Nonparametric instrumental variable analysis of surgical care for gallstone diseases

In collaboration with
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Kenta Takatsu

Motivation

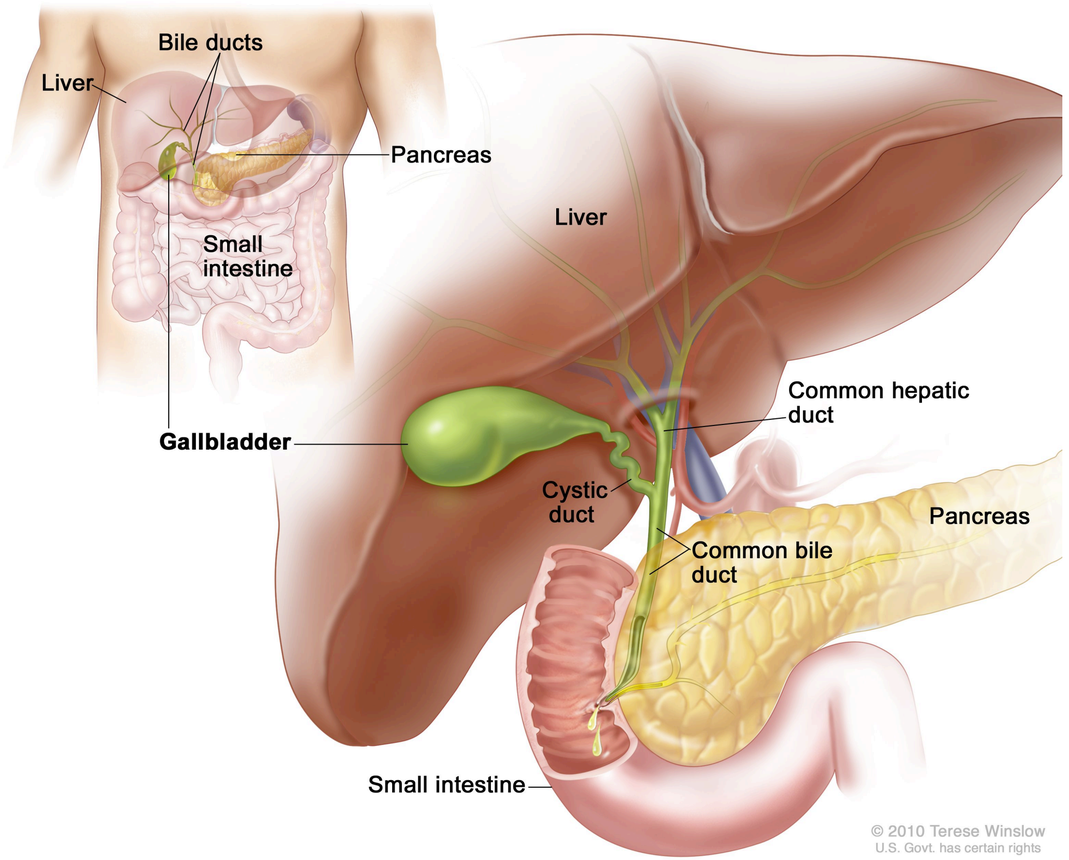

Fig: Anatomy of the gallbladder. Adapted from National Cancer Institute (https://www.cancer.gov/)

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A. No. Surgery may *not* be as effective for certain patients.

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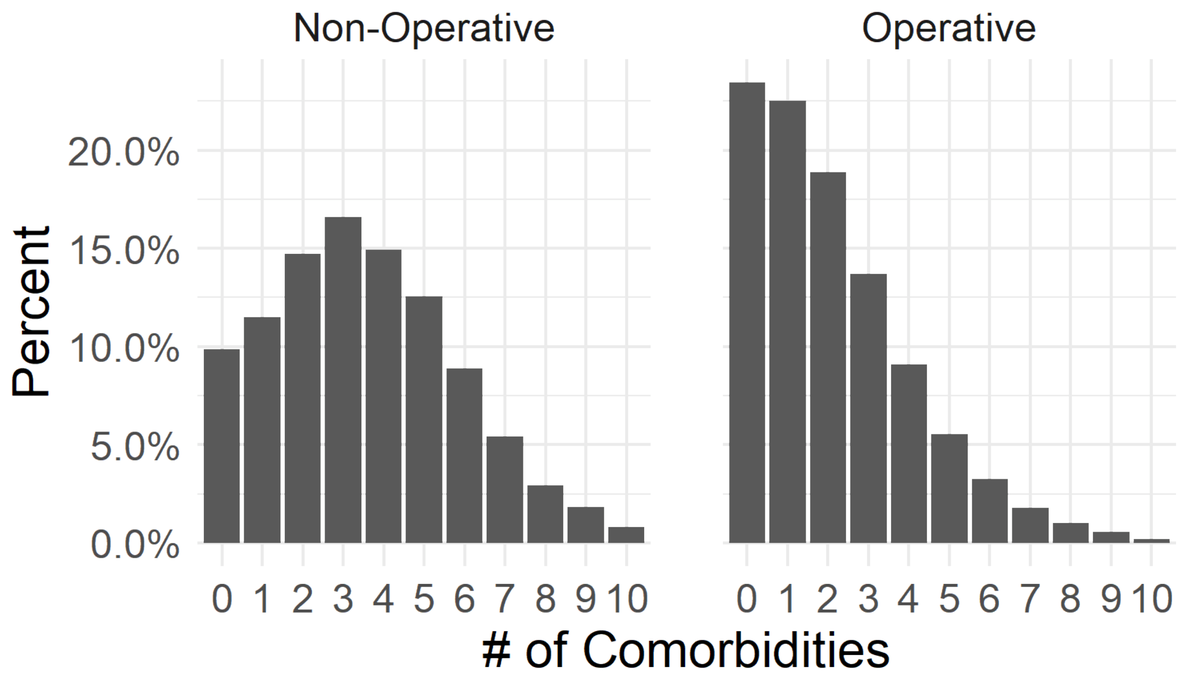

Fig: Empirical distribution of # of comorbidities b/w treatment and control arms.

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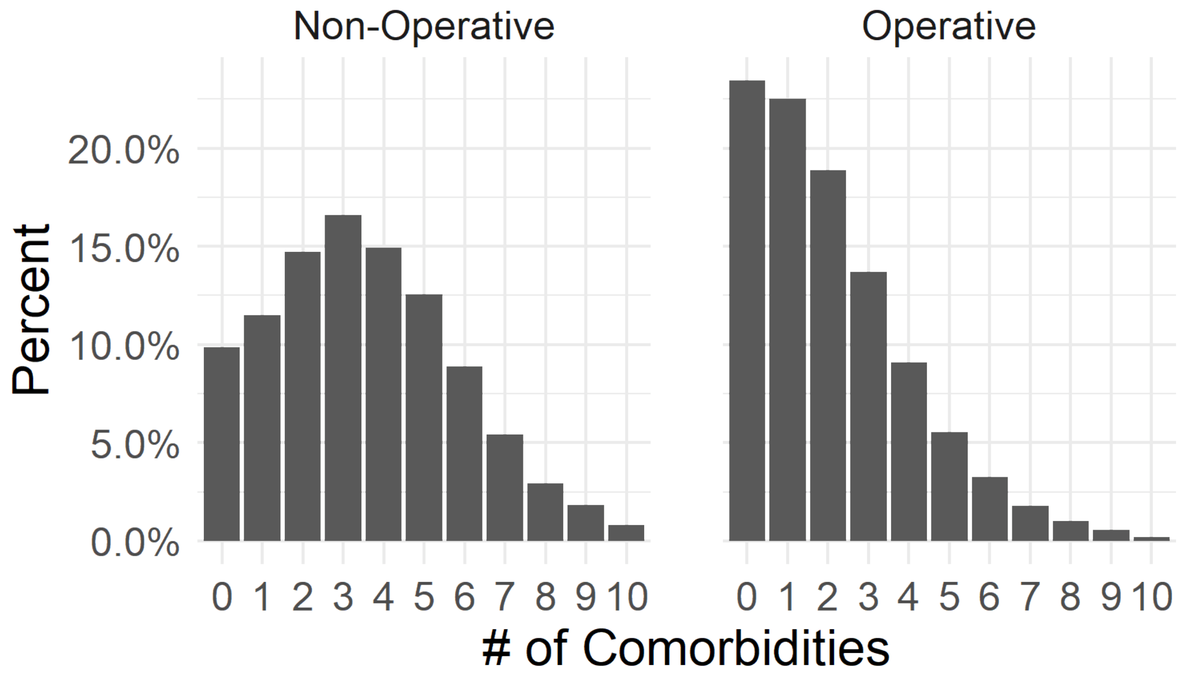
There can be **unmeasured confounding.**



