4)}))G_3(a^{(5)}, G_1(a^{(6)}), G_2(a^{(7)}, G_1(a^{(8)})))).$$

Using the similar procedure in Appendix 3.1, $r\Phi(a^{(1)}, a^{(2)}, a^{(3)}, a^{(4)}, a^{(5)}, a^{(6)}, a^{(7)}, a^{(8)})$

$$= \sum_{m_3} \left[\begin{aligned} &\sum_{m_2} \left\{ \sum_{m_1} E[Y(a^{(1)}, m_1, m_2, m_3)] \times \Pr(M_1(a^{(2)}) = m_1) \right\} \\ &\times \left\{ \sum_{m'_1} \Pr[M_2(a^{(3)}, m'_1) = m_2] \times \Pr(M_1(a^{(4)}) = m'_1) \right\} \\ &\sum_{m''_1, m'''_1, m'_2} \Pr[M_3(a^{(5)}, m''_1, m'_2) = m_3] \times \Pr(M_1(a^{(6)}) = m''_1) \\ &\times \Pr[M_2(a^{(7)}, m'''_1) = m'_2] \times \Pr(M_1(a^{(8)}) = m'''_1) \end{aligned} \right].$$

Under no unmeasured confounding assumptions, each component of above expression can be identified by the g-formula as follows.

$$\begin{aligned}
E[Y(a, m_1, m_2, m_3)] &= \sum_{l_1, l_2, l_3} E[Y|a, l_1, m_1, l_2, m_2, l_3, m_3] \times \Pr(l_1|a) \times \Pr(l_2|a, l_1, m_1) \times \\
&\Pr(l_3|a, l_1, m_1, l_2, m_2)
\end{aligned}$$

$$\Pr(M_1(a) = m_1) = \Pr(m_1|a)$$

$$\Pr[M_2(a, m_1) = m_2] = \sum_{l_1} \Pr(m_2|a, l_1, m_1) \Pr(l_1|a)$$

$$\Pr[M_3(a, m_1, m_2) = m_3] = \sum_{l_1, l_2} \Pr(m_3|a, l_1, m_1, l_2, m_2) \Pr(l_1|a) \Pr(l_2|a, l_1, m_1)$$

We can extend the above formula to any k by the similar procedure.

Appendix 3. A regression-based approach

In Appendix 1, we showed that under four no unmeasured confounding assumptions, $r\Phi(a, a', a'', a''')$ can be identified as $Q(a, a', a'', a''')$. In this section, we provide a regression-based approach for all rPSEs. Consider the mediator-outcome confounders are not affected by exposure, i.e. L_1 and L_2 are empty, the randomly interventional analogue of mediation parameter $Q(a, a', a'', a''')$ reduces to

$$\sum_{m_1, m_2, m'_1} E[Y|c, a, m_1, m_2] \Pr(m_1|c, a') \Pr(m_2|c, a'', m'_1) \Pr(m'_1|c, a''')$$

Then consider linear model for Y , M_1 , and M_2 with interaction term as follows (we omit high-order interaction term $\theta_7 am_1 m_2$ for simplicity).

$$\begin{aligned} E[Y|A = a, M_1 = m_1, M_2 = m_2, C = c] \\ &= \theta_0 + \theta_1 a + \theta_2 m_1 + \theta_3 m_2 + \theta_4 am_1 + \theta_5 am_2 + \theta_6 m_1 m_2 + \theta_c c \\ E[M_2|A = a, M_1 = m_1, C = c] &= \beta_0 + \beta_1 a + \beta_2 m_1 + \beta_3 am_1 + \beta_c c \\ E[M_1|A = a, C = c] &= \gamma_0 + \gamma_1 a + \gamma_c c. \end{aligned}$$

