# Supplementary Text

## S.1. M-splines, I-splines and C-splines

Let $t = \{t_1, t_2, ..., t_{n+k}\}$ denote the knot sequence, $n$ denote the number of free parameters that specify the spline function having the specified continuity characteristics, and $k$ be the order of the basis functions. Then the recursive form of M-splines is as follows (Ramsay, 1988):

For order $k = 1$, $M_i(x|1, t) = \frac{1}{t_{i+1}-t_i}$ if $t_i \leq x < t_{i+1}$, otherwise $M_i(x|1, t) = 0$, and
for order $k > 1$, $M_i(x|k, t) = \frac{k[(x-t_i)M_i(x|k-1,t)+(t_{i+k}-x)M_{i+1}(x|k-1,t)]}{(k-1)(t_{i+k}-t_i)}$ if $t_i \leq x < t_{i+k}$, otherwise $M_i(x|k, t) = 0$.

The quadratic I-splines $I_i(x|2, t)$ are obtained by integrating the M-splines of degree 1 and can be expressed as:

$I_i(x|2, t) = 0$ if $x < t_i$,
$I_i(x|2, t) = \frac{(x-t_i)^2}{(t_{i+2}-t_i)(t_{i+1}-t_i)}$ if $t_i \leq x < t_{i+1}$,
$I_i(x|2, t) = 1 - \frac{(t_{i+2}-x)^2}{(t_{i+2}-t_i)(t_{i+2}-t_{i+1})}$ if $t_{i+1} \leq x < t_{i+2}$, and
$I_i(x|2, t) = 1$ if $x \geq t_{i+2}$.

The cubic C-splines $C_i(x|2, t)$ are obtained by integrating the quadratic I-splines and can be expressed as:

$C_i(x|2, t) = 0$ if $x < t_i$,
$C_i(x|2, t) = \frac{(x-t_i)^3}{3(t_{i+2}-t_i)(t_{i+1}-t_i)}$ if $t_i \leq x < t_{i+1}$,
$C_i(x|2, t) = x - \frac{t_i+t_{i+1}+t_{i+2}}{3} + \frac{(t_{i+2}-x)^3}{3(t_{i+2}-t_i)(t_{i+2}-t_{i+1})}$ if $t_{i+1} \leq x < t_{i+2}$, and
$C_i(x|2, t) = x - \frac{t_i+t_{i+1}+t_{i+2}}{3}$ if $x \geq t_{i+2}$.

## S.2. Proof of Proposition 1

*Proof.* Under the conditions described in Proposition 1, and with the models (1) and (2) being correctly specified, we obtain after some simplifications:

$E[CDE|c] = E[Y_{am} - Y_{a^*m}|c] = E[Y|a, m, c] - E[Y|a^*, m, c] = (\beta_1 + f_1(m) - f_2(m))(a - a^*)$,

$E[NDE|c] = E[Y_{aM_{a^*}} - Y_{a^*M_{a^*}}|c] = \int_m \{E[Y|a,m,c] - E[Y|a^*,m,c]\} f(m|a^*,c)dm$

$= (\beta_1 + E[f_1(M)|a^*,c] - E[f_2(M)|a^*,c])(a - a^*)$, and

$E[NIE|c] = E[Y_{aM_a} - Y_{aM_{a^*}}|c] = \int_m E[Y|a,m,c]\{f(m|a,c) - f(m|a^*,c)\}dm$

$= a(E[f_1(M)|a,c] - E[f_1(M)|a^*,c]) + (1-a)(E[f_2(M)|a,c] - E[f_2(M)|a^*,c])$.

Let the knot sequence be $L = t_1 = t_2 < t_3 < ... < t_k < t_{k+1} = t_{k+2} = U$. If $f_1(M)$ is fitted using I-splines, then $f_1(M) = \beta_{21} I_1(M|2,t) + ... + \beta_{2k} I_k(M|2,t)$. This is a piece-wise function, where, for $t_k \le M < t_{k+1}$, $f_1(M) = \beta_{21} + ... + \beta_{2,k-2} + \beta_{2,k-1}(1 - \frac{(t_{k+1}-M)^2}{(t_{k+1}-t_k)(t_{k+1}-t_{k-1})}) + \beta_{2,k}(\frac{(M-t_k)^2}{(t_{k+1}-t_k)(t_{k+2}-t_k)})$. Then conditional on $a$ and $c$ we obtain:

