Nonparametric Inference on Dose-Response Curves Without the Positivity Condition

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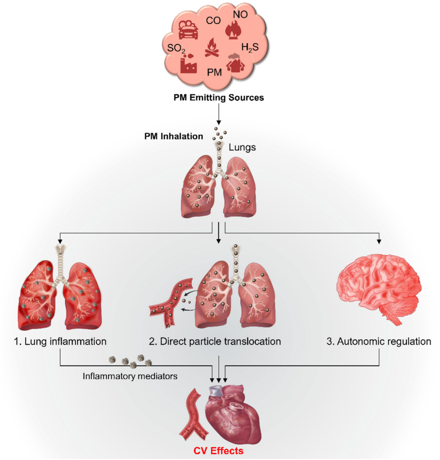
- We want to study the causal effects of $PM_{2.5}$ levels on Cardiovascular Mortality Rates (CMRs).



Biological pathways associated with particulate matter (PM) and cardiovascular disease (Miller and Newby, 2020; Basith et al., 2022).

FIPS	County name	Longitude	Latitude	PM2.5	CMR
1025	Clarke	-87.830772	31.676955	6.766443	379.421713
1061	Geneva	-85.839330	31.094869	8.254272	378.524698
1073	Jefferson	-86.896571	33.554343	10.825441	352.790427
1077	Lauderdale	-87.654117	34.901500	9.208783	332.594557
5085	Lonoke	-91.887917	34.754412	8.213144	365.061085
8045	Garfield	-107.903621	39.599420	2.601772	250.781477

The dataset contains the average annual cardiovascular mortality rates (CMRs) and $PM_{2.5}$ levels across $n = 2132$ U.S. counties from 1990 to 2010 (Wyatt et al., 2020a,b).

Motivation for Continuous Treatments

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- The treatment variable T, *i.e.*, the $PM_{2.5}$ level at each county, is a quantitative measure. In other words, it is *not a binary but continuous variable*!

For *binary* treatment (*i.e.*, $\mathcal{T} = \{0, 1\}$), common causal estimands are

- $\mathbb{E}\left[Y(t)\right] =$ mean counterfactual outcome when we set $T = t$.
- $\mathbb{E}\left[Y(1)\right] - \mathbb{E}\left[Y(0)\right]$ = average treatment effect.

▶ **Question:** What are the counterparts of the above estimands under *continuous* treatment (*i.e.*, $\mathcal{T} \subset \mathbb{R}$)?

Causal Inference For Continuous Treatments

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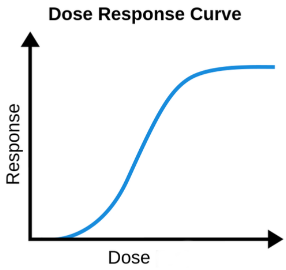
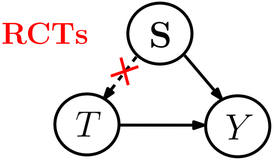
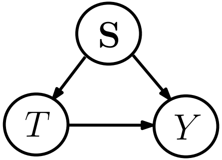
▶ **Question:** What are the counterparts of the above estimands under *continuous* treatment (*i.e.*, $\mathcal{T} \subset \mathbb{R}$)?

- $t \mapsto m(t) := \mathbb{E}[Y(t)]$ = (causal) dose-response curve.
- $t \mapsto \theta(t) := m'(t) = \frac{d}{dt}\mathbb{E}[Y(t)]$ = (causal) derivative effect curve.



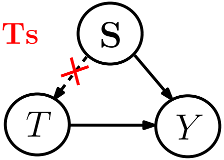
Standard Identification in Observational Studies

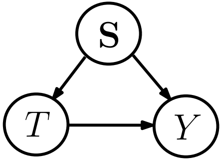




[1]Some mild interchangeability assumptions are needed; see Theorem 1.1 in Shao (2003).

RCTs





Assumption (Identification Conditions)

1. *(Consistency)* $Y = Y(t)$ *whenever* $T = t \in \mathcal{T}$.
2. *(Ignorability)* $Y(t)$ *is conditionally independent of* T *given* $\boldsymbol{S}$ *for all* $t \in \mathcal{T}$.
3. *(**Positivity**) The conditional density satisfies* $p_{T|\boldsymbol{S}}(t|\boldsymbol{s}) \geq p_{\min} > 0$ *for all* $(t, \boldsymbol{s}) \in \mathcal{T} \times \mathcal{S}$.

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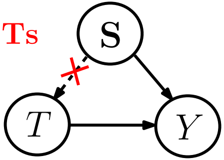

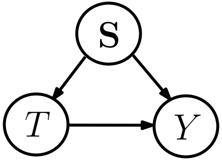

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$$m(t) = \mathbb{E}\left[Y(t)\right] = \mathbb{E}\left[\mathbb{E}(Y|T = t, \boldsymbol{S})\right] \quad \text{and} \quad \theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right] \overset{(*)^1}{=} \mathbb{E}\left[\frac{\partial}{\partial t}\mathbb{E}(Y|T = t, \boldsymbol{S})\right].$$

- The positivity condition is required for $\mu(t, \boldsymbol{s}) = \mathbb{E}\left(Y|T = t, \boldsymbol{S} = \boldsymbol{s}\right)$ and $\frac{\partial}{\partial t}\mu(t, \boldsymbol{s}) = \frac{\partial}{\partial t}\mathbb{E}\left(Y|T = t, \boldsymbol{S} = \boldsymbol{s}\right)$ to be well-defined on $\mathcal{T} \times \mathcal{S}$.

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There are three major strategies for estimating

$$m(t) = \mathbb{E}\left[Y(t)\right] = \mathbb{E}\left[\mu(t, \boldsymbol{S})\right] = \lim_{h \to 0} \mathbb{E}\left[\frac{Y \cdot K\left(\frac{T-t}{h}\right)}{h \cdot p(T|\boldsymbol{S})}\right]$$

from the data $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^n$, where $K : \mathbb{R} \to [0, \infty)$ is a kernel function.

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1. **Regression Adjustment** (Robins, 1986; Gill and Robins, 2001):

$$\widehat{m}_{\mathrm{RA}}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\mu}(t, \boldsymbol{S}_i).$$

2. **Inverse Probability Weighting** (Hirano and Imbens, 2004):

$$\widehat{m}_{\mathrm{IPW}}(t) = \frac{1}{nh}\sum_{i=1}^{n} \frac{K\left(\frac{T_i - t}{h}\right)}{\widehat{p}(T_i|\boldsymbol{S}_i)} \cdot Y_i.$$

3. **Doubly Robust** (Kennedy et al., 2017; Colangelo and Lee, 2020).

Estimation of Dose-Response Curves Under Positivity

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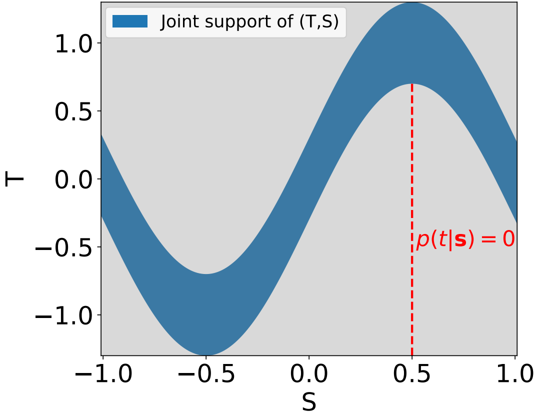
- **Issue:** Positivity is a strong assumption with continuous treatments!