Therefore,

$$\begin{aligned} Q(a, a', a'', a''') &= \sum_{m_1, m_2, m'_1} E[Y|a, m_1, m_2] \Pr(m_1|a') \Pr(m_2|a'', m'_1) \Pr(m'_1|a''') \\ &= \sum_{m_1, m_2, m'_1} (\theta_0 + \theta_1 a + \theta_2 m_1 + \theta_3 m_2 + \theta_4 am_1 + \theta_5 am_2 + \theta_6 m_1 m_2 + \theta_c c) \Pr(m_1|a') \\ &\quad \Pr(m_2|a'', m'_1) \Pr(m'_1|a''') \\ &= \theta_0 + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a) \sum_{m_1} m_1 \Pr(m_1|a') \\ &\quad + (\theta_3 + \theta_5 a) \sum_{m_2, m'_1} m_2 \Pr(m_2|a'', m'_1) \Pr(m'_1|a''') \\ &\quad + \theta_6 \sum_{m_1} m_1 \Pr(m_1|a') \sum_{m_2, m'_1} m_2 \Pr(m_2|a'', m'_1) \Pr(m'_1|a''') \\ &= \theta_0 + \theta_c c + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a) E[M_1|A = a'] \\ &\quad + ((\theta_3 + \theta_5 a) \sum_{m'_1} E[M_2|A = a'', M_1 = m'_1] \Pr(m'_1|a''')) \\ &\quad + \theta_6 E[M_1|A = a'] \sum_{m_2, m'_1} E[M_2|A = a'', M_1 = m'_1] \Pr(m'_1|a''') \\ &= \theta_0 + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a)(\gamma_0 + \gamma_1 a' + \gamma_c c) \\ &\quad + ((\theta_3 + \theta_5 a) \sum_{m'_1} E[M_2|A = a'', M_1 = m'_1] \Pr(m'_1|a''')) \\ &\quad + \theta_6(\gamma_0 + \gamma_1 a' + \gamma_c c) \sum_{m_2, m'_1} E[M_2|A = a'', M_1 = m'_1] \Pr(m'_1|a''') \end{aligned}$$

$$\begin{aligned}
&= \theta_0 + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a)(\gamma_0 + \gamma_1 a' + \gamma_c c) \\
&+ [(\theta_3 + \theta_5 a + \theta_6(\gamma_0 + \gamma_1 a' + \gamma_c c)) \sum_{m'_1} E[M_2|A = a'', M_1 = m'_1] \Pr(m'_1|a''')] \\
&= \theta_0 + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a)(\gamma_0 + \gamma_1 a' + \gamma_c c) \\
&+ [(\theta_3 + \theta_5 a + \theta_6(\gamma_0 + \gamma_1 a' + \gamma_c c)) \sum_{m'_1} (\beta_0 + \beta_1 a'' + \beta_2 m'_1 + \beta_3 a'' m'_1 + \beta_c c) \Pr(m'_1|a''')] \\
&= \theta_0 + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a)(\gamma_0 + \gamma_1 a' + \gamma_c c) \\
&+ [(\theta_3 + \theta_5 a + \theta_6(\gamma_0 + \gamma_1 a' + \gamma_c c))[(\beta_0 + \beta_1 a'' + \beta_c c) + (\beta_2 + \beta_3 a'')E[M_1|A = a''']] \\
&= \theta_0 + \theta_c c + \theta_1 a + (\theta_2 + \theta_4 a)(\gamma_0 + \gamma_1 a' + \gamma_c c) \\
&+ [(\theta_3 + \theta_5 a + \theta_6(\gamma_0 + \gamma_1 a' + \gamma_c c))[(\beta_0 + \beta_1 a'' + \beta_c c) + (\beta_2 + \beta_3 a'')(\gamma_0 + \gamma_1 a''' + \gamma_c c)]] \\
&= [\theta_0 + \theta_c c + \theta_2(\gamma_0 + \gamma_c c) + (\theta_3 + \theta_6 \gamma_0 + \theta_6 \gamma_c c)(\beta_0 + \beta_2 \gamma_0 + \beta_2 \gamma_c c + \beta_c c)] \\
&+ [\theta_1 + \theta_5(\beta_0 + \beta_2 \gamma_0 + \beta_2 \gamma_c c + \beta_c c) + \theta_4(\gamma_0 + \gamma_c c)]a \\
&+ [\theta_2 \gamma_1 + \theta_6 \gamma_1(\beta_0 + \beta_2 \gamma_0 + \beta_2 \gamma_c c + \beta_c c) + \theta_6 \gamma_1(\beta_0 + \beta_2 \gamma_0 + \beta_2 \gamma_c c + \beta_c c)]a' \\
&+ (\theta_3 + \theta_6 \gamma_0 + \theta_6 \gamma_c c)(\beta_1 + \beta_3 \gamma_0 + \beta_3 \gamma_c c)a'' + (\theta_3 + \theta_6 \gamma_0 + \theta_6 \gamma_c c)\beta_2 \gamma_1 a''' \\
&+ \theta_4 \gamma_1 a a' + \theta_5(\beta_1 + \beta_3 \gamma_0 + \beta_3 \gamma_c c)a a'' + \theta_5 \beta_2 \gamma_1 a a''' \\
&+ \theta_6 \gamma_1(\beta_1 + \beta_3 \gamma_0 + \beta_3 \gamma_c c)a' a'' + \theta_6 \beta_2 \gamma_1^2 a' a''' + (\theta_3 + \theta_6 \gamma_0 + \theta_6 \gamma_c c)\beta_3 \gamma_1 a'' a''' \\
&+ \theta_5 \beta_3 \gamma_1 a a'' a''' + \theta_6 \beta_3 \gamma_1^2 a' a'' a'''
\end{aligned}$$