$E[f_1(M)|a,c] = \int_m (\beta_{21} I_1(m|2,t) + ... + \beta_{2k} I_k(m|2,t)) f(m|a,c)dm = \sum_{i=2}^{k} \{\int_{t_i}^{t_{i+1}} [\beta_{21} + ... + \beta_{2,i-2} + \beta_{2,i-1}(1 - \frac{(t_{i+1}-m)^2}{(t_{i+1}-t_i)(t_{i+1}-t_{i-1})}) + \beta_{2,i}(\frac{(m-t_i)^2}{(t_{i+1}-t_i)(t_{i+2}-t_i)})] f(m|a,c)dm\}$, where $f(m|a,c)$ denotes normal density with mean $\gamma_0 + \gamma_1 a + \gamma_2 c$ and variance $\sigma_2^2$. Similar expressions can be derived for $f_2(M)$ and $E[f_2(M)|a,c]$.

If $f_1(M)$ is fitted using C-splines, then $f_1(M) = \beta_{20} M + \beta_{21} C_1(M|2,t) + ... + \beta_{2k} C_k(M|2,t)$, which is also a piece-wise function. For either $M < t_2$ or $M \ge t_{k+1}$, $f_1(M) = \beta_{20} M$. For $t_k \le M < t_{k+1}$, $f_1(M) = \beta_{20} M + \beta_{21}(M - \frac{t_1+t_2+t_3}{3}) + ... + \beta_{2,k-2}(M - \frac{t_{k-2}+t_{k-1}+t_k}{3}) + \beta_{2,k-1}(m - \frac{t_{k-1}+t_k+t_{k+1}}{3} + \frac{(t_{k+1}-m)^3}{3(t_{k+1}-t_k)(t_{k+1}-t_{k-1})}) + \beta_{2,k}(\frac{(m-t_k)^3}{3(t_{k+1}-t_k)(t_{k+2}-t_k)})$. Then conditional on $a$ and $c$ we obtain:

$E[f_1(M)|a,c] = \int_m (\beta_{20} m + \beta_{21} C_1(m|2,t) + ... + \beta_{2k} C_k(m|2,t)) f(m|a,c)dm =$

$\beta_{20}(\gamma_0 + \gamma_1 a + \gamma_2 c) + \sum_{i=2}^{k} \{\int_{t_i}^{t_{i+1}} [\beta_{21}(m - \frac{t_1+t_2+t_3}{3}) + ... + \beta_{2,i-2}(m - \frac{t_{i-2}+t_{i-1}+t_i}{3})$

$+\beta_{2,i-1}(m - \frac{t_{i-1}+t_i+t_{i+1}}{3} + \frac{(t_{i+1}-m)^3}{3(t_{i+1}-t_i)(t_{i+1}-t_{i-1})}) + \beta_{2,i}(\frac{(m-t_i)^3}{3(t_{i+1}-t_i)(t_{i+2}-t_i)})] f(m|a,c)dm\}$.

Similar expressions can be derived for $f_2(M)$ and $E[f_2(M)|a,c]$. □

## S.3. Proposition 3

**Proposition 3.** *Let $\theta_{CDE} = (\beta_1, \beta_2, \beta_3)$, $\theta_{NDE} = (\beta_1, \beta_2, \beta_3, \gamma_0, \gamma_1, \gamma_2, \sigma_2^2)$ and $\theta_{NIE} = (\beta_2, \gamma_0, \gamma_1, \gamma_2, \sigma_2^2)$, where $\beta_2 = (\beta_{21}, ..., \beta_{2k})$ and $\beta_3 = (\beta_{31}, ..., \beta_{3k})$ in case of quadratic I-splines, and $\beta_2 = (\beta_{20}, \beta_{21}, ..., \beta_{2k})$ and $\beta_3 = (\beta_{30}, \beta_{31}, ..., \beta_{3k})$ in case of cubic C-splines.*