Assumption (Positivity Condition)

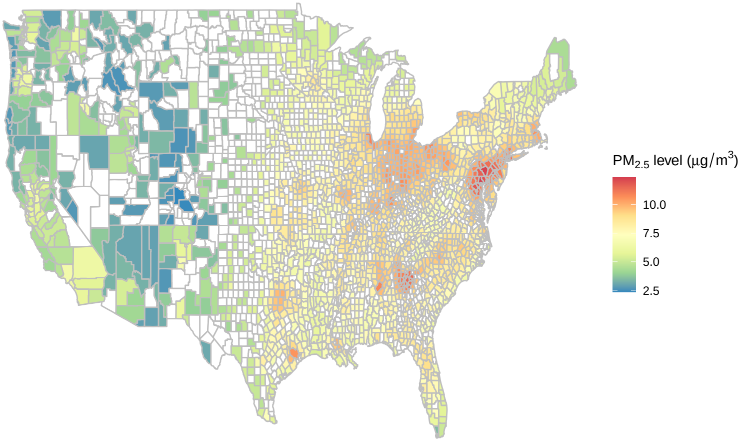
The conditional density $p(t|\mathbf{s})$ is uniformly bounded away from zero for all $(t,\mathbf{s}) \in \mathcal{T} \times \mathcal{S}$.

$$T = \sin(\pi S) + E, \quad E \sim \text{Unif}[-0.3, 0.3], \quad S \sim \text{Unif}[-1, 1], \quad \text{and} \quad E \perp\!\!\!\perp S.$$



- **Note:** $p(t|s) = 0$ in the gray regions, and the positivity condition fails.

$PM_{2.5}$ Distribution at the County Level



Average $PM_{2.5}$ levels from 1990 to 2010 in $n = 2132$ counties.

- T is $PM_{2.5}$ level, and S consists of the county location and socioeconomic factors.
- Only one or several $PM_{2.5}$ levels are available per county in the dataset, and the positivity condition is violated!

$$t \mapsto m(t) = \mathbb{E}\left[Y(t)\right] \quad \text{and} \quad t \mapsto \theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right] \quad \text{for} \quad t \in \mathcal{T}.$$

1. The positivity condition may fail in some regions of $\mathcal{T} \times \mathcal{S}$.
   - We propose a new identification strategy for $m(t)$ and $\theta(t)$.

Highlight of Today's Talk

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   - Construct a localized derivative estimator $\widehat{\theta}_C(t)$ of $\theta(t) = m'(t)$ around the observations $T_i, i = 1, ..., n$.
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3. Nonparametric bootstrap inference with our proposed estimators $\widehat{m}_\theta(t)$ and $\widehat{\theta}_C(t)$ for $m(t)$ and $\theta(t)$ is asymptotically valid.

Identification and Estimation

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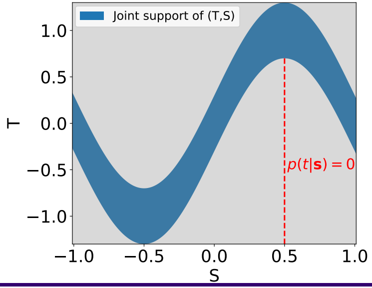
2. *(Ignorability or Unconfoundedness)* $Y(t) \perp\!\!\!\perp T \,\big|\, \boldsymbol{S}$ *for all* $t \in \mathcal{T}$.
3. ***(Positivity)*** $p_{T|\boldsymbol{S}}(t|\boldsymbol{s}) \geq p_{\min} > 0$ *for all* $(t, \boldsymbol{s}) \in \mathcal{T} \times \mathcal{S}$.

The RA (or G-computation) formulae are given by

$$m(t) = \mathbb{E}\left[Y(t)\right] = \mathbb{E}\left[\mu(t, \boldsymbol{S})\right] \quad \text{and} \quad \theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right] = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S})\right].$$



Why Do We Need Positivity?

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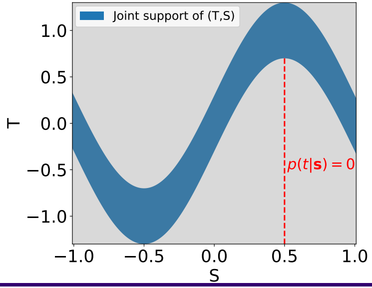

▶ **Identification Issue:** Without positivity,

$$\mu(t, \boldsymbol{s}) = \mathbb{E}\left(Y | T = t, \boldsymbol{S} = \boldsymbol{s}\right)$$

is *not well-defined* outside the support $\mathcal{E} \subset \mathcal{T} \times \mathcal{S}$ of the joint density $p(t, \boldsymbol{s})$.

Key Example: Additive Confounding Model

Consider the additive confounding model, which is commonly assumed in spatial statistics (Paciorek, 2010; Schnell and Papadogeorgou, 2020; Gilbert et al., 2023):

$$Y(t) = \bar{m}(t) + \eta(\boldsymbol{S}) + \epsilon \quad \text{with} \quad \mathbb{E}(\epsilon) = 0 \quad \text{and} \quad \text{Var}(\epsilon) > 0. \tag{1}$$

- $\bar{m} : \mathcal{T} \to \mathbb{R}, \eta : \mathcal{S} \to \mathbb{R}$ are unknown functions, while $\epsilon \in \mathbb{R}$ is exogenous.
- $m(t) = \mathbb{E}\left[Y(t)\right] = \bar{m}(t) + \mathbb{E}\left[\eta(\boldsymbol{S})\right]$ and $\theta(t) = m'(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right] = \bar{m}'(t)$.

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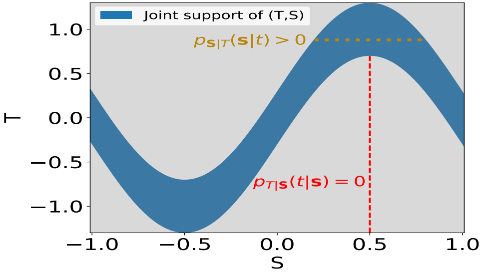
Proposition 2 in Zhang et al. (2024)

Under model (1) and consistency, we have

$$\theta(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S}) \Big| T = t\right] := \theta_C(t)$$

and $\mathbb{E}(Y) = \mathbb{E}\left[\bar{m}(T) + \eta(\boldsymbol{S})\right] = \mathbb{E}\left[m(T)\right]$.



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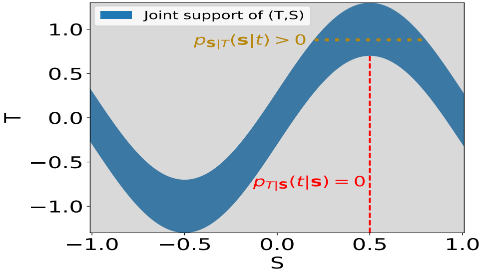

▶ **Identification of** $m(t)$**:** By the fundamental theorem of calculus,

$$m(t) = \mathbb{E}\left[Y + \int_{u=T}^{u=t} \theta_C(u)\, du\right] = \mathbb{E}(Y) + \mathbb{E}\left\{\int_{u=T}^{u=t} \mathbb{E}\left[\frac{\partial}{\partial t}\mu(T, \boldsymbol{S}) \middle| T = u\right] du\right\} \quad \text{for any } t \in \mathcal{T}.$$

Recall our identification formulae

$$m(t) = \mathbb{E}\left[Y + \int_{\widetilde{t}=T}^{\widetilde{t}=t} \theta_C(\widetilde{t})\, d\widetilde{t}\right] \quad \text{and} \quad \theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S}) \Big| T = t\right] = \int \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})\, d\mathrm{P}(\boldsymbol{s}|t).$$