and

$$\begin{aligned}
rPSE_{A \rightarrow Y} &= Q(a_1, a_0, a_0, a_0) - Q(a_0, a_0, a_0, a_0) \\
&= \left\{ \begin{aligned} &[\theta_1 + \theta_5(\beta_0 + \beta_2 \gamma_0 + \beta_2 \gamma_c c + \beta_c c) + \theta_4(\gamma_0 + \gamma_c c)] \\ &+ [\theta_4 \gamma_1 + \theta_5(\beta_1 + \beta_3 \gamma_0 + \beta_3 \gamma_c c + \beta_2 \gamma_1)]a_0 \\ &+ \theta_5 \beta_3 \gamma_1 a_0^2 \end{aligned} \right\} (a_1 - a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow Y} &= Q(a_1, a_1, a_0, a_0) - Q(a_1, a_0, a_0, a_0) \\
&= \left\{ \begin{aligned} &(\theta_2 \gamma_1 + \theta_6 \gamma_1(\beta_0 + \beta_2 \gamma_0 + \beta_2 \gamma_c c + \beta_c c)) \\ &+ (\theta_4 \gamma_1)a_1 \\ &+ \theta_6 \gamma_1(\beta_1 + \beta_3 \gamma_0 + \beta_3 \gamma_c c)a_0 \\ &+ \theta_6 \beta_3 \gamma_1^2 a_0^2 \end{aligned} \right\} (a_1 - a_0) \\
rPSE_{A \rightarrow M_2 \rightarrow Y} &= Q(a_1, a_1, a_1, a_0) - Q(a_1, a_1, a_0, a_0)
\end{aligned}$$

$$\begin{aligned}
&= \left\{ \begin{aligned} &(\theta_3 + \theta_6\gamma_0 + \theta_6\gamma_c c)(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c) \\ &+ (\theta_5 + \theta_6\gamma_1)(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c)a_1 \\ &+ (\theta_3 + \theta_6\gamma_0 + \theta_6\gamma_c c)\beta_3\gamma_1 a_0 \\ &+ (\theta_5\beta_3\gamma_1 + \theta_6\beta_3\gamma_1^2)a_1 a_0 \end{aligned} \right\} (a_1 - a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow M_2 \rightarrow Y} &= Q(a_1, a_1, a_1, a_1) - Q(a_1, a_1, a_1, a_0) \\
&= \left\{ \begin{aligned} &(\theta_3 + \theta_6\gamma_0 + \theta_6\gamma_c c)\beta_2\gamma_1 \\ &+ [(\theta_5\beta_2\gamma_1 + \theta_6\beta_2\gamma_1^2 + (\theta_3 + \theta_6\gamma_0 + \theta_6\gamma_c c)\beta_3\gamma_1)]a_1 \\ &+ (\theta_5\beta_3\gamma_1 + \theta_6\beta_3\gamma_1^2)a_1^2 \end{aligned} \right\} (a_1 - a_0)
\end{aligned}$$