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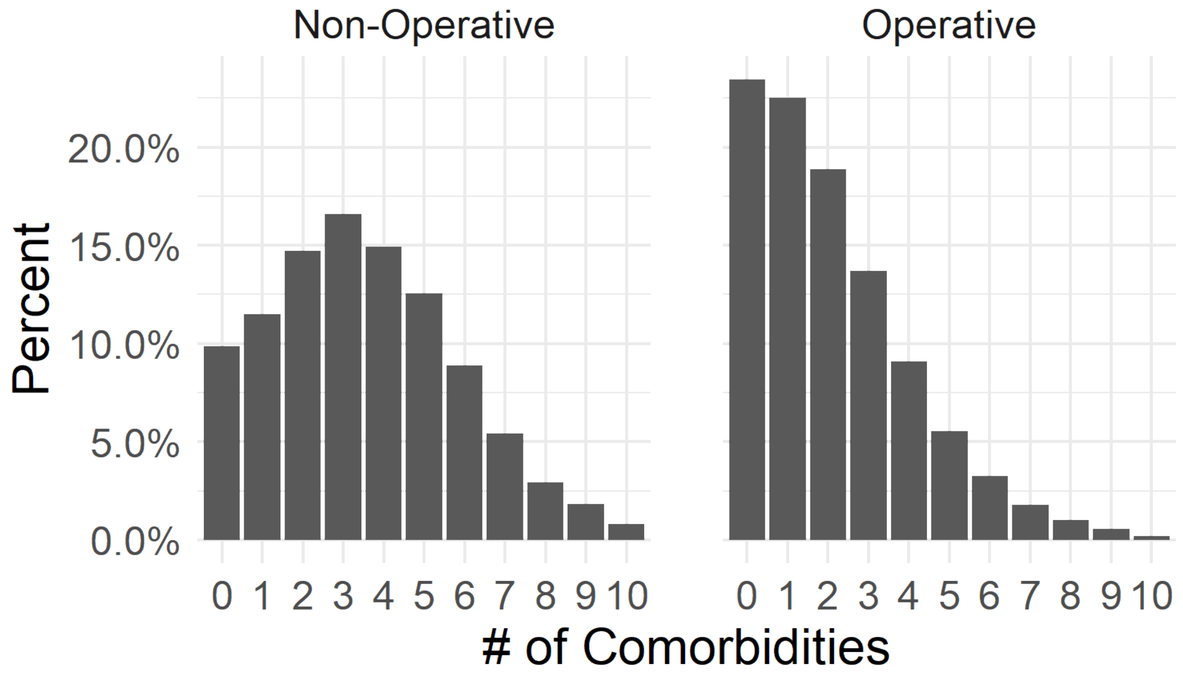

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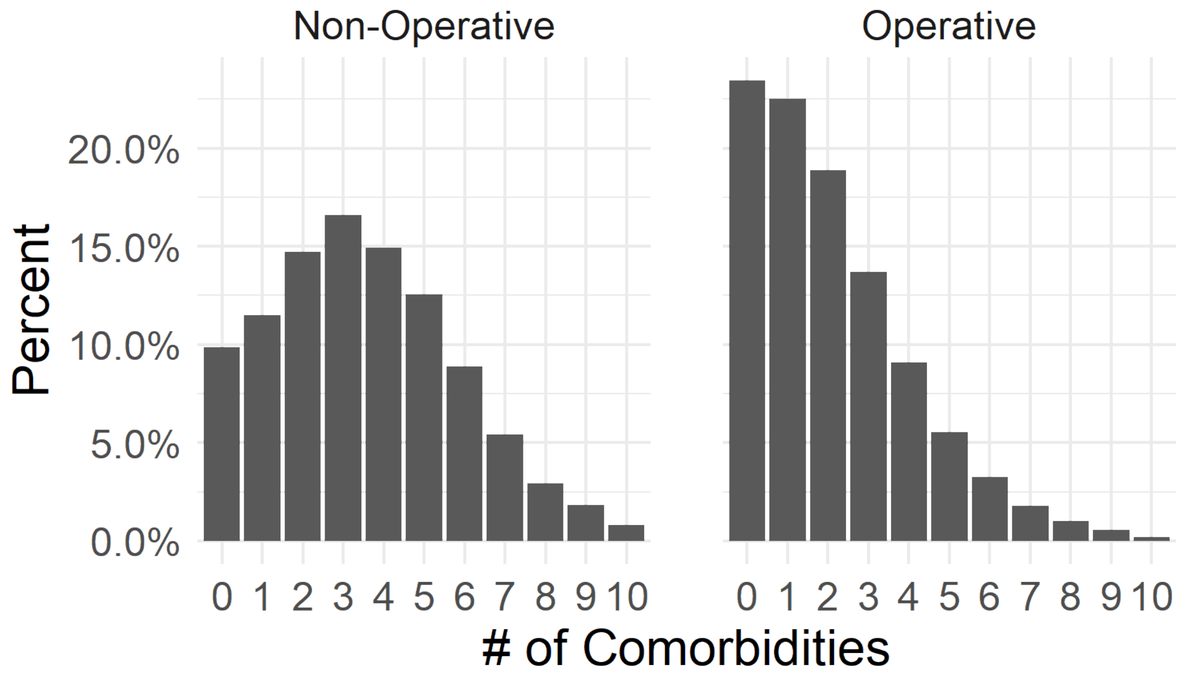
What can we do?

If you have a special variable called an ***instrumental variable*** (IV), you can still estimate “certain” treatment effect.