Proposed Estimators of $m(t)$ and $\theta(t)$

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Our **integral estimator** of $m(t)$ is given by

$$\widehat{m}_\theta(t) = \frac{1}{n}\sum_{i=1}^{n}\left[Y_i + \int_{\tilde{t}=T_i}^{\tilde{t}=t} \widehat{\theta}_C(\tilde{t})\, d\tilde{t}\right],$$

and our **localized derivative** estimator of $\theta(t)$ is

$$\widehat{\theta}_C(t) = \int \widehat{\beta}_2(t, \boldsymbol{s})\, d\widehat{\mathrm{P}}(\boldsymbol{s}|t) = \frac{\sum_{i=1}^{n} \widehat{\beta}_2(t, \boldsymbol{S}_i) \cdot \bar{K}_T\left(\frac{T_i - t}{\hbar}\right)}{\sum_{j=1}^{n} \bar{K}_T\left(\frac{T_j - t}{\hbar}\right)}.$$

- $\beta_2(t, \boldsymbol{s}) := \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$ is fitted by (partial) local polynomial regression.
- $\mathrm{P}(\boldsymbol{s}|t)$ is estimated by Nadaraya-Watson conditional cumulative distribution function (CDF) estimator.

$$m(t) = \mathbb{E}\left[Y + \int_{\widetilde{t}=T}^{\widetilde{t}=t} \theta_C(\widetilde{t})\, d\widetilde{t}\right] \quad \text{and} \quad \theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S})\Big| T = t\right] = \int \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})\, d\mathrm{P}(\boldsymbol{s}|t).$$

1. Other methods can be applied to estimate $\frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$ and $\mathrm{P}(\boldsymbol{s}|t)$.
    - $\widehat{m}_\theta(t)$ and $\widehat{\theta}_C(t)$, under our kernel-based estimators, are *linear smoothers*.

Some Remarks on Proposed Estimators $\widehat{m}_\theta(t)$ and $\widehat{\theta}_C(t)$

$$m(t) = \mathbb{E}\left[Y + \int_{\tilde{t}=T}^{\tilde{t}=t} \theta_C(\tilde{t})\, d\tilde{t}\right] \quad \text{and} \quad \theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S}) \Big| T = t\right] = \int \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})\, d\mathrm{P}(\boldsymbol{s}|t).$$

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   - $\widehat{m}_\theta(t)$ and $\widehat{\theta}_C(t)$, under our kernel-based estimators, are *linear smoothers*.

2. Practically, the integral in $\widehat{m}_\theta(t) = \frac{1}{n}\sum_{i=1}^{n}\left[Y_i + \int_{u=T_i}^{u=t} \widehat{\theta}_C(u)\, du\right]$ could be analytically difficult to compute.
   - We provide a fast computing recipe via Riemann sum approximation.
   - The approximation error is at most $O_P\left(\frac{1}{n}\right)$, which is *asymptotically negligible*.

Some Remarks on Proposed Estimators $\widehat{m}_\theta(t)$ and $\widehat{\theta}_C(t)$

$$m(t) = \mathbb{E}\left[Y + \int_{\tilde{t}=T}^{\tilde{t}=t} \theta_C(\tilde{t})\, d\tilde{t}\right] \quad \text{and} \quad \theta_C(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S}) \Big| T = t\right] = \int \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})\, d\mathrm{P}(\boldsymbol{s}|t).$$

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   - We provide a fast computing recipe via Riemann sum approximation.
   - The approximation error is at most $O_P\left(\frac{1}{n}\right)$, which is *asymptotically negligible*.
3. We can construct (simultaneous) inference on $m(t)$ and $\theta(t)$ with the proposed estimators $\widehat{m}_\theta(t)$ and $\widehat{\theta}_C(t)$ via *nonparametric bootstrap*.

Asymptotic Theory

Uniform Consistencies of Proposed Estimators

Combining the theory for local polynomial regression on $\widehat{\beta}_2(t,\boldsymbol{s})$ with the consistency of $\widehat{\mathrm{P}}_\hbar(\boldsymbol{s}|t)$ via the technique in Fan et al. (1998), we have the following results.

Theorem (Theorem 4 in Zhang et al. 2024)

Let $\mathcal{T}' \subset \mathcal{T}$ be a compact set so that $p_T(t) \geq p_{T,\min} > 0$ for all $t \in \mathcal{T}'$. When $q = 2$ and $h, b, \hbar, \frac{\max\{h,b\}^4}{h} \to 0$ and $\frac{n\max\{h,\hbar\}b^d}{\log n}, \frac{n\hbar}{\log n} \to \infty$,

$$\sup_{t\in\mathcal{T}'}\left|\widehat{\theta}_C(t) - \theta_C(t)\right| = \underbrace{O\left(h^2 + b^2 + \frac{\max\{b,h\}^4}{h}\right)}_{\textit{Bias term}} + \underbrace{O_P\left(\sqrt{\frac{\log n}{nh^3}} + \hbar^2 + \sqrt{\frac{\log n}{n\hbar}}\right)}_{\textit{Stochastic variation}},$$

$$\sup_{t\in\mathcal{T}'}\left|\widehat{m}_\theta(t) - m(t)\right| = O\left(h^2 + b^2 + \frac{\max\{b,h\}^4}{h}\right) + O_P\left(\frac{1}{\sqrt{n}} + \sqrt{\frac{\log n}{nh^3}} + \hbar^2 + \sqrt{\frac{\log n}{n\hbar}}\right).$$

Uniform Rate of Convergence For the Integral Estimator

$$\widehat{m}_\theta(t) = \frac{1}{n}\sum_{i=1}^{n} Y_i + \frac{1}{n}\sum_{i=1}^{n}\int_{u=T_i}^{u=t} \widehat{\theta}_C(u)\, du \quad \text{and} \quad \widehat{\theta}_C(t) = \frac{\sum_{i=1}^{n} \widehat{\beta}_2(t, \boldsymbol{S}_i)\cdot \bar{K}_T\left(\frac{T_i - t}{\hbar}\right)}{\sum_{j=1}^{n} \bar{K}_T\left(\frac{T_j - t}{\hbar}\right)}.$$

$$\sup_{t\in\mathcal{T}'} \left|\widehat{m}_\theta(t) - m(t)\right| = O\left(h^2 + b^2 + \frac{\max\{b,h\}^4}{h}\right) + O_P\left(\frac{1}{\sqrt{n}} + \sqrt{\frac{\log n}{nh^3}} + \hbar^2 + \sqrt{\frac{\log n}{n\hbar}}\right).$$

- Blue term: the estimation bias of local polynomial estimator $\widehat{\beta}_2(t, \boldsymbol{s})$.
- Orange term: additional bias of $\widehat{\beta}_2(t, \boldsymbol{s})$ at the boundary $\partial\mathcal{E}$.

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- Cyan term: asymptotic rate from the Nadaraya-Watson conditional CDF estimator $\widehat{\mathrm{P}}_\hbar(\boldsymbol{s}|t)$.

Case Study: $PM_{2.5}$ on CMR

$PM_{2.5}$ and CMRs Data Recap

FIPS	County name	Longitude	Latitude	PM2.5	CMR
1025	Clarke	-87.830772	31.676955	6.766443	379.421713
1061	Geneva	-85.839330	31.094869	8.254272	378.524698
1073	Jefferson	-86.896571	33.554343	10.825441	352.790427
1077	Lauderdale	-87.654117	34.901500	9.208783	332.594557
5085	Lonoke	-91.887917	34.754412	8.213144	365.061085
8045	Garfield	-107.903621	39.599420	2.601772	250.781477

1. The dataset (Wyatt et al., 2020a,b) contains the average annual CMRs (Y) and $PM_{2.5}$ levels (T) across $n = 2132$ U.S. counties over 1990-2010.