*Denote the expected controlled direct effect as $g_{CDE}(\theta_{CDE})$, the expected natural direct effect as $g_{NDE}(\theta_{NDE})$ and the expected natural indirect effect as $g_{NIE}(\theta_{NIE})$. Then the asymptotic variances of expected CDE, NDE and NIE are $\nabla_{\theta_{CDE}} g_{CDE}(\theta_{CDE})^T \Sigma_{\theta_{CDE}} \nabla_{\theta_{CDE}} g_{CDE}(\theta_{CDE})$, $\nabla_{\theta_{NDE}} g_{NDE}(\theta_{NDE})^T \Sigma_{\theta_{NDE}} \nabla_{\theta_{NDE}} g_{NDE}(\theta_{NDE})$ and $\nabla_{\theta_{NIE}} g_{NIE}(\theta_{NIE})^T \Sigma_{\theta_{NIE}} \nabla_{\theta_{NIE}} g_{NIE}(\theta_{NIE})$ respectively, where $\Sigma_{\theta_{CDE}}$, $\Sigma_{\theta_{NDE}}$ and $\Sigma_{\theta_{NIE}}$ are the covariance matrices corresponding to the estimated $\theta_{CDE}$, $\theta_{NDE}$ and $\theta_{NIE}$.*

If $f_1(M)$ is fitted using I-splines, then:

$\frac{\partial E[f_1(M)|a,c]}{\partial \beta_{2i}} = \int_{t_i}^{t_{i+1}} \frac{(m-t_i)^2}{(t_{i+1}-t_i)(t_{i+2}-t_i)} f(m|a,c)dm + \int_{t_{i+1}}^{t_{i+2}} (1 - \frac{(t_{i+2}-m)^2}{(t_{i+2}-t_{i+1})(t_{i+2}-t_i)}) f(m|a,c)dm + \int_{t_{i+2}}^{t_{i+3}} f(m|a,c)dm + ... + \int_{t_k}^{t_{k+1}} f(m|a,c)dm$, for $i = 1, 2, \ldots, k$,

$\frac{\partial E[f_1(M)|a,c]}{\partial \gamma_0} = \sum_{i=2}^{k} \{ \int_{t_i}^{t_{i+1}} [\beta_{21} + ... + \beta_{2,i-2} + \beta_{2,i-1}(1 - \frac{(t_{i+1}-m)^2}{(t_{i+1}-t_i)(t_{i+1}-t_{i-1})}) + \beta_{2,i}(\frac{(m-t_i)^2}{(t_{i+1}-t_i)(t_{i+2}-t_i)})] f(m|a,c) \frac{2(m-(\gamma_0+\gamma_1 a+\gamma_2 c))}{2\sigma_2^2} dm \}$,

$\frac{\partial E[f_1(M)|a,c]}{\partial \sigma_2^2} = \sum_{i=2}^{k} \{ \int_{t_i}^{t_{i+1}} [\beta_{21} + ... + \beta_{2,i-2} + \beta_{2,i-1}(1 - \frac{(t_{i+1}-m)^2}{(t_{i+1}-t_i)(t_{i+1}-t_{i-1})}) + \beta_{2,i}(\frac{(m-t_i)^2}{(t_{i+1}-t_i)(t_{i+2}-t_i)})] f(m|a,c)(-\frac{1}{2\sigma_2^2} + \frac{(m-(\gamma_0+\gamma_1 a+\gamma_2 c))^2}{2(\sigma_2^2)^2}) dm \}$.

Similar expressions can be derived for $\frac{\partial E[f_1(M)|a,c]}{\partial \gamma_1}$ and $\frac{\partial E[f_1(M)|a,c]}{\partial \gamma_2}$.

If $f_1(M)$ is fitted using C-splines, then:

$\frac{\partial E[f_1(M)|a,c]}{\partial \beta_{20}} = \gamma_0 + \gamma_1 a + \gamma_2 c$,

$\frac{\partial E[f_1(M)|a,c]}{\partial \beta_{2i}} = \int_{t_i}^{t_{i+1}} \frac{(m-t_i)^3}{3(t_{i+1}-t_i)(t_{i+2}-t_i)} f(m|a,c)dm + \int_{t_{i+1}}^{t_{i+2}} (m - \frac{t_i+t_{i+1}+t_{i+2}}{3} + \frac{(t_{i+2}-m)^3}{3(t_{i+2}-t_{i+1})(t_{i+2}-t_i)}) f(m|a,c)dm + \int_{t_{i+2}}^{t_{i+3}} (m - \frac{t_i+t_{i+1}+t_{i+2}}{3}) f(m|a,c)dm + ... + \int_{t_k}^{t_{k+1}} (m - \frac{t_i+t_{i+1}+t_{i+2}}{3}) f(m|a,c)dm$, for $i = 1, 2, \ldots, k$