Without the mediator-mediator interaction, i.e. $\theta_6 = 0$, all formulae reduced to

$$\begin{aligned}
&Q(a, a', a'', a''') \\
&= [\theta_0 + \theta_c c + \theta_2(\gamma_0 + \gamma_c c) + \theta_3(\beta_0 + \beta_2\gamma_0 + \beta_2\gamma_c c + \beta_c c)] \\
&+ [\theta_1 + \theta_5(\beta_0 + \beta_2\gamma_0 + \beta_2\gamma_c c + \beta_c c) + \theta_4(\gamma_0 + \gamma_c c)]a \\
&+ \theta_2\gamma_1 a' + \theta_3(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c)a'' + \theta_3\beta_2\gamma_1 a''' \\
&+ \theta_4\gamma_1 a a' + \theta_5(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c)a a'' + \theta_5\beta_2\gamma_1 a a''' + \theta_3\beta_3\gamma_1 a'' a''' + \theta_5\beta_3\gamma_1 a a'' a''' \\
rPSE_{A \rightarrow Y} &= \left\{ \begin{aligned} &[\theta_1 + \theta_5(\beta_0 + \beta_2\gamma_0 + \beta_2\gamma_c c + \beta_c c) + \theta_4(\gamma_0 + \gamma_c c)] \\ &+ [\theta_4\gamma_1 + \theta_5(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c + \beta_2\gamma_1)]a_0 + \theta_5\beta_3\gamma_1 a_0^2 \end{aligned} \right\} (a_1 - a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow Y} &= \{\theta_2\gamma_1 + \theta_4\gamma_1 a_1\} (a_1 - a_0) \\
rPSE_{A \rightarrow M_2 \rightarrow Y} &= \left\{ \begin{aligned} &\theta_3(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c) + \theta_5(\beta_1 + \beta_3\gamma_0 + \beta_3\gamma_c c)a_1 \\ &+ \theta_3\beta_3\gamma_1 a_0 + \theta_5\beta_3\gamma_1 a_1 a_0 \end{aligned} \right\} (a_1 - a_0) \\
rPSE_{A \rightarrow M_1 \rightarrow M_2 \rightarrow Y} &= \{\theta_3\beta_2\gamma_1 + [(\theta_5\beta_2\gamma_1 + \theta_3\beta_3\gamma_1)]a_1 + \theta_5\beta_3\gamma_1 a_1^2\} (a_1 - a_0)
\end{aligned}$$

In addition, when interaction terms in outcome model are always zero, i.e. $\theta_4 = \theta_5 = 0$,

then

$$\begin{aligned}
rPSE_{A \rightarrow Y} &= \theta_1(a_1 - a_0); \quad rPSE_{A \rightarrow M_1 \rightarrow Y} = \theta_2\gamma_1(a_1 - a_0); \\
rPSE_{A \rightarrow M_2 \rightarrow Y} &= \{\theta_3\beta_1 + \theta_3\beta_3\gamma_0 + \theta_3\beta_3\gamma_c c + \theta_3\beta_3\gamma_1 a_0\} (a_1 - a_0); \\
\text{and } rPSE_{A \rightarrow M_1 \rightarrow M_2 \rightarrow Y} &= \{\theta_3\beta_2\gamma_1 + \theta_3\beta_3\gamma_1 a_1\} (a_1 - a_0).
\end{aligned}$$

Furthermore, when interaction terms in the second mediator model is zero, i.e. $\beta_3 = 0$,

then

$rPSE_{A \rightarrow Y} = \theta_1(a_1 - a_0)$; $rPSE_{A \rightarrow M_1 \rightarrow Y} = \theta_2\gamma_1(a_1 - a_0)$; $rPSE_{A \rightarrow M_2 \rightarrow Y} = \theta_3\beta_1(a_1 - a_0)$;
 and $rPSE_{A \rightarrow M_1 \rightarrow M_2 \rightarrow Y} = \theta_3\beta_2\gamma_1(a_1 - a_0)$, which have the same form of the path analysis.