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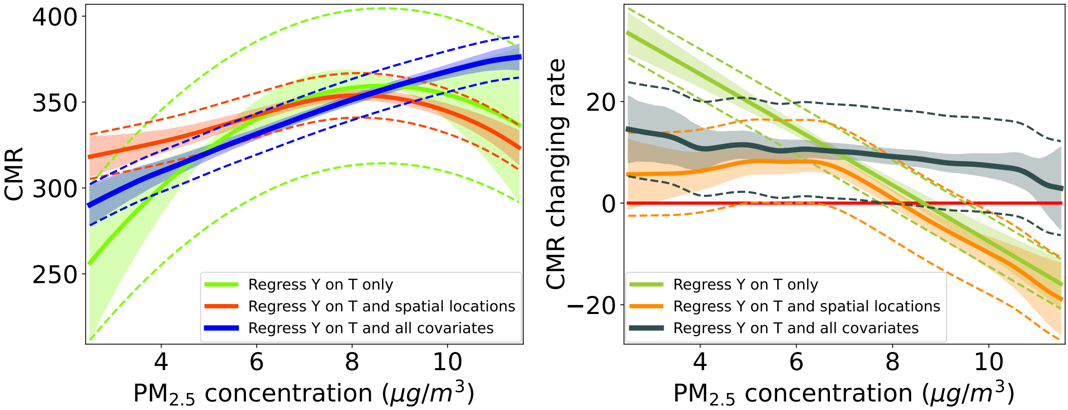
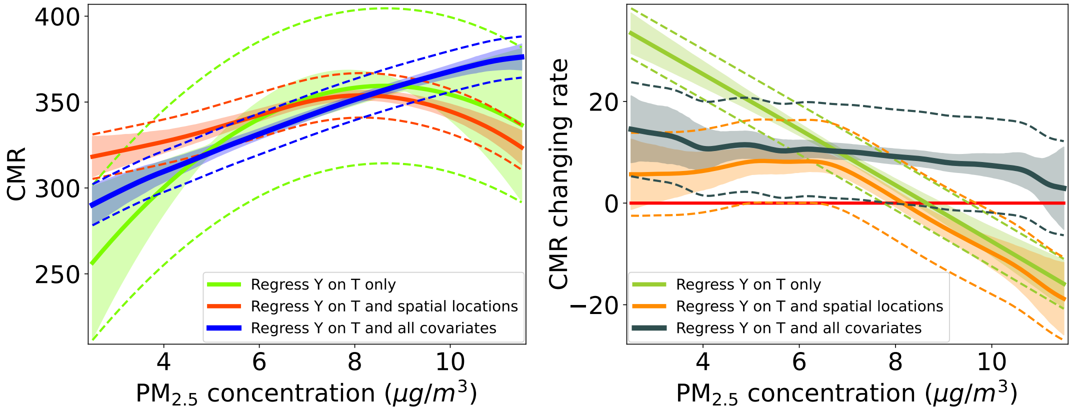
   - 8 county-level socioeconomic factors acquired from the US census.
3. Focus on the values of $\text{PM}_{2.5}$ between 2.5 $\mu g/m^3$ and 11.5 $\mu g/m^3$ to avoid boundary effects (Takatsu and Westling, 2022).

Effect of $PM_{2.5}$ on the Cardiovascular Mortality Rate (CMR)



Shaded areas: 95% pointwise confidence intervals; **Regions between dashed lines:** 95% uniform confidence bands.

- We compare three models:
  1. Regress Y on T alone via local quadratic regression.
  2. Regress Y on T with spatial locations.
  3. Regress Y on T with both spatial and socioeconomic covariates.



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  1. Regress Y on T alone via local quadratic regression.
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  3. Regress Y on T with both spatial and socioeconomic covariates.
- For model 3, the increasing trends are **significant** when $PM_{2.5} < 8\,\mu g/m^3$.

Discussion

We study nonparametric inference on $m(t) = \mathbb{E}\left[Y(t)\right]$ and $\theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right]$ without the **positivity** condition.

- Our key techniques rely on two pillars in calculus:

$$\underbrace{\theta(t) = \mathbb{E}\left[\frac{\partial}{\partial t}\mu(t, \boldsymbol{S})\Big| T = t\right]}_{\textbf{Differentiation}} \quad \text{and} \quad \underbrace{m(t) = \mathbb{E}\left[Y + \int_{u=T}^{u=t} \theta(u)\, du\right]}_{\textbf{Integration}}.$$

Summary and Future Work

We study nonparametric inference on $m(t) = \mathbb{E}\left[Y(t)\right]$ and $\theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right]$ without the **positivity** condition.

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▶ **Ongoing and Future Directions:**

- Generalize our proposed estimators to inverse probability weighting and doubly robust forms (Zhang and Chen, 2025).
- Use additive models (Guo et al., 2019) to address the high-dimensional covariates.

Thank you!

More details can be found in

[1] Y. Zhang, Y.-C. Chen, and A. Giessing. Nonparametric Inference on Dose-Response Curves Without the Positivity Condition. *arXiv preprint*, 2024. https://arxiv.org/abs/2405.09003.

All the code and data are available at
https://github.com/zhangyk8/npDoseResponse/tree/main.

Python Package: npDoseResponse and R Package: npDoseResponse.

I will present the following paper in the invited Session "Advances in Modern Causal Inference" on **Tuesday at 8:30am**.

[2] Y. Zhang and Y.-C. Chen. Doubly Robust Inference on Causal Derivative Effects for Continuous Treatments. *arXiv preprint*, 2025. https://arxiv.org/abs/2501.06969.

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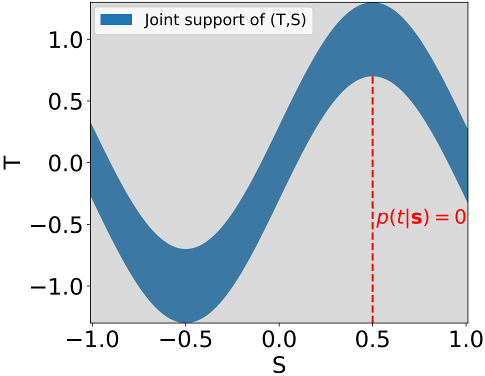
Assumption (Identification Conditions)

1. *(Consistency)* $Y = Y(t)$ *whenever* $T = t \in \mathcal{T}$.
2. *(Ignorability)* $Y(t)$ *is conditionally independent of* T *given* $\boldsymbol{S}$ *for all* $t \in \mathcal{T}$.
3. *(Treatment Variation)* $\mathrm{Var}(T|\boldsymbol{S} = \boldsymbol{s}) > 0$ *for all* $\boldsymbol{s} \in \mathcal{S}$.