$\frac{\partial E[f_1(M)|a,c]}{\partial \gamma_0} = \beta_{20} + \sum_{i=2}^{k} \{ \int_{t_i}^{t_{i+1}} [\beta_{21}(m - \frac{t_1+t_2+t_3}{3}) + ... + \beta_{2,i-2}(m - \frac{t_{i-2}+t_{i-1}+t_i}{3}) + \beta_{2,i-1}(m - \frac{t_{i-1}+t_i+t_{i+1}}{3} + \frac{(t_{i+1}-m)^3}{3(t_{i+1}-t_i)(t_{i+1}-t_{i-1})}) + \beta_{2,i}(\frac{(m-t_i)^3}{3(t_{i+1}-t_i)(t_{i+2}-t_i)})] f(m|a,c) \frac{2(m-(\gamma_0+\gamma_1 a+\gamma_2 c))}{2\sigma_2^2} dm \}$,

$\frac{\partial E[f_1(M)|a,c]}{\partial \sigma_2^2} = \sum_{i=2}^{k} \{ \int_{t_i}^{t_{i+1}} [\beta_{21}(m - \frac{t_1+t_2+t_3}{3}) + ... + \beta_{2,i-2}(m - \frac{t_{i-2}+t_{i-1}+t_i}{3}) + \beta_{2,i-1}(m - \frac{t_{i-1}+t_i+t_{i+1}}{3} + \frac{(t_{i+1}-m)^3}{3(t_{i+1}-t_i)(t_{i+1}-t_{i-1})}) + \beta_{2,i}(\frac{(m-t_i)^3}{3(t_{i+1}-t_i)(t_{i+2}-t_i)})] f(m|a,c)(-\frac{1}{2\sigma_2^2} + \frac{(m-(\gamma_0+\gamma_1 a+\gamma_2 c))^2}{2(\sigma_2^2)^2}) dm \}$.

Similarly expressions can be derived for $\frac{\partial E[f_1(M)|a,c]}{\partial \gamma_1}$ and $\frac{\partial E[f_1(M)|a,c]}{\partial \gamma_2}$.

## S.4. Proof of Proposition 2

*Proof.* Using linear regression, the exposure-outcome model is expressed as

$$Y = \beta_0 + \beta_1 A + \beta_2 M + \beta_3 AM + \beta_4 C + \epsilon_1 \tag{S.1}$$

where $\epsilon_1 \sim N(0, \sigma_1^2)$, while the exposure-mediator model keeps the same as model (2). Then the expected CDE, NDE and NIE, conditioning on $C = c$, are given by

$$E[Y_{am} - Y_{a^*m}|c] = (\beta_1 + \beta_3 m)(a - a^*), \tag{S.2}$$

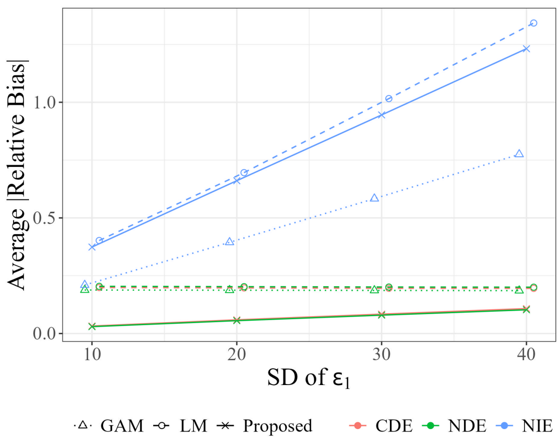
$$E[Y_{aM_{a^*}} - Y_{a^*M_{a^*}}|c] = (\beta_1 + \beta_3(\gamma_0 + \gamma_1 a^* + \gamma_2 c))(a - a^*), \tag{S.3}$$

and

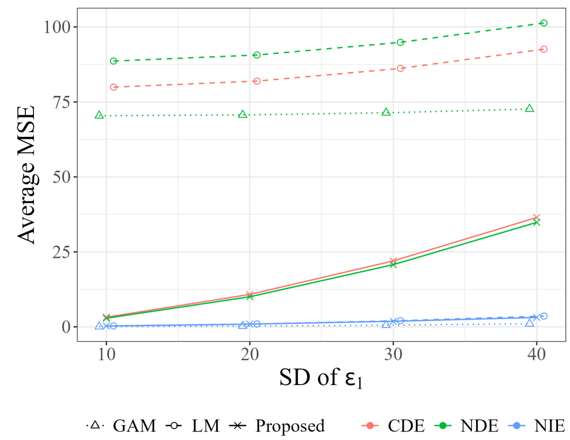
$$E[Y_{aM_a} - Y_{aM_{a^*}}|c] = (\beta_2\gamma_1 + \beta_3\gamma_1 a)(a - a^*), \tag{S.4}$$