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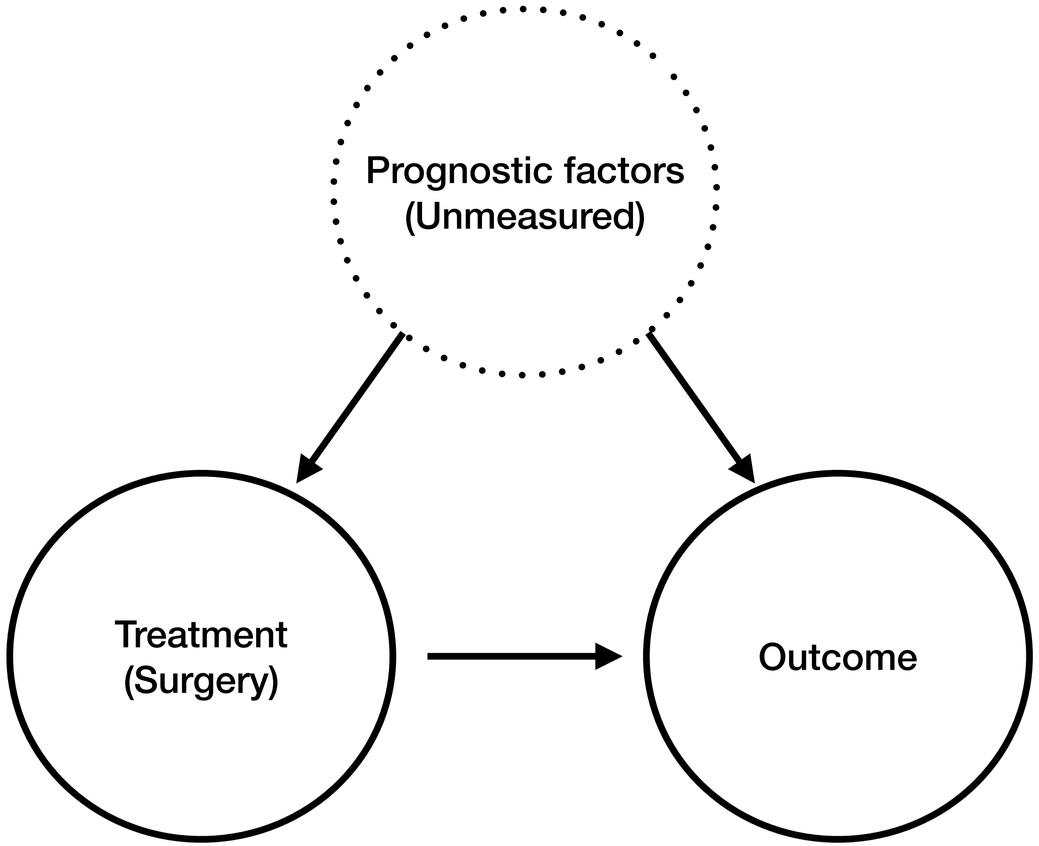
Prognostic factors
(Unmeasured)
Treatment
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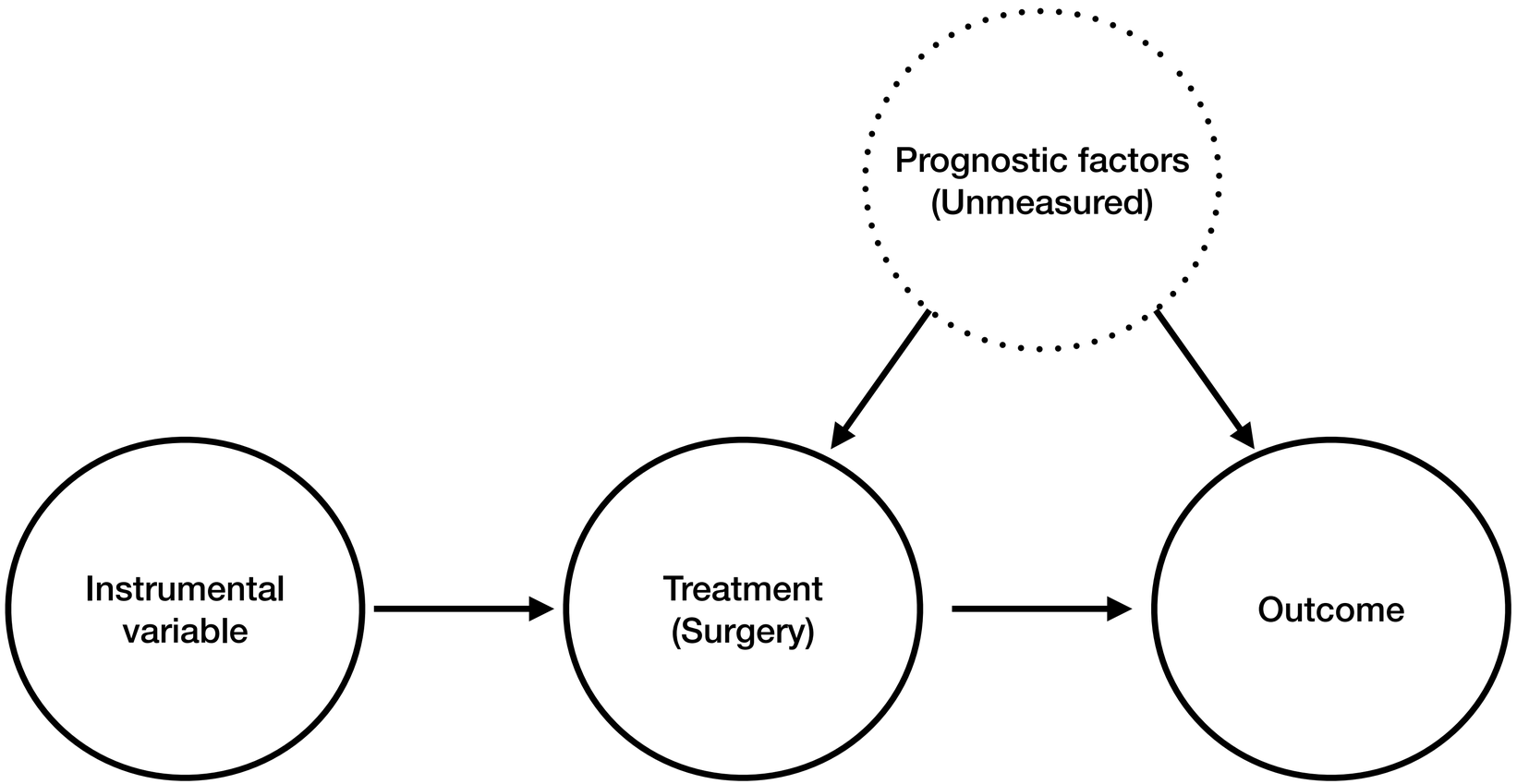
Outcome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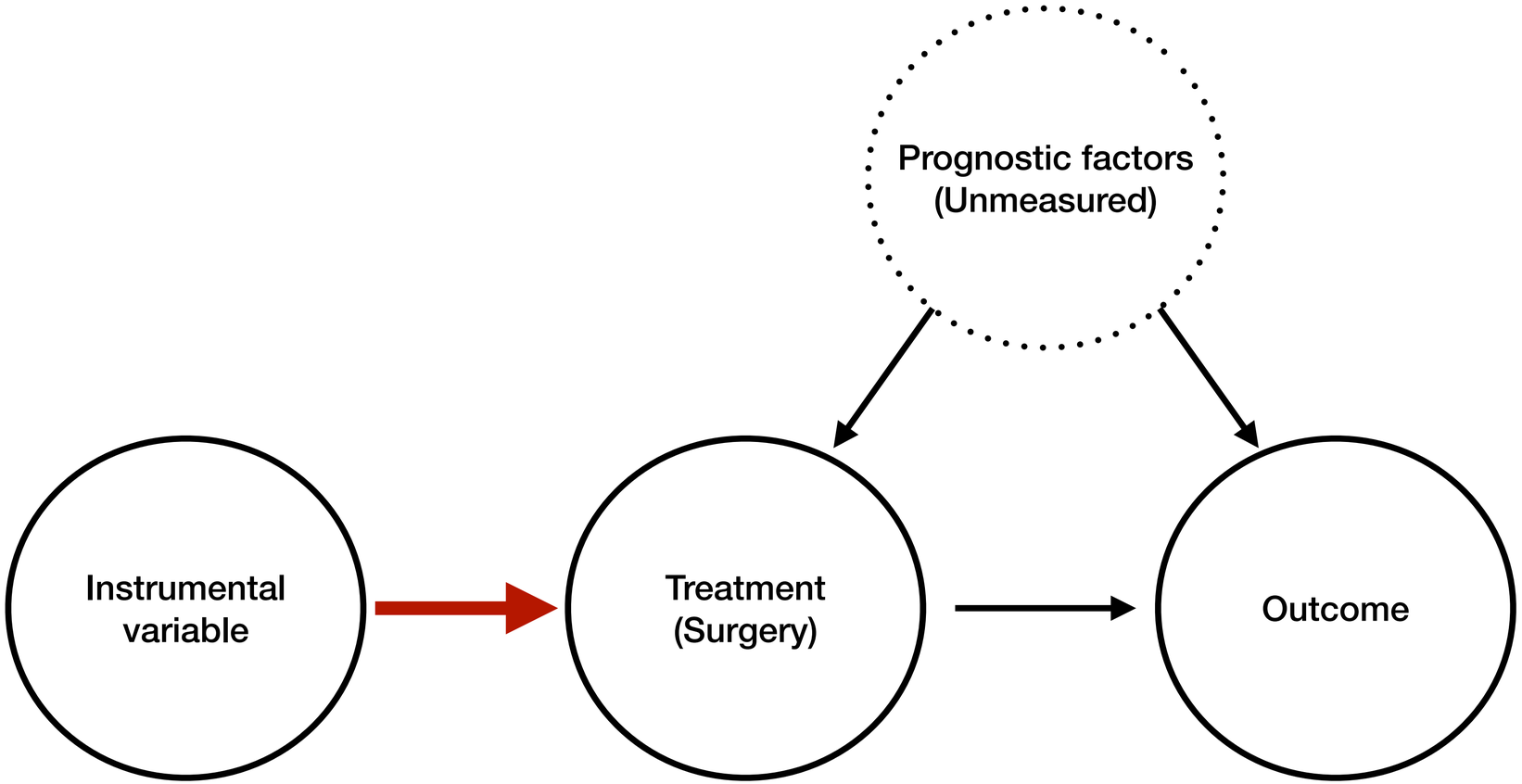
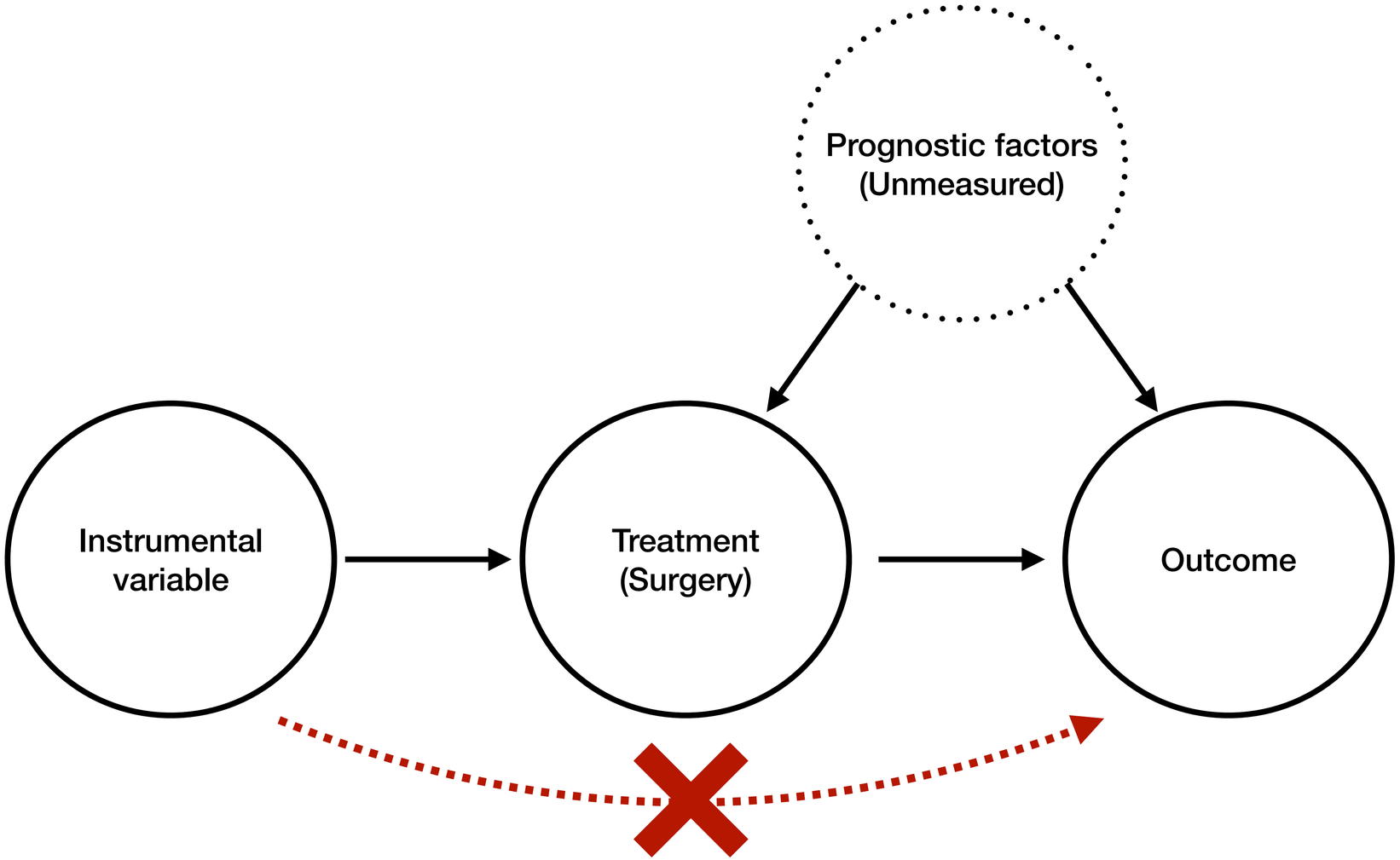
Relevance