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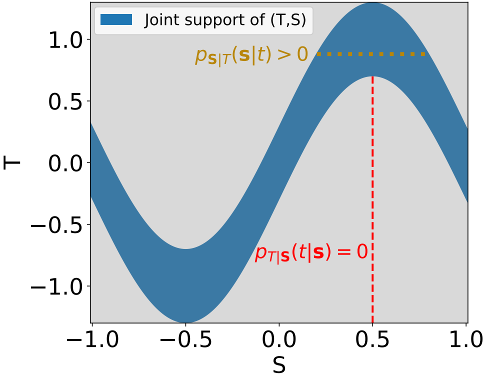


Assumption (Extrapolation; Zhang et al. 2024)

Assume $(t, \boldsymbol{s}) \mapsto \mathbb{E}\left[Y(t)|\boldsymbol{S} = \boldsymbol{s}\right]$ *to be differentiable w.r.to* t *for any* $(t, \boldsymbol{s}) \in \mathcal{T} \times \mathcal{S}$ *with* $p_{\boldsymbol{S}|T}(\boldsymbol{s}|t) > 0$ *and*

$$\theta(t) = \frac{d}{dt}\mathbb{E}\left[Y(t)\right] = \mathbb{E}\left[\frac{\partial}{\partial t}\mathbb{E}\left[Y(t)|\boldsymbol{S}\right]\right] \stackrel{\star}{=} \mathbb{E}\left[\frac{\partial}{\partial t}\mathbb{E}\left[Y(t)|\boldsymbol{S}\right]\Big|T = t\right].$$

Additionally, it holds true that $\mathbb{E}(Y) = \mathbb{E}\left[m(T)\right]$.

Estimation of Nuisance Functions

1. **Order q (Partial) Local Polynomial Regression** (Fan and Gijbels, 1996): Let $\widehat{\boldsymbol{\beta}}(t, \boldsymbol{s}) \in \mathbb{R}^{q+1}$ and $\widehat{\boldsymbol{\alpha}}(t, \boldsymbol{s}) \in \mathbb{R}^{d}$ be the minimizer of

$$\arg\min_{(\boldsymbol{\beta},\boldsymbol{\alpha})^T \in \mathbb{R}^{q+1+d}} \sum_{i=1}^{n} \left[Y_i - \sum_{j=0}^{q} \beta_j (T_i - t)^q - \sum_{\ell=1}^{d} \alpha_\ell (S_{i,\ell} - s_\ell) \right]^2 K_T\left(\frac{T_i - t}{h}\right) K_S\left(\frac{\boldsymbol{S}_i - \boldsymbol{s}}{b}\right).$$

   - $K_T : \mathbb{R} \to [0, \infty), K_S : \mathbb{R}^d \to [0, \infty)$ are two symmetric kernel functions, and $h, b > 0$ are smoothing bandwidth parameters.
   - The second component $\widehat{\beta}_2(t, \boldsymbol{s})$ is a consistent estimator of $\beta_2(t, \boldsymbol{s}) = \frac{\partial}{\partial t}\mu(t, \boldsymbol{s})$.

2. **Nadaraya-Watson conditional CDF Estimator** (Hall et al., 1999):

$$\widehat{P}_{\hbar}(\boldsymbol{s}|t) = \frac{\sum_{i=1}^{n} \mathbb{1}_{\{\boldsymbol{S}_i \leq \boldsymbol{s}\}} \cdot \bar{K}_T\left(\frac{T_i - t}{\hbar}\right)}{\sum_{j=1}^{n} \bar{K}_T\left(\frac{T_j - t}{\hbar}\right)}.$$

   - $\bar{K}_T : \mathbb{R} \to [0, \infty)$ is a kernel function and $\hbar > 0$ is its smoothing bandwidth parameter.

Our integral estimator takes the form

$$\widehat{m}_\theta(t) = \frac{1}{n}\sum_{i=1}^{n}\left[Y_i + \int_{\widetilde{t}=T_i}^{\widetilde{t}=t} \widehat{\theta}_C(\widetilde{t})\, d\widetilde{t}\right].$$

▶ **Riemann Sum Approximation:** Let $T_{(1)} \leq \cdots \leq T_{(n)}$ be the order statistics of $T_1, ..., T_n$ and $\Delta_j = T_{(j+1)} - T_{(j)}$ for $j = 1, ..., n-1$.

- Approximate $\widehat{m}_\theta(T_{(j)})$ for each $j = 1, ..., n$ as:

$$\widehat{m}_\theta(T_{(j)}) \approx \frac{1}{n}\sum_{i=1}^{n} Y_i + \frac{1}{n}\sum_{i=1}^{n-1}\Delta_i\Big[i \cdot \widehat{\theta}_C(T_{(i)})\mathbb{1}_{\{i<j\}} - (n-i)\cdot \widehat{\theta}_C(T_{(i+1)})\mathbb{1}_{\{i\geq j\}}\Big].$$

- Evaluate $\widehat{m}_\theta(t)$ at any $t \in \left[T_{(j)}, T_{(j+1)}\right]$ by a linear interpolation between $\widehat{m}_\theta(T_{(j)})$ and $\widehat{m}_\theta(T_{(j+1)})$.
- The approximation error is at most $O_P\left(\frac{1}{n}\right)$, which is *asymptotically negligible*.

Nonparametric Bootstrap Inference

1. Compute $\widehat{m}_\theta(t)$ on the original data $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^n$.

2. Generate B bootstrap samples $\left\{\left(Y_i^{*(b)}, T_i^{*(b)}, \boldsymbol{S}_i^{*(b)}\right)\right\}_{i=1}^n$ by sampling with replacement and compute $\widehat{m}_\theta^{*(b)}(t)$ for each $b = 1, ..., B$.

3. Let $\alpha \in (0,1)$ be a pre-specified significance level.
   - For pointwise inference at $t_0 \in \mathcal{T}$, calculate the $1-\alpha$ quantile $\zeta_{1-\alpha}^*(t_0)$ of $\{D_1(t_0), ..., D_B(t_0)\}$, where $D_b(t_0) = \left|\widehat{m}_\theta^{*(b)}(t_0) - \widehat{m}_\theta(t_0)\right|$ for $b = 1, ..., B$.
   - For uniform inference on $m(t)$, compute the $1-\alpha$ quantile $\xi_{1-\alpha}^*$ of $\{D_{\sup,1}, ..., D_{\sup,B}\}$, where $D_{\sup,b} = \sup_{t\in\mathcal{T}} \left|\widehat{m}_\theta^{*(b)}(t) - \widehat{m}_\theta(t)\right|$ for $b = 1, ..., B$.

4. Define the $1-\alpha$ confidence interval for $m(t_0)$ as:

$$\left[\widehat{m}_\theta(t_0) - \zeta_{1-\alpha}^*(t_0),\ \widehat{m}_\theta(t_0) + \zeta_{1-\alpha}^*(t_0)\right]$$

and the simultaneous $1-\alpha$ confidence band for every $t \in \mathcal{T}$ as:

$$\left[\widehat{m}_\theta(t) - \xi_{1-\alpha}^*,\ \widehat{m}_\theta(t) + \xi_{1-\alpha}^*\right].$$

Let $\mathcal{E} \subset \mathcal{T} \times \mathcal{S}$ be the support of $p(t, \boldsymbol{s})$, $\mathcal{E}^\circ$ be the interior of $\mathcal{E}$, and $\partial\mathcal{E}$ be the boundary of $\mathcal{E}$.

1. For any $(t, \boldsymbol{s}) \in \mathcal{E}^\circ$, $\mu(t, \boldsymbol{s})$ is at least $(q+1)$ times continuously differentiable with respect to t and at least four times continuously differentiable with respect to $\boldsymbol{s}$. All these partial derivatives of $\mu(t, \boldsymbol{s})$ are continuous up to the boundary $\partial\mathcal{E}$. Furthermore, $\mu(t, \boldsymbol{s})$ and the partial derivatives are uniformly bounded on $\mathcal{E}$. Finally, there exist absolute constants $\sigma, A_0 > 0$ such that $\mathrm{Var}(Y|T = t, \boldsymbol{S} = \boldsymbol{s}) = \sigma^2$ and $\mathbb{E}|Y|^4 < A_0 < \infty$ uniformly in $\mathcal{E}$.
2. $p(t, \boldsymbol{s})$ is bounded and at least twice continuously differentiable with bounded partial derivatives up to the second order on $\mathcal{E}^\circ$. All these partial derivatives of $p(t, \boldsymbol{s})$ are continuous up to the boundary $\partial\mathcal{E}$. Furthermore, $\mathcal{E}$ is compact and $p(t, \boldsymbol{s})$ is uniformly bounded away from 0 on $\mathcal{E}$. Finally, the marginal density $p_T(t)$ of T is non-degenerate, *i.e.*, its support $\mathcal{T}$ has a nonempty interior.