respectively. Let $X = [1, A, M, AM, C]$, then $\hat{\beta} \sim N(\beta, \sigma_1^2(X^TX)^{-1})$. The expected CDE, NDE and NIE can all be expressed as a linear combination of $\beta$. Assuming $\hat{\theta}_{LR} = a\hat{\beta} \sim N(a\beta, \sigma_1^2 a(X^TX)^{-1}a^T)$, then we obtain $P(|\hat{\theta}_{LR} - \theta_{true}| \leq z_{\alpha/2}\sqrt{Var(\hat{\theta}_{LR})}) = \phi(z_{\alpha/2} + \frac{\theta_{true}-\theta_{LR}}{\sigma_1\sqrt{a(X^TX)^{-1}a^T}}) - \phi(-z_{\alpha/2} + \frac{\theta_{true}-\theta_{LR}}{\sigma_1\sqrt{a(X^TX)^{-1}a^T}})$, where $\phi(\cdot)$ denotes normal density function. Therefore, if $\theta_{true} \neq \theta_{LR}$ then as $\sigma_1 \to 0$, the coverage probability $\to 0$. $\square$

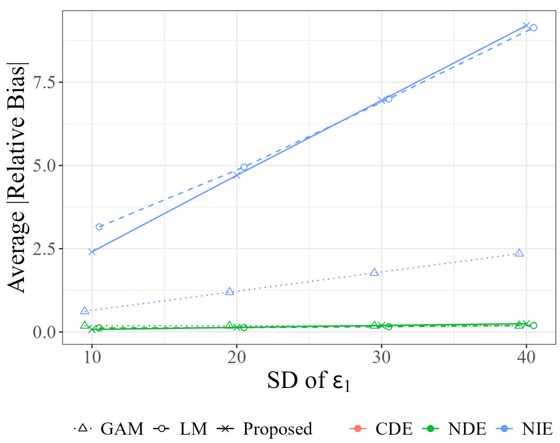
## S.5. Simulation results of average absolute relative bias and average MSE for each pattern



