# 1 Simulation

We carried out a small simulation study to assess the finite sample properties of the proposed estimator. We generated 10000 samples of 1000 subjects each, from the model

$$\begin{aligned}
C_1 &\sim Bernoulli(0.5) \\
C_2 &\sim N(0,1) \\
A &\sim Bernoulli\{\text{expit}(-0.5 + C_1 + C_2)\} \\
M &\sim N(-1 + \beta_1 A + C_1 + C_2, 1) \\
T &\sim Weibull\left[3, 0.8\text{exp}\left\{-\frac{1}{3}(-3 + \gamma_1 A + \gamma_2 M + C_1 + 0.1C_2)\right\}\right]
\end{aligned}$$

with $\beta_1 = \gamma_1 = 1$ and $\gamma_2 = 0.1$. The top-left panel of Figure 1 shows the marginal survival function $S(t) = p(T > t)$ for this model. For $t < 0.3$ the survival function is fairly close to 1, and then drops quite steeply to 0.7 at $t = 1$. The top-right panel of Figure 1 shows the true PE functions $\text{PE}^1_{1,0}(t)$ (solid line) and $\text{PE}^0_{1,0}(t)$ (dashed line). We observe that these are fairly constant up to $t = 0.3$. When using the true values of $(\beta_1, \gamma_1, \gamma_2)$ in (3), we obtain the approximations $\text{PE}^1_{1,0}(t) \approx 0.14$ and $\text{PE}^1_{1,0}(t) \approx 0.05$, which agree fairly well with the true values observed in the top-right panel of Figure 1, up to $t = 0.3$.

For each sample we fitted a linear regression model for $M$ and a Cox PH model for $T$, as in assumptions 2 and 3, respectively, with $h(C) = \beta_2 C_1 + \beta_3 C_2$

and $s(C) = \gamma_3 C_1 + \gamma_4 C_2$. We then used the fitted models to estimate $\text{PE}^1_{1,0}(t)$ and $\text{PE}^0_{1,0}(t)$ as in expression (3), together with 95% Wald confidence intervals. The bottom-left panel in Figure 1 shows the mean (over the 10000 samples) bias of the estimates, and the bottom-right panel shows the empirical coverage probability of the confidence intervals, i.e. the probability that the confidence intervals cover the true values of $\text{PE}^1_{1,0}(t)$ and $\text{PE}^0_{1,0}(t)$. We observe that, up to $t = 0.3$, the estimates are virtually unbiased, and that the coverage probabilities are fairly close to 95%. When $t$ increases beyond $t = 0.3$, the estimates become increasingly biased, and the coverage probability decreases below the nominal 95%.

# 2 Derivations

Define $\Lambda_0(t) = \int_0^t \lambda_0(u)du$. Under the assumptions outlined in the main text we have that

$$
\begin{aligned}
S_{aM_{a^*}}(t) &= \int_{m,c} \exp\left\{-\int_0^t \lambda(u|a,m,c)du\right\} p(m|a^*,c)p(c)dmdc \\
&\approx 1 - \int_{m,c}\int_0^t \lambda(u|a,m,c)dup(m|a^*,c)p(c)dmdc \\
&= 1 - \Lambda_0(t)\exp(\gamma_1 a)\int_c \exp\{s(c)\}\int_m \exp(\gamma_2 m)p(m|a^*,c)dmp(c)dc \\
&= 1 - \Lambda_0(t)\exp(\gamma_1 a + \beta_1\gamma_2 a^* + \sigma^2\gamma_2^2/2)\int_c \exp\{s(c) + h(c)\gamma_2\}p(c)dc.
\end{aligned}
$$