An instrument must be associated with treatment



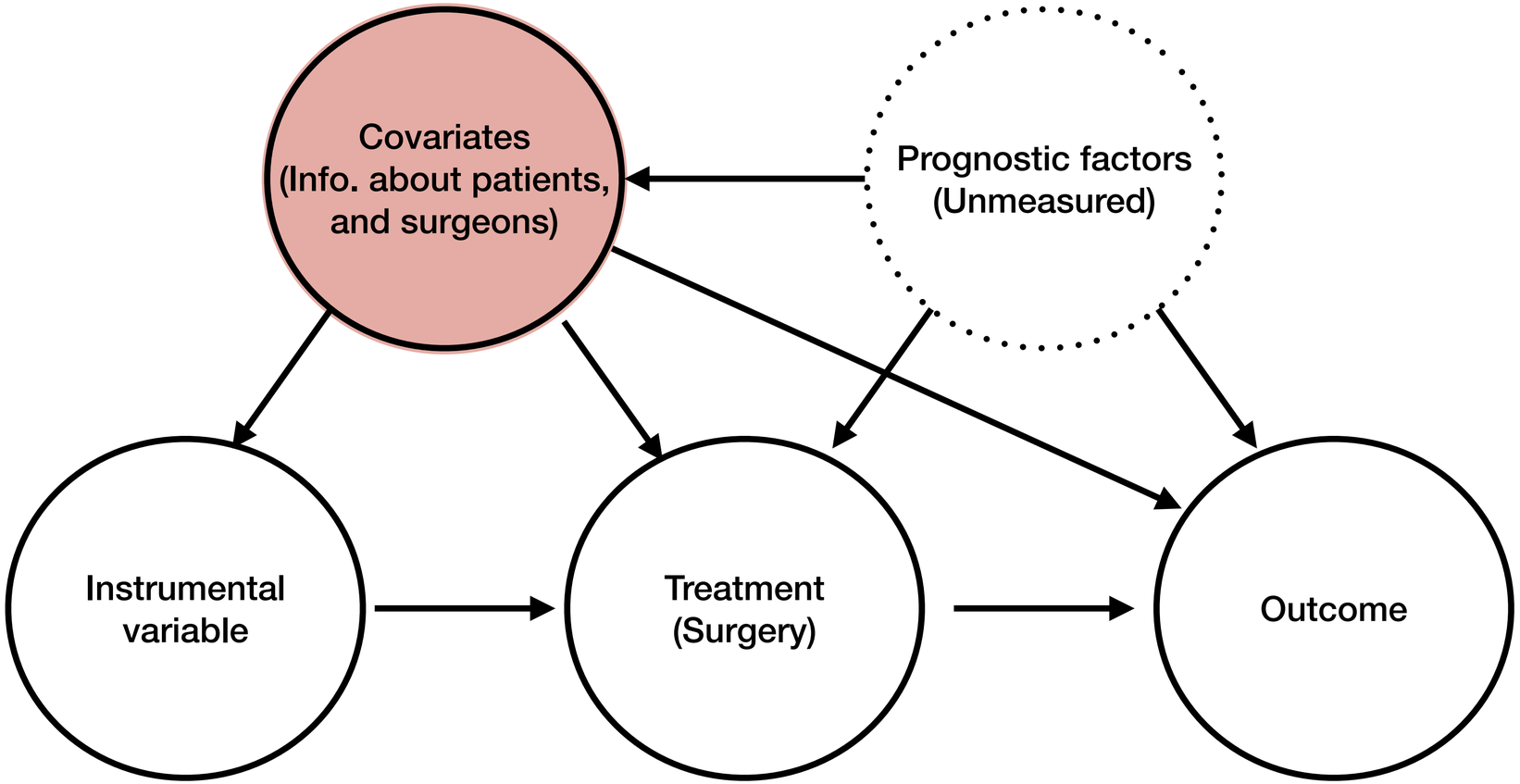
Exclusion Restriction

An instrument must not affect outcomes directly



Unconfounded IV

An instrument must itself be unconfounded



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For each surgeon, compute # of operations/# of patients on a separate data. (Brookhart (2007) and Keele et al. (2018)).

$O := (Y, A, Z, W)$ and observe $\{O_i\}_{i=1}^{n} \overset{iid}{\sim} P_0$

$Y \in \{0,1\}$ denotes the outcomes. 1:="Adverse" outcomes.

$A \in \{0,1\}$ denotes the treatment. 1:=Surgery.

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$W \in \mathscr{W} \subseteq \mathbb{R}^d$ where d=226.

Ex) # of comorbidities, an indicator for sepsis, and age.

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2. Never-takers
3. Compliers

   Patients who follow surgeon's preference

4. Defiers

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Monotonicity

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Remedy for 1

We can estimate covariate density for each patient type:
$P(V = v \mid$ Complier$)$, $P(V = v \mid$ Always-taker$)$, and
$P(V = v \mid$ Never-taker$)$.

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Remedy for 2

We can study the robustness of our estimates when there are defiers.

$$\mathbb{P}(I\{\text{\# of Comorb. = v}\} \mid \text{Patient type})$$

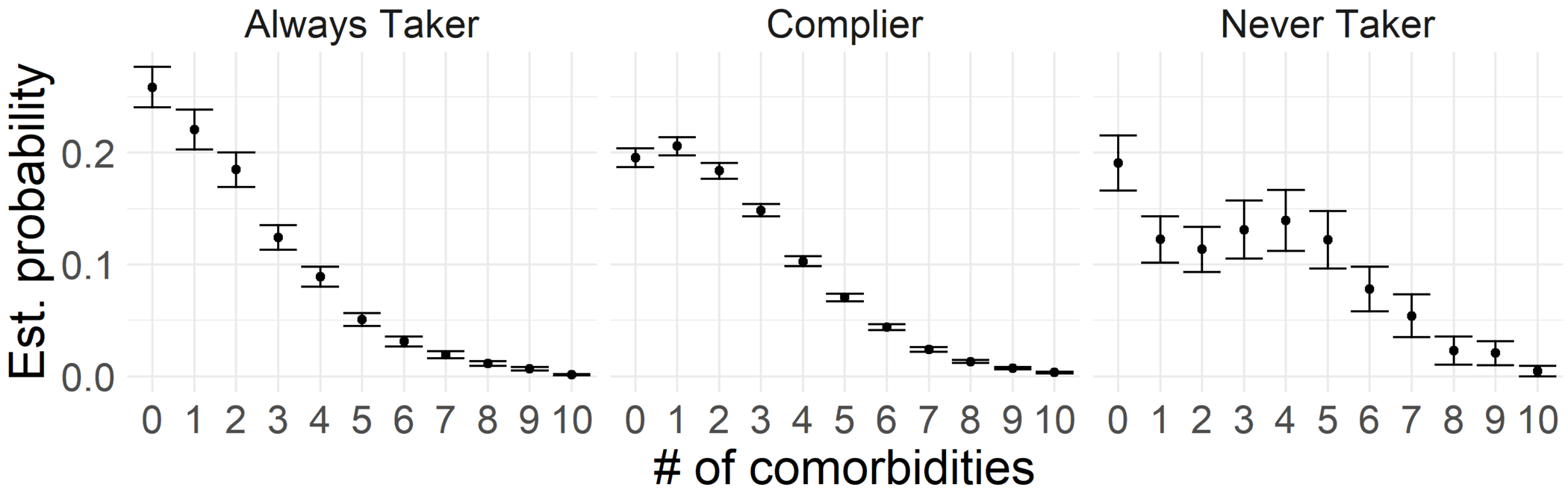

Fig: Estimated conditional probability of # of comorbidities for each patient type. Vertical bars are pointwise 95% CIs.

Nonparametric estimation and inference

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$$\approx \frac{n^{-1} \sum_{i=1}^{n} \widehat{\mu_n}(1, W_i) - n^{-1} \sum_{i=1}^{n} \widehat{\mu_n}(0, W_i)}{n^{-1} \sum_{i=1}^{n} \widehat{\lambda_n}(1, W_i) - n^{-1} \sum_{i=1}^{n} \widehat{\lambda_n}(0, W_i)}$$

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This estimator is suboptimal.

There *is* a root-n consistent estimator.

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We have to estimate:

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An estimator of LATE ψ_0

$$\widehat{\psi_n} := \frac{n^{-1}\sum_{i=1}^{n} \phi_1(O_i; \widehat{\mu_n}, \widehat{\pi_n})}{n^{-1}\sum_{i=1}^{n} \phi_2(O_i; \widehat{\lambda_n}, \widehat{\pi_n})}$$

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Asymptotic normality

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$$\Longrightarrow \left[\widehat{\psi_n} \pm 1.96\, n^{-1/2}\hat{\sigma}\right]$$

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LATE *cannot* answer the following:

Does surgery become more effective if a patient is young?
How does the efficacy vary as the number of comorbidities increases?
“I am septic but have no comorbidities. Should I receive surgery?”

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Inference of $\psi_0(v)$ is generally challenging.
We use bootstrap to construct CIs.

Empirical results

Surgery is effective on average if you are a complier

We first estimate LATE.

- Lower the better (i.e., surgery reduces the rate of “adverse” outcomes).

Unadjusted estimator ignores confounding.

TSLS is a parametric method based on linear regression.