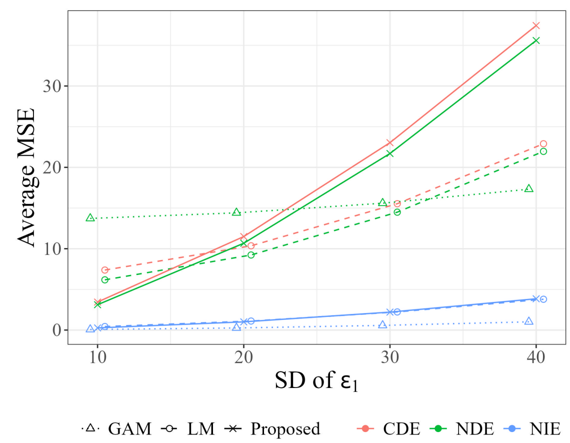

(a) Average |Relative Bias| under pattern 1



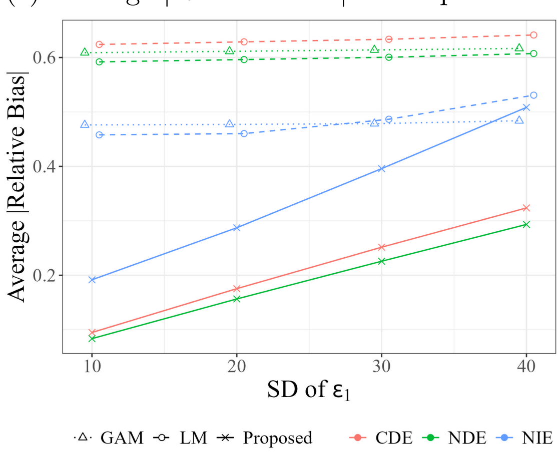

(b) Average MSE under pattern 1



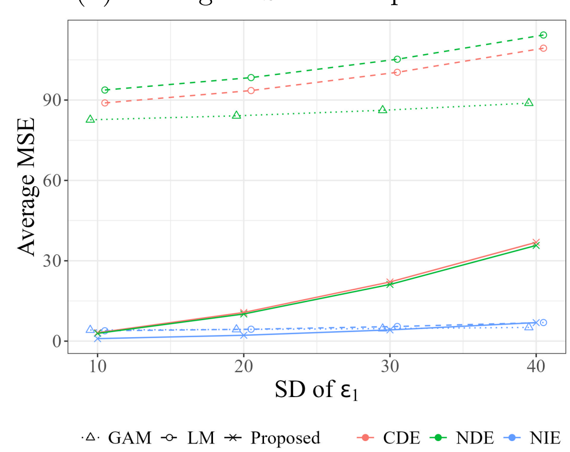

(c) Average |Relative Bias| under pattern 2




(d) Average MSE under pattern 2



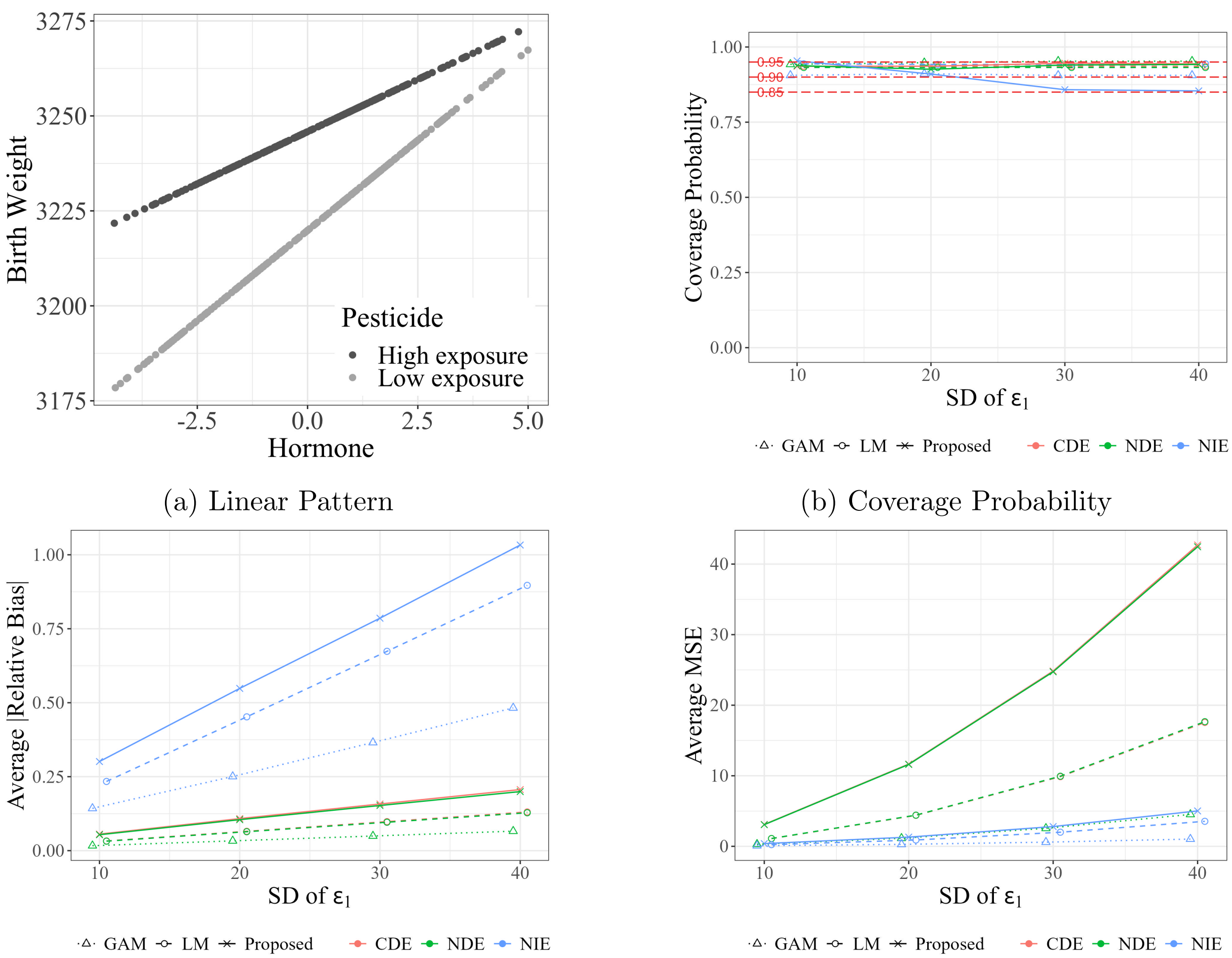

(e) Average |Relative Bias| under pattern 3




(f) Average MSE under pattern 3

Figure S.1: Simulation results of average absolute relative bias and average MSE for each pattern