3. There exists some constants $r_1, r_2 \in (0,1)$ such that for any $(t, \boldsymbol{s}) \in \mathcal{E}$ and all $\delta \in (0, r_1]$, there is a point $(t', \boldsymbol{s}') \in \mathcal{E}$ satisfying

$$\mathcal{B}\left((t', \boldsymbol{s}'),\ r_2\delta\right) \subset \mathcal{B}\left((t, \boldsymbol{s}),\ \delta\right) \cap \mathcal{E},$$

where

$$\mathcal{B}((t, \boldsymbol{s}),\ r) = \left\{(t_1, \boldsymbol{s}_1) \in \mathbb{R}^{d+1} : ||(t_1 - t, \boldsymbol{s}_1 - \boldsymbol{s})||_2 \leq r\right\}$$

with $||\cdot||_2$ being the standard Euclidean norm.

4. For any $(t, \boldsymbol{s}) \in \partial\mathcal{E}$, the boundary of $\mathcal{E}$, it satisfies that $\frac{\partial}{\partial t} p(t, \boldsymbol{s}) = \frac{\partial}{\partial s_j} p(t, \boldsymbol{s}) = 0$ and $\frac{\partial^2}{\partial s_j^2} \mu(t, \boldsymbol{s}) = 0$ for all $j = 1, ..., d$.

5. For any $\delta > 0$, the Lebesgue measure of the set $\partial\mathcal{E} \oplus \delta$ satisfies $|\partial\mathcal{E} \oplus \delta| \leq A_1 \cdot \delta$ for some absolute constant $A_1 > 0$, where

$$\partial\mathcal{E} \oplus \delta = \left\{\boldsymbol{z} \in \mathbb{R}^{d+1} : \inf_{\boldsymbol{x} \in \partial\mathcal{E}} ||\boldsymbol{z} - \boldsymbol{x}||_2 \leq \delta\right\}.$$

6. $K_T : \mathbb{R} \to [0,\infty)$ and $K_S : \mathbb{R}^d \to [0,\infty)$ are compactly supported and Lispchitz continuous kernels such that $\int_{\mathbb{R}} K_T(t)\,dt = \int_{\mathbb{R}^d} K_S(\boldsymbol{s})\,d\boldsymbol{s} = 1$, $K_T(t) = K_T(-t)$, and K_S is radially symmetric with $\int \boldsymbol{s} \cdot K_S(\boldsymbol{s})d\boldsymbol{s} = \mathbf{0}$. In addition, for all $j = 1, 2, ...,$ and $\ell = 1, ..., d$,

$$\kappa_j^{(T)} := \int_{\mathbb{R}} u^j K_T(u)\,du < \infty, \quad \nu_j^{(T)} := \int_{\mathbb{R}} u^j K_T^2(u)\,du < \infty,$$
$$\kappa_{j,\ell}^{(S)} := \int_{\mathbb{R}^d} u_\ell^j K_S(\boldsymbol{u})\,d\boldsymbol{u} < \infty, \quad \text{and} \quad \nu_{j,k}^{(S)} := \int_{\mathbb{R}^d} u_\ell^j K_S^2(\boldsymbol{u})\,d\boldsymbol{u} < \infty.$$

Finally, both K_T and K_S are second-order kernels, *i.e.*, $\kappa_2^{(T)} > 0$ and $\kappa_{2,\ell}^{(S)} > 0$ for all $\ell = 1, ..., d$.

7. Let $\mathcal{K}_{q,d} = \left\{(y,\boldsymbol{z}) \mapsto \left(\frac{y-t}{h}\right)^\ell \left(\frac{z_i - s_i}{b}\right)^{k_1} \left(\frac{z_j - s_j}{b}\right)^{k_2} K_T\left(\frac{y-t}{h}\right) K_S\left(\frac{\boldsymbol{z}-\boldsymbol{s}}{b}\right) : (t,\boldsymbol{s}) \in \mathcal{T} \times \mathcal{S}; i,j = 1,...,d; \ell = 0,...,2q; k_1,k_2 = 0,1; h,b > 0\right\}$. It holds that $\mathcal{K}_{q,d}$ is a bounded VC-type class of measurable functions on $\mathbb{R}^{d+1}$.

Regularity Assumptions (Kernel Conditions)

8. The function $\bar{K}_T : \mathbb{R} \to [0, \infty)$ is a second-order, Lipschitz continuous, and symmetric kernel with a compact support, *i.e.*, $\int_{\mathbb{R}} \bar{K}_T(t)\,dt = 1$, $\bar{K}_T(t) = \bar{K}_T(-t)$, and $\int_{\mathbb{R}} t^2 \bar{K}_T(t)\,dt \in (0, \infty)$.

9. Let $\bar{\mathcal{K}} = \left\{ y \mapsto \bar{K}_T\left(\frac{y-t}{\hbar}\right) : t \in \mathcal{T}, \hbar > 0 \right\}$. It holds that $\bar{\mathcal{K}}$ is a bounded VC-type class of measurable functions on $\mathbb{R}$.

Recall that the class $\mathcal{G}$ of measurable functions on $\mathbb{R}^{d+1}$ is VC-type if there exist constants $A_2, \upsilon_2 > 0$ such that for any $0 < \epsilon < 1$,

$$\sup_Q N\left(\mathcal{G}, L_2(Q), \epsilon\, ||G||_{L_2(Q)}\right) \leq \left(\frac{A_2}{\epsilon}\right)^{\upsilon_2},$$

where $N\left(\mathcal{G}, L_2(Q), \epsilon\, ||G||_{L_2(Q)}\right)$ is the $\epsilon\, ||G||_{L_2(Q)}$-covering number of the (semi-)metric space $\left(\mathcal{G}, ||\cdot||_{L_2(Q)}\right)$, Q is any probability measure on $\mathbb{R}^{d+1}$, G is an envelope function of $\mathcal{G}$, and $||G||_{L_2(Q)}$ is defined as $\left[\int_{\mathbb{R}^{d+1}} [G(x)]^2\, dQ(x)\right]^{\frac{1}{2}}$.