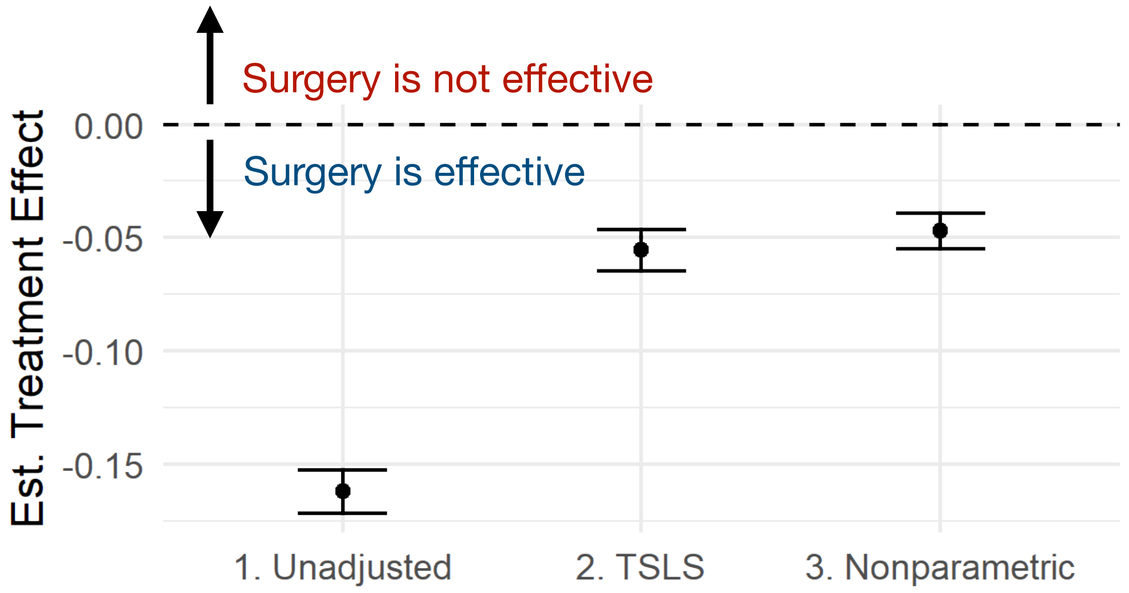


Fig: The point estimates of LATE and 95% CIs from three estimators.

Surgery *may not* be effective for most people

We estimate $E[Y(1) - Y(0) \mid \text{Complier}, W = w]$ where W is all covariates.

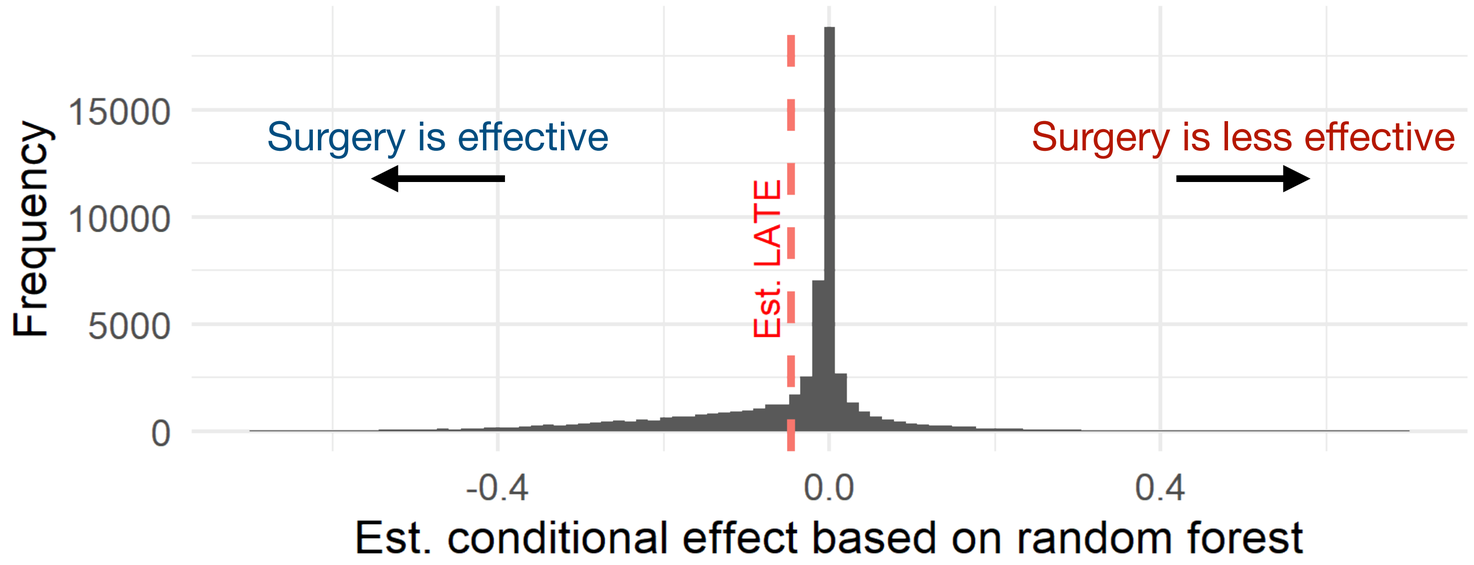


Fig: The distribution of the estimated cond. LATE on all available covariates.

How does the efficacy vary as a function of covariates?

1. We estimate $E[Y(1) - Y(0) \mid \text{Complier}, V = v]$ for V including # of comorbidities, an indicator for sepsis, and age.

2. For the regression model, we use a generalized additive model.

3. We use bootstrap samples to construct 95% confidence sets.

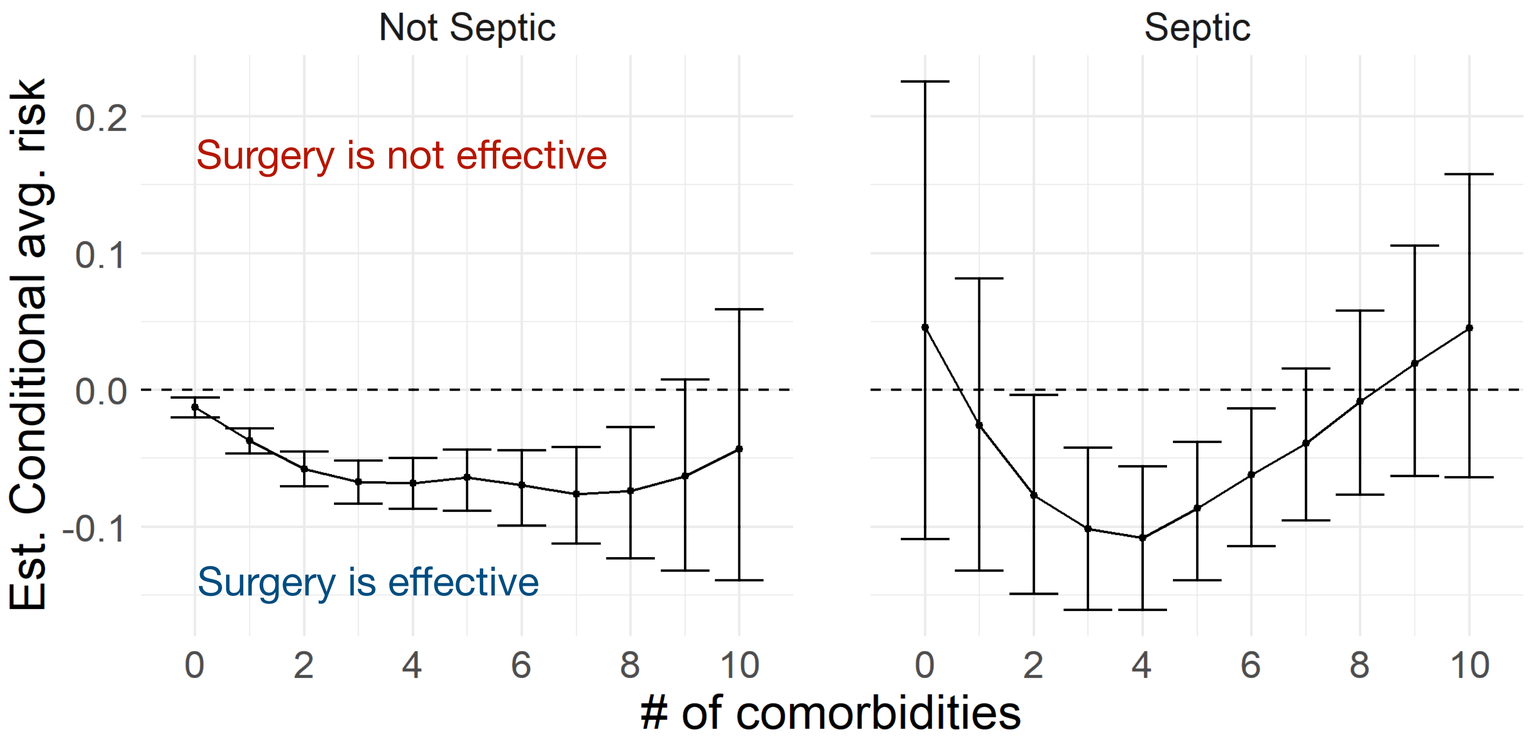
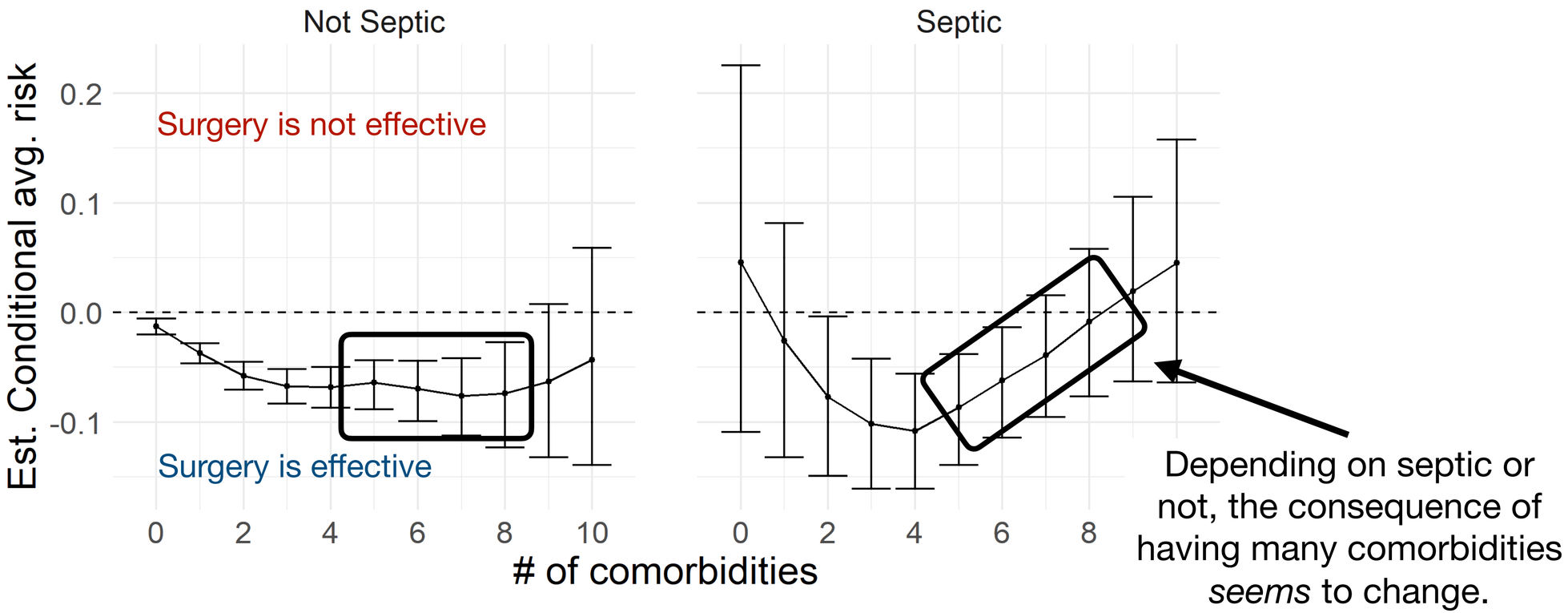