## S.6. Plots of hormone vs. birth weight under linear pattern and simulation results for linear pattern




(a) Linear Pattern

(b) Coverage Probability

(c) Average |Relative Bias|

(d) Average MSE

Figure S.2: Plots of hormone vs. birth weight under linear pattern, and simulation results of coverage probability, average absolute relative bias and average MSE for linear pattern

## S.7. Tables of Simulation Results

Table S.1: Simulation results of coverage probability, average absolute relative bias and average MSE for pattern 1 (true CDE: $\sim 44.62$, true NDE: 45.82, true NIE: 1.10)

| Semi-parametric shape-restricted regression spline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.922 | 0.948 | 0.958 | 0.032 | 0.030 | 0.374 | 3.223 | 2.879 | 0.281 |
| $20^2$ | 0.932 | 0.948 | 0.950 | 0.059 | 0.056 | 0.661 | 10.808 | 10.030 | 0.902 |
| $30^2$ | 0.954 | 0.952 | 0.958 | 0.084 | 0.080 | 0.945 | 21.982 | 20.739 | 1.852 |
| $40^2$ | 0.952 | 0.952 | 0.960 | 0.108 | 0.103 | 1.232 | 36.465 | 34.837 | 3.129 |
| **Linear regression** | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.000 | 0.000 | 0.922 | 0.199 | 0.204 | 0.402 | 79.924 | 88.628 | 0.312 |
| $20^2$ | 0.018 | 0.008 | 0.928 | 0.197 | 0.203 | 0.696 | 81.953 | 90.648 | 0.959 |
| $30^2$ | 0.198 | 0.158 | 0.936 | 0.196 | 0.201 | 1.016 | 86.176 | 94.878 | 2.048 |
| $40^2$ | 0.444 | 0.400 | 0.940 | 0.195 | 0.200 | 1.343 | 92.594 | 101.316 | 3.580 |
| **Generalized additive model** | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | - | 0.000 | 0.895 | - | 0.188 | 0.210 | - | 70.406 | 0.072 |
| $20^2$ | - | 0.000 | 0.901 | - | 0.187 | 0.394 | - | 70.662 | 0.257 |
| $30^2$ | - | 0.005 | 0.901 | - | 0.186 | 0.583 | - | 71.381 | 0.565 |
| $40^2$ | - | 0.016 | 0.911 | - | 0.186 | 0.775 | - | 72.631 | 0.996 |

Table S.2: Simulation results of coverage probability, average absolute relative bias and average MSE for pattern 2 (true CDE: $\sim$ 19.85, true NDE: 19.17, true NIE: -0.17)

| Semi-parametric shape-restricted regression spline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.950 | 0.974 | 0.972 | 0.076 | 0.074 | 2.405 | 3.442 | 3.114 | 0.264 |
| $20^2$ | 0.948 | 0.966 | 0.968 | 0.138 | 0.137 | 4.704 | 11.496 | 10.673 | 1.008 |
| $30^2$ | 0.944 | 0.956 | 0.962 | 0.195 | 0.195 | 6.954 | 23.035 | 21.703 | 2.205 |
| $40^2$ | 0.946 | 0.962 | 0.962 | 0.247 | 0.249 | 9.200 | 37.434 | 35.597 | 3.847 |
| Linear regression | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.560 | 0.638 | 0.928 | 0.124 | 0.116 | 3.157 | 7.376 | 6.172 | 0.434 |
| $20^2$ | 0.796 | 0.836 | 0.940 | 0.134 | 0.130 | 4.953 | 10.357 | 9.227 | 1.109 |
| $30^2$ | 0.888 | 0.892 | 0.938 | 0.159 | 0.159 | 7.000 | 15.533 | 14.491 | 2.226 |
| $40^2$ | 0.908 | 0.928 | 0.938 | 0.192 | 0.195 | 9.135 | 22.902 | 21.964 | 3.786 |
| Generalized additive model | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | - | 0.000 | 0.895 | - | 0.186 | 0.619 | - | 13.722 | 0.068 |
| $20^2$ | - | 0.037 | 0.901 | - | 0.185 | 1.195 | - | 14.407 | 0.257 |
| $30^2$ | - | 0.356 | 0.901 | - | 0.185 | 1.771 | - | 15.593 | 0.571 |
| $40^2$ | - | 0.550 | 0.901 | - | 0.187 | 2.351 | - | 17.313 | 1.010 |