Lemma (Lemma 5 in Zhang et al. 2024)

Under the same regularity conditions, if $h \asymp n^{-\frac{1}{\gamma}}$ *and* $\hbar \asymp n^{-\frac{1}{\varpi}}$ *for some* $\gamma \geq \varpi > 0$ *such that* $\frac{nh^5}{\log n} \to c_1$ *and* $\frac{n\hbar^5}{\log n} \to c_2$ *for some* $c_1, c_2 \geq 0$ *and* $\frac{n \max\{h,\hbar\} b^d}{\log n}, \frac{n\hbar}{\log n}, \frac{h^3 \log n}{\hbar}, \frac{nh^3\hbar^4}{\log n} \to \infty$ *as* $n \to \infty$*, then for any* $t \in \mathcal{T}'$*,*

$$\sqrt{nh^3}\left[\widehat{\theta}_C(t) - \theta(t)\right] = \mathbb{G}_n \bar{\varphi}_t + o_P(1), \quad \text{and} \quad \sqrt{nh^3}\left[\widehat{m}_\theta(t) - m(t)\right] = \mathbb{G}_n \varphi_t + o_P(1),$$

where

$$\bar{\varphi}_t(Y, T, \boldsymbol{S}) = \frac{C_{K_T}\left[Y - \mu(T, \boldsymbol{S})\right]}{\sqrt{h} \cdot p_T(t)} \left(\frac{T-t}{h}\right) K_T\left(\frac{T-t}{h}\right)$$

and $\varphi_t\left(Y, T, \boldsymbol{S}\right) = \mathbb{E}_{T_1}\left[\int_{T_1}^t \bar{\varphi}_{\tilde{t}}(Y, T, \boldsymbol{S})\, d\tilde{t}\right]$ *with* $\mathbb{G}_n = \sqrt{n}\left(\mathbb{P}_n - \mathrm{P}\right)$*, where* $C_{K_T} > 0$ *is a constant that only depends on* K_T*.*

▶ **Note:** $\bar{\varphi}_t$ and φ_t are the IPW components of the *approximated* efficient influence functions.

Theorem (Theorems 6 and 7 in Zhang et al. 2024)

Under the same regularity conditions, if $h \asymp n^{-\frac{1}{\gamma}}$ *and* $b \lesssim \hbar \asymp n^{-\frac{1}{\varpi}}$ *for some* $\gamma \geq \varpi > 0$ *such that* $\frac{nh^{d+5}}{\log n} \to c_1$ *and* $\frac{n\hbar^5}{\log n} \to c_2$ *for some* $c_1, c_2 \geq 0$ *and* $\frac{\hbar}{h^3 \log n}, \hbar n^{\frac{1}{3}} \log n, \frac{\sqrt{n\hbar}}{\log n}, \frac{n \max\{h,\hbar\} b^d}{\log n} \to \infty$ *as* $n \to \infty$*,*

1. $$\left| \sqrt{nh^3} \sup_{t \in \mathcal{T}} \left| \widehat{m}_\theta(t) - m(t) \right| - \sup_{t \in \mathcal{T}} \left| \mathbb{G}_n \varphi_t \right| \right| = O_P\left(\sqrt{nh^3 \max\{h, \hbar\}^4} + \sqrt{\frac{h^3 \log n}{\hbar}} + \frac{\log n}{\sqrt{n\hbar}} + \sqrt{\frac{\log n}{nb^d \hbar}} \right).$$

2. *there exists a mean-zero Gaussian process* $\mathbb{B}$ *such that*

$$\sup_{u \geq 0} \left| \mathrm{P}\left(\sqrt{nh^3} \sup_{t \in \mathcal{T}} \left| \widehat{m}_\theta(t) - m(t) \right| \leq u \right) - \mathrm{P}\left(\sup_{f \in \mathcal{F}} \left| \mathbb{B}(f) \right| \leq u \right) \right| = O\left(\left(\frac{\log^5 n}{nh^3} \right)^{\frac{1}{8}} + \left(\frac{\log^2 n}{nb^d \hbar} \right)^{\frac{3}{8}} \right).$$

3. $$\sup_{u \geq 0} \left| \mathrm{P}\left(\sqrt{nh^3} \sup_{t \in \mathcal{T}} \left| \widehat{m}_\theta^*(t) - \widehat{m}_\theta(t) \right| \leq u \middle| \mathbb{U}_n \right) - \mathrm{P}\left(\sup_{f \in \mathcal{F}} \left| \mathbb{B}(f) \right| \leq u \right) \right| = O_P\left(\left(\frac{\log^5 n}{nh^3} \right)^{\frac{1}{8}} + \left(\frac{\log^2 n}{nb^d \hbar} \right)^{\frac{3}{8}} \right),$$
   where $\mathcal{F} = \{(v, x, z) \mapsto \varphi_t(v, x, z) : t \in \mathcal{T}\}$.

Remarks on Our Asymptotic Results

1. $\mathcal{F}$ is not Donsker because φ_t is not uniformly bounded as $h \to 0$.
   - However, $\widetilde{\mathcal{F}} = \left\{(v, x, z) \mapsto \sqrt{h^3} \cdot \varphi_t(v, x, z) : t \in \mathcal{T}'\right\}$ is of VC-type.
   - Gaussian approximation in Chernozhukov et al. (2014) can be applied to bound the difference between $\sup_{f\in\mathcal{F}} |\mathbb{G}_n(f)|$ and $\sup_{f\in\mathcal{F}} |\mathbb{B}(f)|$.
2. As long as $\mathrm{Var}(Y|T = t, \boldsymbol{S} = \boldsymbol{s}) \geq \sigma^2 > 0$, $\mathrm{Var}\left[\varphi_t(Y, T, \boldsymbol{S})\right]$ is a positive finite number.
   - The asymptotic linearity (or V-statistic) is non-degenerate.
   - Pointwise bootstrap confidence intervals are asymptotically valid.
3. For the validity of uniform bootstrap confidence band, one can choose the bandwidths $h \asymp \hbar = O\left(n^{-\frac{1}{5}}\right)$ and $\left(\frac{\log n}{n}\right)^{\frac{4}{5d}} \lesssim b \lesssim n^{-\frac{1}{5}}$.
   - These orders align with the outputs from the usual bandwidth selection methods (Bashtannyk and Hyndman, 2001; Li and Racine, 2004).
   - No explicit undersmoothing is required!!

Simulation Setup for Estimating $m(t)$ and $\theta(t)$ Without Positivity

- Use the Epanechnikov kernel for K_T and K_S (with the product kernel technique) and Gaussian kernel for $\bar{K}_T$.
- Select the bandwidth parameters $h, b > 0$ by modifying the rule-of-thumb method in Yang and Tschernig (1999).
- Set the bandwidth parameter $\hbar > 0$ to the normal reference rule in Chacón et al. (2011); Chen et al. (2016).
- Set the bootstrap resampling time $B = 1000$ and the nominal level for confidence intervals or bands to 95%.
- Compare our proposed estimators with the regression adjustment estimators under the same choices of bandwidth parameters:

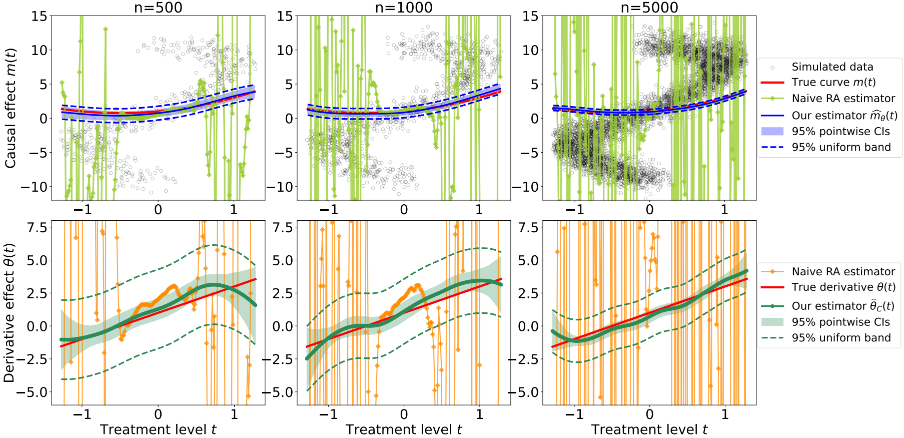
$$\widehat{m}_{\mathrm{RA}}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\mu}(t, \boldsymbol{S}_i) \quad \text{and} \quad \widehat{\theta}_{\mathrm{RA}}(t) = \frac{1}{n}\sum_{i=1}^{n} \widehat{\beta}_2(t, \boldsymbol{S}_i).$$

Single Confounder Model Without Positivity

Generate i.i.d. observations $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^{2000}$ from

$$Y = T^2 + T + 1 + 10S + \epsilon, \quad T = \sin(\pi S) + E, \quad \text{and} \quad S \sim \text{Uniform}[-1,1].$$

- $E \sim \text{Uniform}[-0.3, 0.3]$ is an independent treatment variation,
- $\epsilon \sim \mathcal{N}(0,1)$ is an exogenous normal noise.