Fig: Estimated cond. LATE and bootstrap CIs as a function of comorbidities and sepsis.



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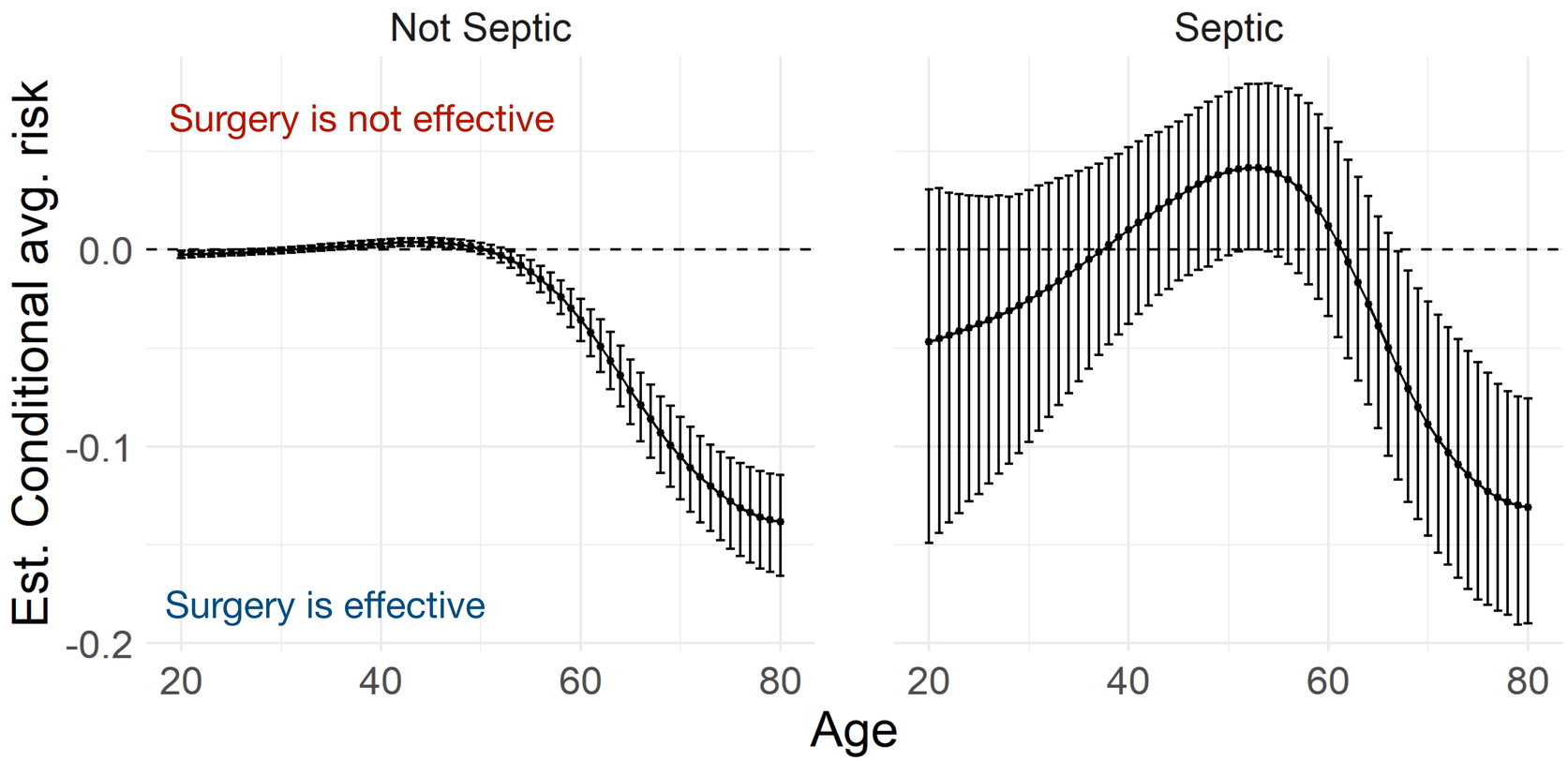
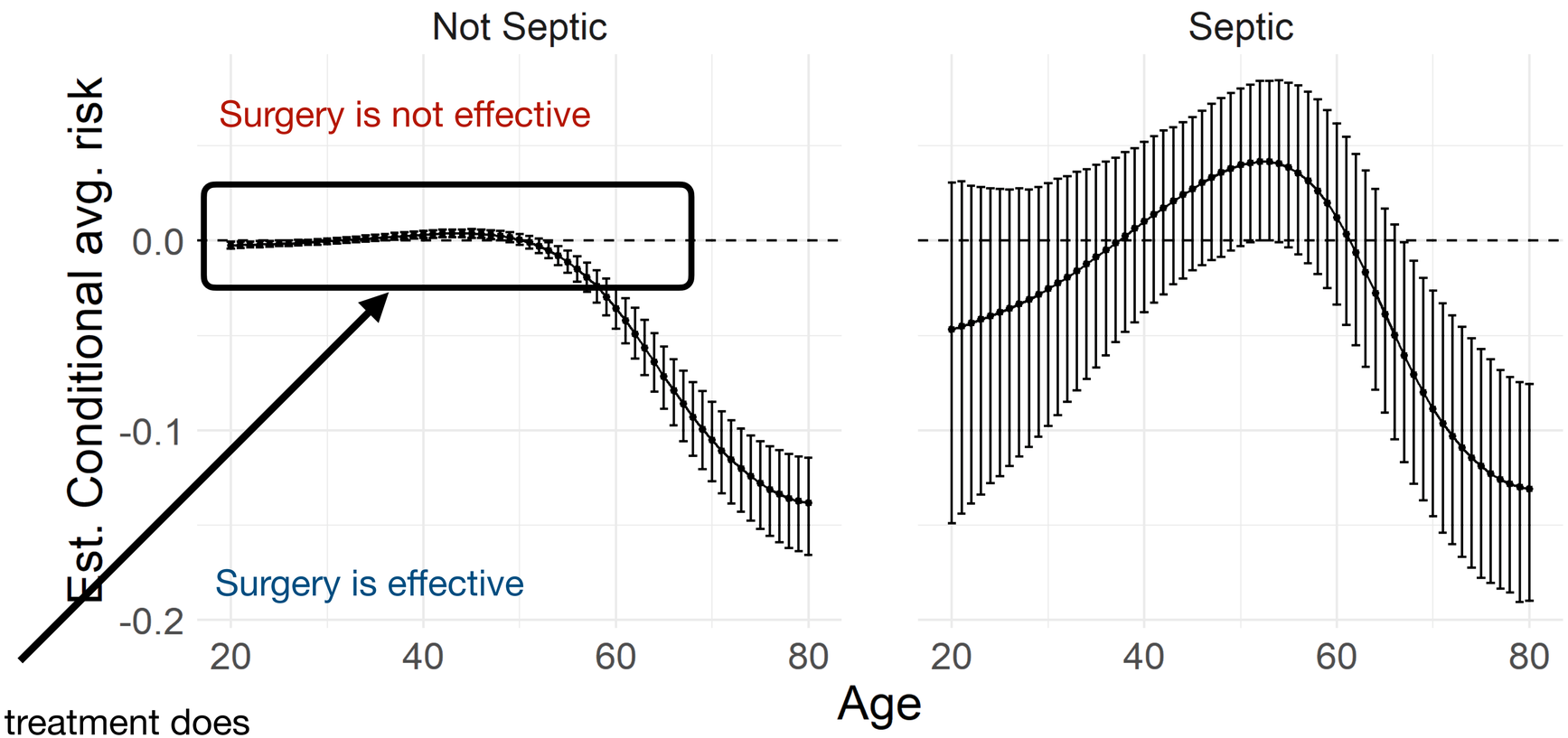


Fig: Estimated cond. LATE and bootstrap CIs as a function of age and sepsis.