Table S.3: Simulation results of coverage probability, average absolute relative bias and average MSE for pattern 3 (true CDE: $\sim$ -15.00, true NDE: -16.24, true NIE: 4.08)

| Semi-parametric shape-restricted regression spline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.920 | 0.944 | 0.894 | 0.095 | 0.084 | 0.192 | 3.145 | 2.910 | 0.940 |
| $20^2$ | 0.934 | 0.946 | 0.924 | 0.175 | 0.156 | 0.287 | 10.708 | 10.134 | 2.193 |
| $30^2$ | 0.940 | 0.950 | 0.934 | 0.252 | 0.226 | 0.396 | 22.092 | 21.157 | 4.190 |
| $40^2$ | 0.942 | 0.954 | 0.936 | 0.324 | 0.293 | 0.508 | 36.892 | 35.725 | 6.915 |
| Linear regression | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.000 | 0.000 | 0.130 | 0.624 | 0.592 | 0.458 | 88.930 | 93.747 | 3.865 |
| $20^2$ | 0.010 | 0.010 | 0.532 | 0.629 | 0.596 | 0.460 | 93.545 | 98.385 | 4.448 |
| $30^2$ | 0.148 | 0.134 | 0.736 | 0.634 | 0.601 | 0.487 | 100.355 | 105.232 | 5.473 |
| $40^2$ | 0.352 | 0.336 | 0.820 | 0.641 | 0.607 | 0.531 | 109.360 | 114.288 | 6.940 |
| Generalized additive model | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | - | 0.000 | 0.000 | - | 0.609 | 0.476 | - | 82.627 | 4.150 |
| $20^2$ | - | 0.000 | 0.068 | - | 0.611 | 0.477 | - | 84.116 | 4.360 |
| $30^2$ | - | 0.000 | 0.288 | - | 0.614 | 0.479 | - | 86.181 | 4.684 |
| $40^2$ | - | 0.010 | 0.503 | - | 0.617 | 0.484 | - | 88.846 | 5.125 |

Table S.4: Simulation results of coverage probability, average absolute relative bias and average MSE for linear pattern (true CDE: $\sim 25.44$, true NDE: 26.07, true NIE: 1.65)

| Semi-parametric shape-restricted regression spline | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.936 | 0.938 | 0.954 | 0.056 | 0.054 | 0.301 | 3.101 | 3.070 | 0.387 |
| $20^2$ | 0.936 | 0.926 | 0.910 | 0.108 | 0.105 | 0.548 | 11.657 | 11.608 | 1.303 |
| $30^2$ | 0.946 | 0.940 | 0.858 | 0.158 | 0.153 | 0.786 | 24.839 | 24.736 | 2.800 |
| $40^2$ | 0.944 | 0.942 | 0.854 | 0.206 | 0.200 | 1.033 | 42.702 | 42.454 | 5.016 |
| **Linear regression** | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | 0.936 | 0.932 | 0.944 | 0.033 | 0.032 | 0.234 | 1.097 | 1.107 | 0.239 |
| $20^2$ | 0.936 | 0.932 | 0.942 | 0.065 | 0.064 | 0.452 | 4.389 | 4.417 | 0.898 |
| $30^2$ | 0.936 | 0.932 | 0.942 | 0.098 | 0.096 | 0.674 | 9.875 | 9.936 | 1.999 |
| $40^2$ | 0.936 | 0.932 | 0.944 | 0.131 | 0.128 | 0.897 | 17.556 | 17.664 | 3.543 |
| **Generalized additive model** | | | | | | | | | |
| Variance of $\epsilon_1$ | Coverage Probability | | | Average \|Relative Bias\| | | | Average MSE | | |
| | CDE | NDE | NIE | CDE | NDE | NIE | CDE | NDE | NIE |
| $10^2$ | - | 0.942 | 0.906 | - | 0.017 | 0.143 | - | 0.295 | 0.088 |
| $20^2$ | - | 0.948 | 0.911 | - | 0.033 | 0.251 | - | 1.143 | 0.276 |
| $30^2$ | - | 0.953 | 0.906 | - | 0.049 | 0.366 | - | 2.553 | 0.589 |
| $40^2$ | - | 0.953 | 0.906 | - | 0.066 | 0.482 | - | 4.523 | 1.026 |