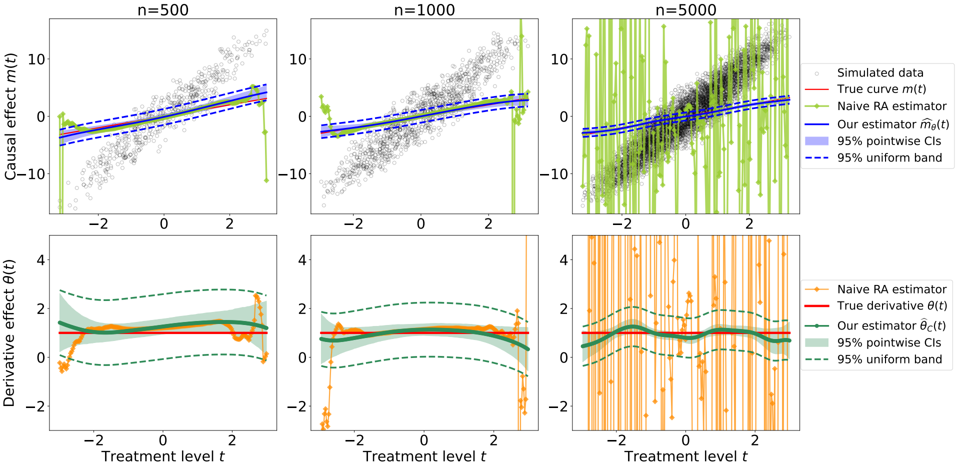


Linear Confounding Model Without Positivity

Generate i.i.d. observations $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^{2000}$ from

$$Y = T + 6S_1 + 6S_2 + \epsilon, \quad T = 2S_1 + S_2 + E, \quad \text{and} \quad (S_1, S_2) \sim \text{Uniform}[-1,1]^2,$$

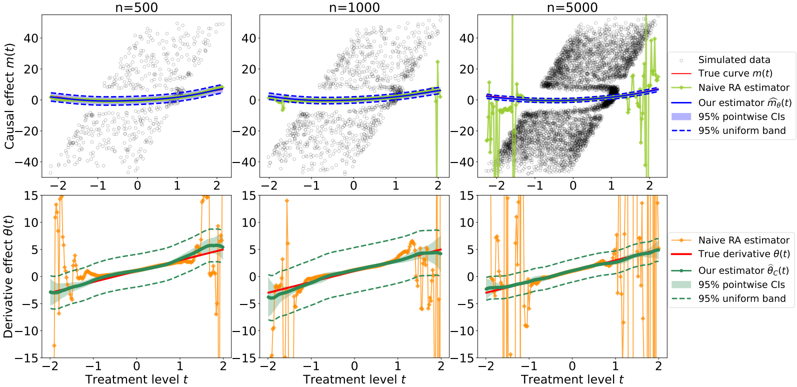
- $E \sim \text{Uniform}[-0.5, 0.5]$ and $\epsilon \sim \mathcal{N}(0,1)$.



Generate i.i.d. observations $\{(Y_i, T_i, \boldsymbol{S}_i)\}_{i=1}^{2000}$ from

$$Y = T^2 + T + 10Z + \epsilon, \quad T = \cos\left(\pi Z^3\right) + \frac{Z}{4} + E, \quad \text{and} \quad Z = 4S_1 + S_2,$$

- $(S_1, S_2) \sim \text{Uniform}[-1,1]^2$, $E \sim \text{Uniform}[-0.1, 0.1]$, and $\epsilon \sim \mathcal{N}(0,1)$.
- Those doubly robust methods based on pseudo-outcomes (Kennedy et al., 2017; Takatsu and Westling, 2022) do not work in this example.



Nonparametric Bound on $m(t)$ When $\mathrm{Var}(E) = 0$

For simplicity, we assume the additive confounding model

$$Y = \bar{m}(T) + \eta(\boldsymbol{S}) + \epsilon, \quad T = f(\boldsymbol{S}) + E \quad \text{with} \quad \mathbb{E}\left[\eta(\boldsymbol{S})\right] = 0 \quad \text{and} \quad \mathbb{E}(E) = 0.$$

When $\mathrm{Var}(E) = 0$,

- $\mu(t, \boldsymbol{s})$ can be identified only on a lower-dimensional surface $\{(t, \boldsymbol{s}) \in \mathcal{T} \times \mathcal{S} : t = f(\boldsymbol{s})\}$ so that

$$\mu\left(f(\boldsymbol{s}), \boldsymbol{s}\right) = \bar{m}\left(f(\boldsymbol{s})\right) + \eta(\boldsymbol{s}) = m\left(f(\boldsymbol{s})\right) + \eta(\boldsymbol{s}). \tag{2}$$

- The relation $T = f(\boldsymbol{S})$ can be recovered from the data $\{(T_i, \boldsymbol{S}_i)\}_{i=1}^n$.

Assumption (Bounded random effect)

Let $L_f(t) = \{\boldsymbol{s} \in \mathcal{S} : f(\boldsymbol{s}) = t\}$ be a level set of the function $f : \mathcal{S} \to \mathbb{R}$ at $t \in \mathcal{T}$. There exists a constant $\rho_1 > 0$ such that

$$\rho_1 \geq \max\left\{\sup_{t \in \mathcal{T}} \sup_{\boldsymbol{s} \in L_f(t)} |\eta(\boldsymbol{s})|, \ \frac{\sup_{t \in \mathcal{T}} \sup_{\boldsymbol{s} \in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s}) - \inf_{t \in \mathcal{T}} \inf_{\boldsymbol{s} \in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s})}{2}\right\}.$$

Nonparametric Bound on $m(t)$ When $\mathrm{Var}(E) = 0$

By (2) and the first lower bound on $\rho_1 \geq \sup_{t \in \mathcal{T}} \sup_{\boldsymbol{s} \in L_f(t)} |\eta(\boldsymbol{s})|$ in the previous assumption, we know that

$$|\mu(f(\boldsymbol{s}), \boldsymbol{s}) - m(t)| = |\eta(\boldsymbol{s})| \leq \rho_1$$

for any $\boldsymbol{s} \in L_f(t)$. It also implies that

$$\begin{aligned} m(t) &\in \bigcap_{\boldsymbol{s} \in L_f(t)} \left[\mu(f(\boldsymbol{s}), \boldsymbol{s}) - \rho_1,\, \mu(f(\boldsymbol{s}), \boldsymbol{s}) + \rho_1\right] \\ &= \left[\sup_{\boldsymbol{s} \in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s}) - \rho_1,\, \inf_{\boldsymbol{s} \in L_f(t)} \mu(f(\boldsymbol{s}), \boldsymbol{s}) + \rho_1\right], \end{aligned}$$

which is the nonparametric bound on $m(t)$ that contains all the possible values of $m(t)$ for any fixed $t \in \mathcal{T}$ when $\mathrm{Var}(E) = 0$.

- This bound is well-defined and nonempty under the second lower bound on ρ_1 in the previous assumption.