The choice of treatment does not really matter for non-septic and young patients

Fig: Estimated cond. LATE and bootstrap CIs as a function of age and sepsis.

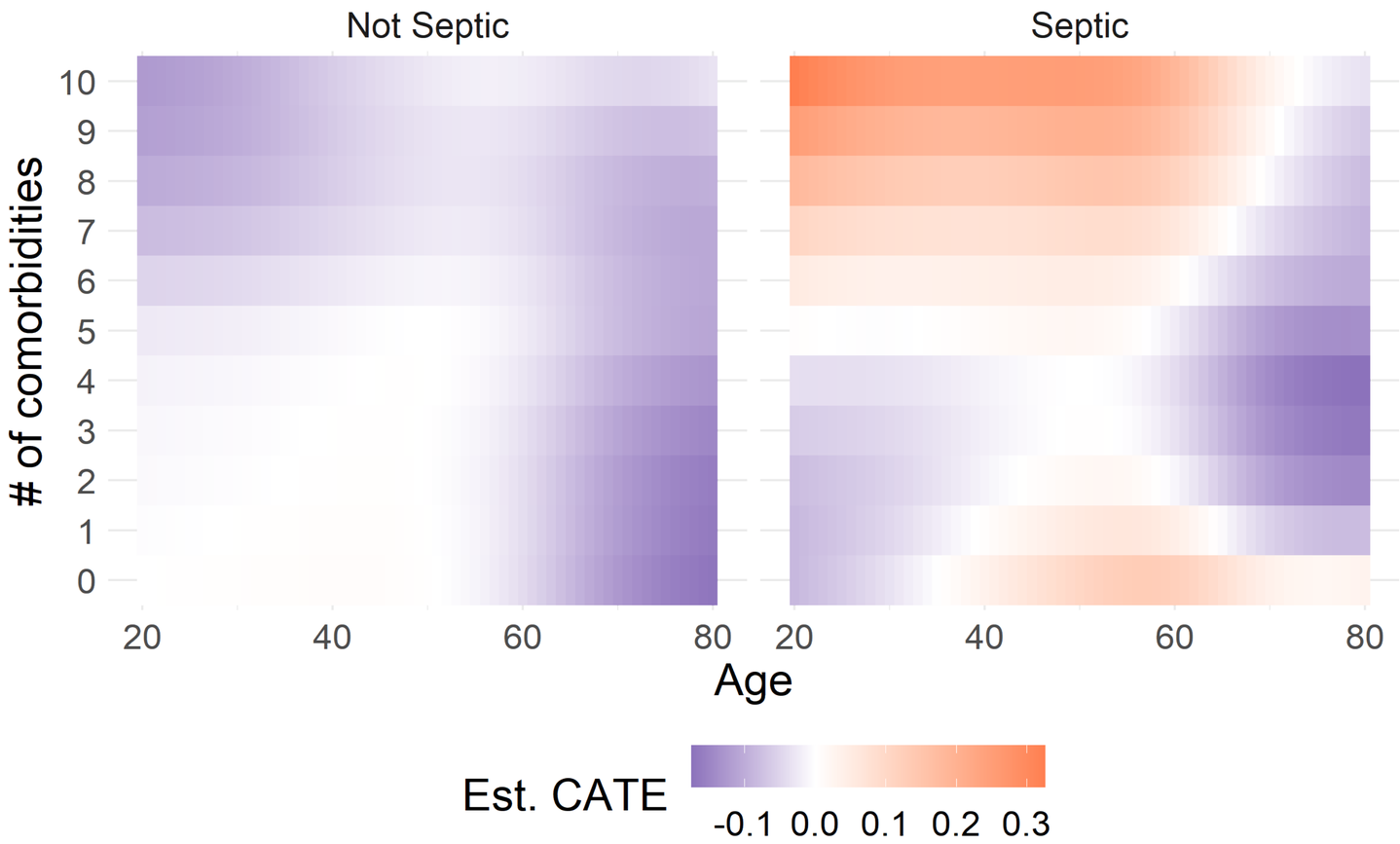
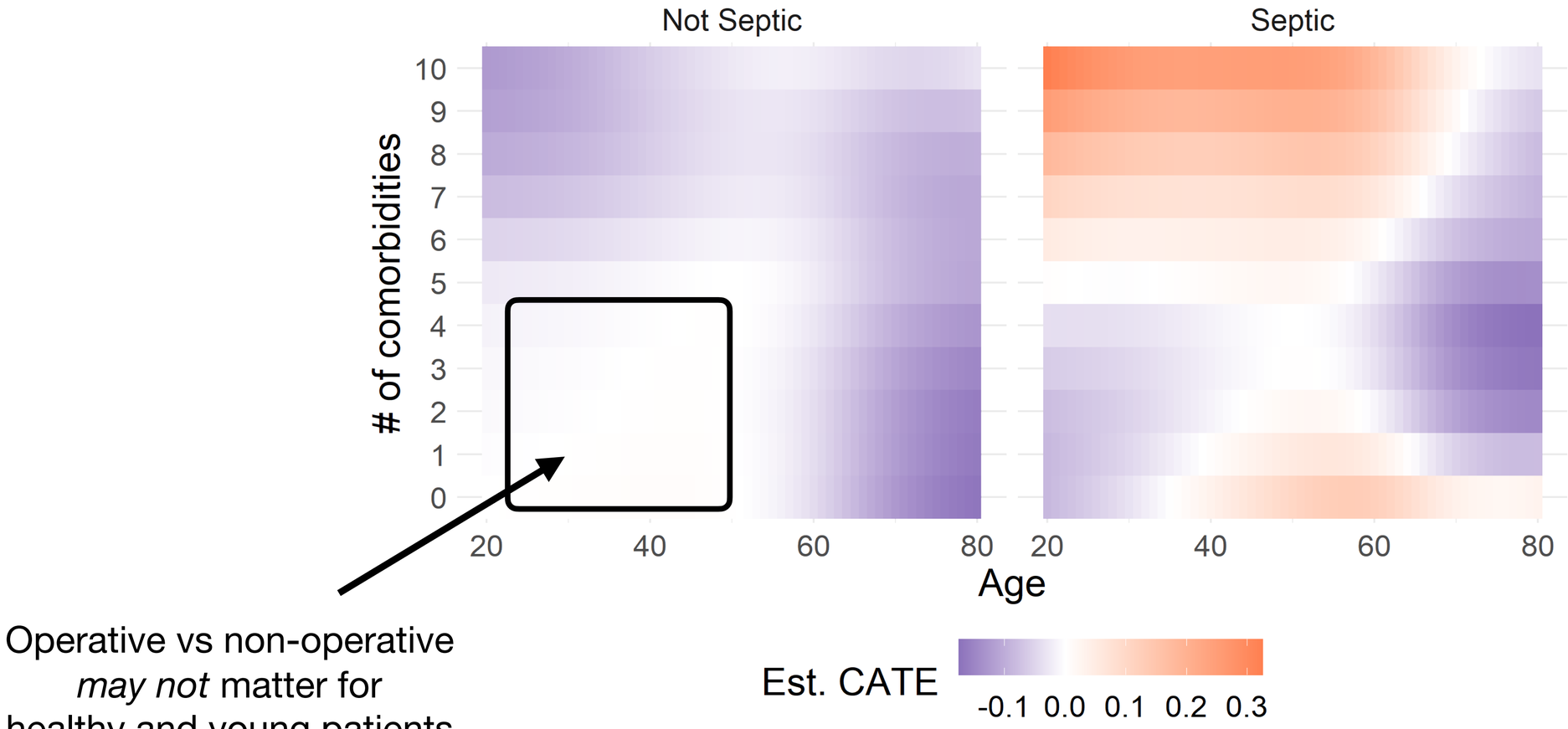


Fig: Heatmap of cond. LATE as a function of age, comorbidities and sepsis.



Operative vs non-operative *may not* matter for healthy and young patients

Fig: Heatmap of cond. LATE as a function of age, comorbidities and sepsis.