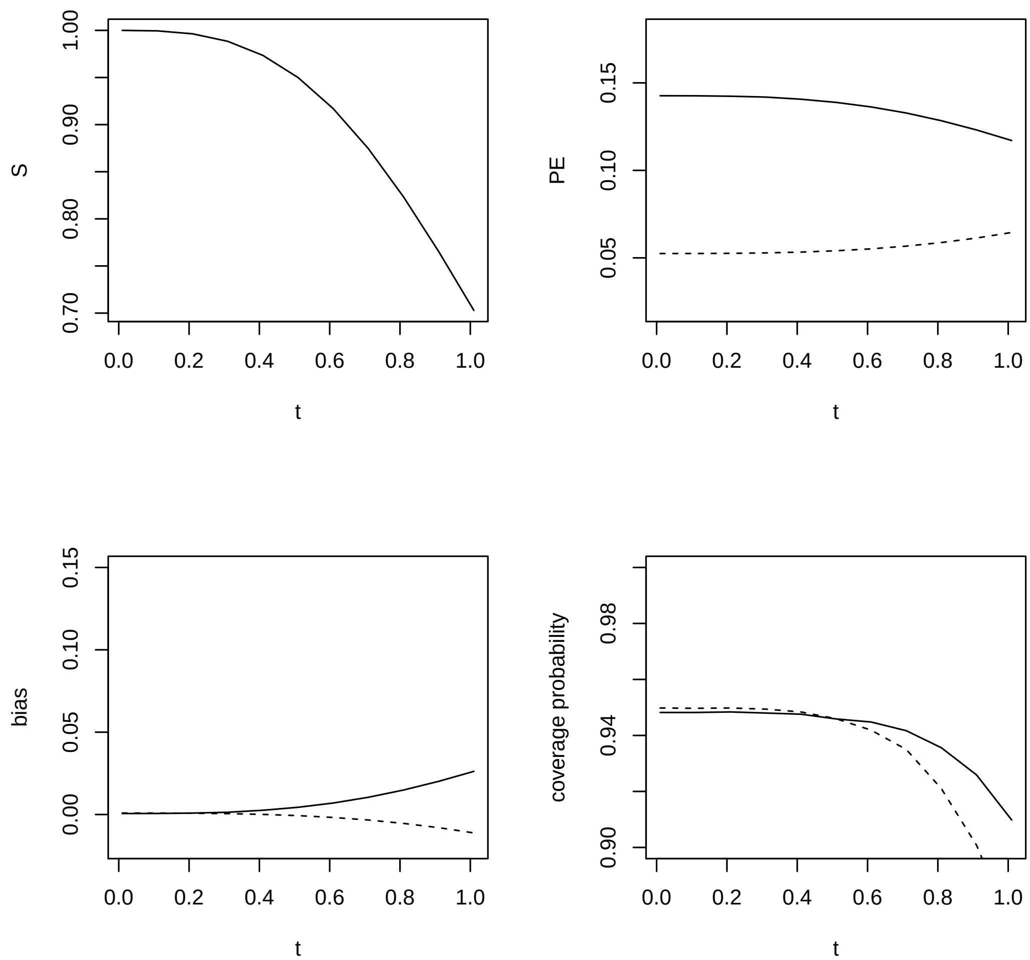


Figure 1: Simulation results. Top-left panel: marginal survival function; top-right panel: true PE functions $\mathrm{PE}^1_{1,0}(t)$ (solid line) and $\mathrm{PE}^0_{1,0}(t)$ (dashed line); bottom-left panel: mean bias of the estimated PEs; bottom-right panel: coverage probability of the 95% confidence intervals.

The first equality follows from assumption 1[1], the approximation follows from assumption 4, the second equality follows from assumption 3, and the third equality follows from assumption 2, by utilizing the moment generating function $E\{\exp(Xk)\} = \exp(\mu k + \sigma^2 k^2/2)$ for the normal distribution. The expression in (3) now follows directly.

Let $\hat{\beta}_1$ be the maximum likelihood estimate of $\beta_1$ obtained from the fitted mediator model, and let $(\hat{\gamma}_1, \hat{\gamma}_2)$ be the partial likelihood estimate of $(\gamma_1, \gamma_2)$ obtained from the fitted outcome model. Define $\theta = (\beta_1, \gamma_1, \gamma_2)^T$ and $\hat{\theta} = (\hat{\beta}_1, \hat{\gamma}_1, \hat{\gamma}_2)^T$. Finally, let $\psi^{a'}_{a,a^*}$ be the right-hand side of (3), and let $\hat{\psi}^{a'}_{a,a^*}$ be the right-hand side of (3) with $\theta$ replaced with $\hat{\theta}$. Using the delta method, together with standard results for (partial) maximum likelihood estimates, it follows that $\hat{\psi}^{a'}_{a,a^*}$ has an asymptotic normal distribution. The asymptotic variance of $\hat{\psi}^{a'}_{a,a^*}$ is given by

$$var(\hat{\psi}^{a'}_{a,a^*}) = \frac{d\psi^{a'}_{a,a^*}}{d\theta^T} var(\hat{\theta}) \frac{d\psi^{a'}_{a,a^*}}{d\theta}. \tag{1}$$

The asymptotic variance-covariance matrix $var(\hat{\theta})$ is obtained from the inverse Fisher information matricies of the fitted models; we note that $cov(\hat{\beta}_1, \hat{\gamma}_1) = cov(\hat{\beta}_1, \hat{\gamma}_2) = 0$ since $\beta_1$ and $(\gamma_1, \gamma_2)$ are orthogonal. Finally, an estimate of $var(\hat{\psi}^{a'}_{a,a^*})$ is obtained by replacing $\theta$ with $\hat{\theta}$ in (1).

# 3 R code

The `PE` function below has six arguments. `fitT` is a fitted Cox PH model for the outcome, as obtained from the `coxph` function in the `survival` package. `fitM` is a fitted linear regression model for the mediator, as obtained from the `lm` function. `A` specifies the name of the exposure, as a string. `a`, `astar` and `aprim` specify the values of $a$, $a^*$ and $a'$ in (3). The function outputs a list with two elements; `est` (the estimate of $\text{PE}_{a,a^*}^{a'}(t)$) and `var` (the estimated variance).

```
library(numDeriv)
PE <- function(fitT, fitM, A, a, astar, aprim){
  if(aprim!=a & aprim!=astar)
    stop("aprim must be equal to a or astar")
  M <- as.character(fitM$call$formula[2])
  b1 <- fitM$coefficients[A]
  g1 <- fitT$coefficients[A]
  g2 <- fitT$coefficients[M]
  theta <- c(b1, g1, g2)
  tmp <- function(theta){
    b1 <- theta[1]
    g1 <- theta[2]
    g2 <- theta[3]
    return((exp(g1*aprim)*(exp(b1*g2*a)-exp(b1*g2*astar)))/
```

```
    (exp((g1+b1*g2)*a)-exp((g1+b1*g2)*astar)))
  }
  est <- tmp(theta)
  dPE <- matrix(grad(func=tmp, x=theta))
  vb1 <- vcov(fitM)[A, A]
  vg1 <- vcov(fitT)[A, A]
  vg2 <- vcov(fitT)[M, M]
  vg1g2 <- vcov(fitT)[A, M]
  vcov <- matrix(c(vb1, 0, 0, 0, vg1, vg1g2, 0, vg1g2, vg2), 3, 3)
  var <- as.vector(t(dPE)%*%vcov%*%dPE)
  out <- list(est=est, var=var)
  return(out)
}
```

# References


[1] VanderWeele, T. Causal mediation analysis with survival data. *Epidemiology.* 2011;22:582–585.