Appendix 4. SAS code for randomly interventional analogues of path-specific effects

This SAS code is developed to estimate the randomly interventional analogues of path-specific effects (PSE) of exposure A on a continuous outcome Y with continuous mediators M1 and M2 under the regression models in the “A regression based approach and illustration” section. Suppose we have a dataset named mydata with outcome variable “Y”, exposure variables “A”, two mediators “M1” and “M2”, and three covariates “c1”, “c2”, and “c3”. If there were more or fewer covariates the user would have to modify the second to seven, thirteen, and fourteen lines of the code below to include these covariates. In the fourth line of code, the user has to specify the two levels of A (a1=1 and a0=0) that are being compared and the value of the covariates C at which the effects are to be calculated (cc1=1; cc2=50; cc3=0;), according to the values in the application of interest. The output demonstrates estimates, confidence intervals, and p-value for the total effect, four rPSEs, the effect via the first mediator (with/without the second one), the effect via the second mediator (with/without the first one), the total indirect effect, and the proportion divided by total effect.

```
proc nlmixed data=mydata; /* specify dataset named “mydata” */
parms t0=0 t1=0 t2=0 t3=0 t4=0 t5=0 tc1=0 tc2=0 tc3=0 b0=0 b1=0 b2=0 b3=0
bc1=0 bc2=0 bc3=0 r0=0 r1=0 rc1=0 rc2=0 rc3=0 ss_m1=1 ss_m2=1 ss_y=1; /* para-
meter to be estimated*/

a1=1; a0=0; cc1=1; cc2=50; cc3=0; /*parameter to be intervened*/

/* regression model for mean of all variables */
mu_y=t0 + t1*A + t2*M1 + t3*M2 + t4*A*M1 + t5*A*M2 + tc1*C1 + tc2*C2 +
tc3*C3;

mu_m2 =b0 + b1*A + b2*M1 + b3*A*M1 + bc1*C1 + bc2*C2 + bc3*C3;

mu_m1 =r0 + r1*A + rc1*C1 + rc2*C2 + rc3*C3;

/* score function for all variables*/
```

```

ll_y= -((y-mu_y)**2)/(2*ss_y)-0.5*log(ss_y);
ll_m2= -((m2-mu_m2)**2)/(2*ss_m2)-0.5*log(ss_m2);
ll_m1= -((m1-mu_m1)**2)/(2*ss_m1)-0.5*log(ss_m1);
ll_o= ll_m1 + ll_m2 + ll_y;
model Y ~general(ll_o); /* estimate parameters */
/* calculate all estimate we want */
bcc = bc1*cc1 + bc2*cc2 + bc3*cc3;
rcc = rc1*cc1 + rc2*cc2 + rc3*cc3;
pse0 = ((t1+t5*(b0+b2*r0+b2*rcc+bcc)+t4*(r0+rcc))
        +(t4*r1+t5*(b1+b3*r0+b3*rcc+b2*r1))*a0+t5*b3*r1*a0*a0)*(a1-a0);
pse1 =(t2*r1+t4*r1*a1)*(a1-a0);
pse2 =(t3*(b1+b3*r0+b3*rcc)
        +t5*(b1+b3*r0+b3*rcc)*a1+t3*b3*r1*a0+t5*b3*r1*a1*a0)*(a1-a0);
pse12 =(t3*b2*r1+((t5*b2*r1+t3*b3*r1))*a1+t5*b3*r1*a1*a1)*(a1-a0);
ie1=pse1+pse12;
ie2=pse2+pse12;
ie = pse1+pse2+pse12;
te = pse0+ie;
estimate 'Direct Effect' pse0;
estimate 'Path Specific Effect via M1 alone' pse1;
estimate 'Path Specific Effect via M2 alone' pse2;
estimate 'Path Specific Effect via both M1 and M2' pse12;
estimate 'Path Specific Effect via M1 (with/out M2)' ie1;
estimate 'Path Specific Effect via M2 (with/out M1)' ie2;
estimate 'Total Indirect Effect' ie;
estimate 'Total Effect' te;
estimate 'Proportion Direct Effect' pse0/te;

```

```
estimate 'Proportion via M1' pse1/te;  
estimate 'Proportion via M2' pse2/te;  
estimate 'Proportion via both M1 and M2' pse12/te;  
estimate 'Total Proportion via M1' ie1/te;  
estimate 'Total Proportion via M2' ie2/te;  
estimate 'Proportion via M1 or M2' ie/te;  
run;
```