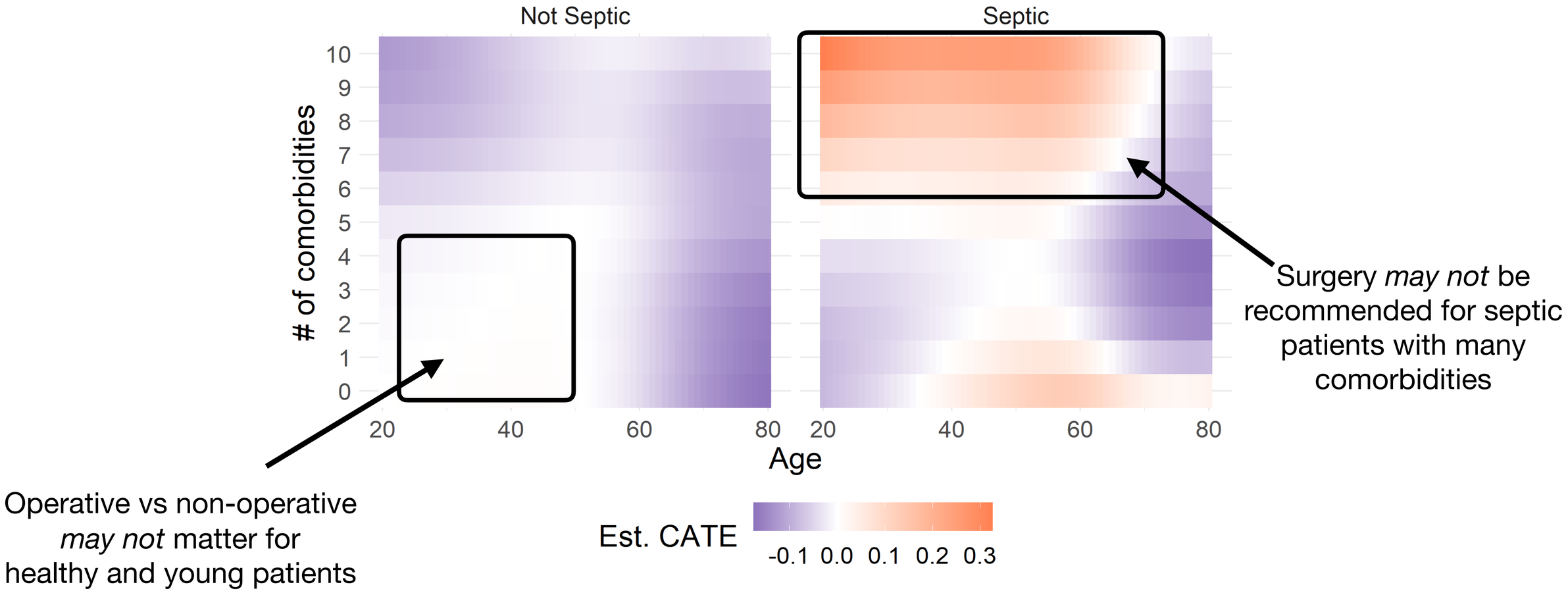


Fig: Heatmap of cond. LATE as a function of age, comorbidities and sepsis.

Sensitivity analysis

What if our data contained defiers?

When there are defiers, LATE can take any values in the following interval:

$$E[Y(1) - Y(0) \mid \text{Complier}] \in \left[\psi_0 - \frac{\delta_1 \delta_2}{\delta_3}, \psi_0 + \frac{\delta_1 \delta_2}{\delta_3}\right]$$

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Angrist, et al (1996)

What if our data contained defiers?

Recall LATE $\leq \psi_0 + \frac{\delta_1 \delta_2}{\delta_3}$

and $\widehat{\psi_n} = -0.05$

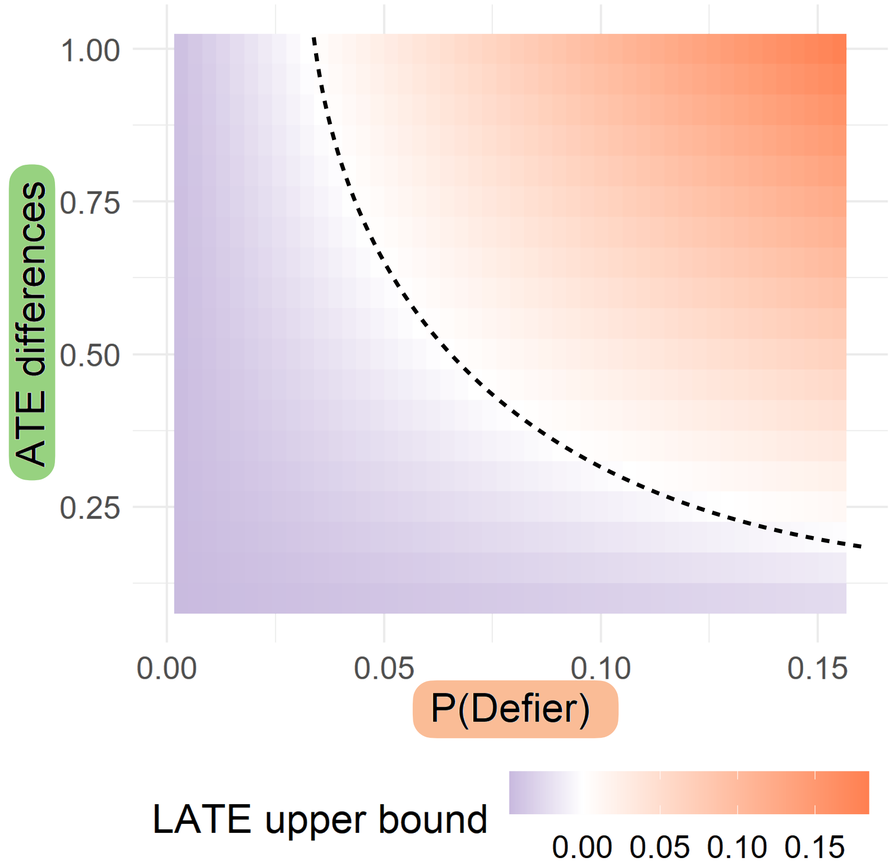

Fig: Heatmap of LATE upper bound as a function of two sensitivity parameters.

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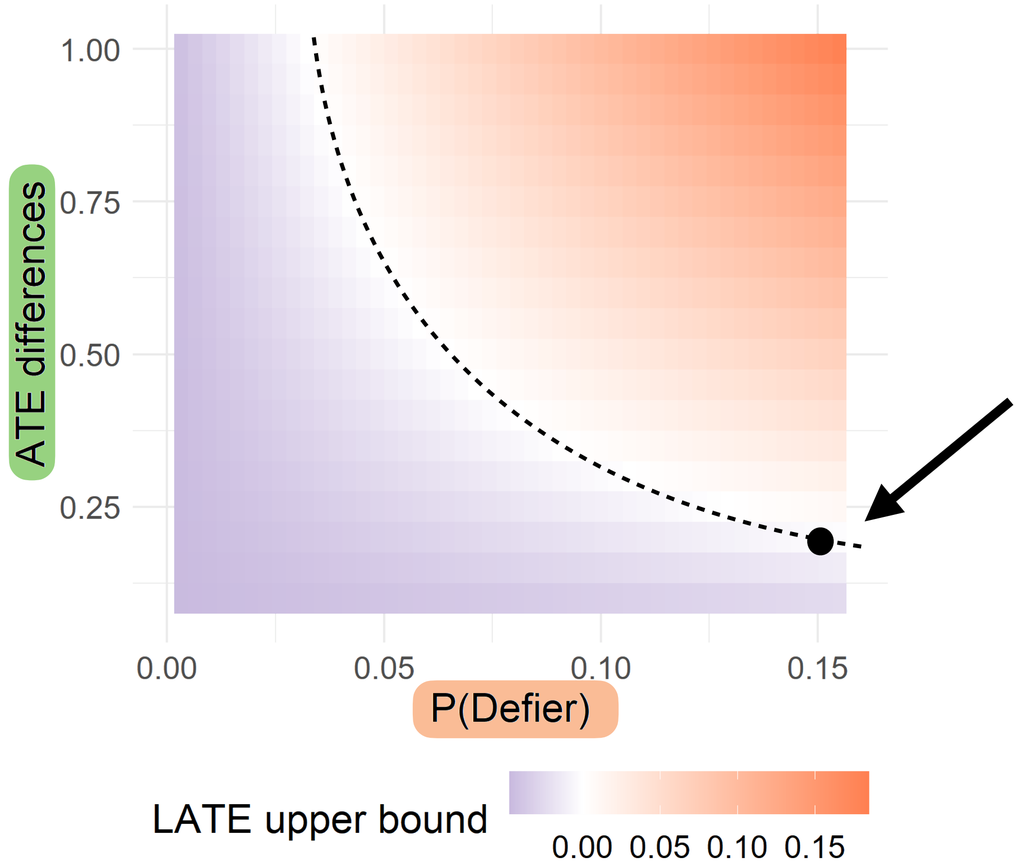


15% of the studied population is defiers.

Surgery is 25% risker for defiers than compliers.

Fig: Heatmap of LATE upper bound as a function of two sensitivity parameters.

Conclusion

Morals of the story

We *can* estimate treatment effect under unmeasured confouding using an IV.

- Although it is an effect for compliers only, we can investigate their characteristics.
- We can conduct the sensitivity analysis against the no-defiers assumption.

We *should* look at conditional LATE.

- The conclusion from LATE can be misleading and may not be applicable to most people.

Thank you.

Appendix

A.1 Computing surgeon's "preference"

1. For each surgeon, we split his or her patient population in half.

2. Using one half of the data, we calculate the proportion of times a surgeon operates.

3. Surgeons were removed from our study if they did not perform at least 5 operations per year.

4. The resulting variable is binarized at median.

A.2 Definition of adverse outcomes

1. Prolonged length of stay is an indicator that equals one when the hospital and operation-specific length of stay is greater than the 75th percentile (5790 cases)

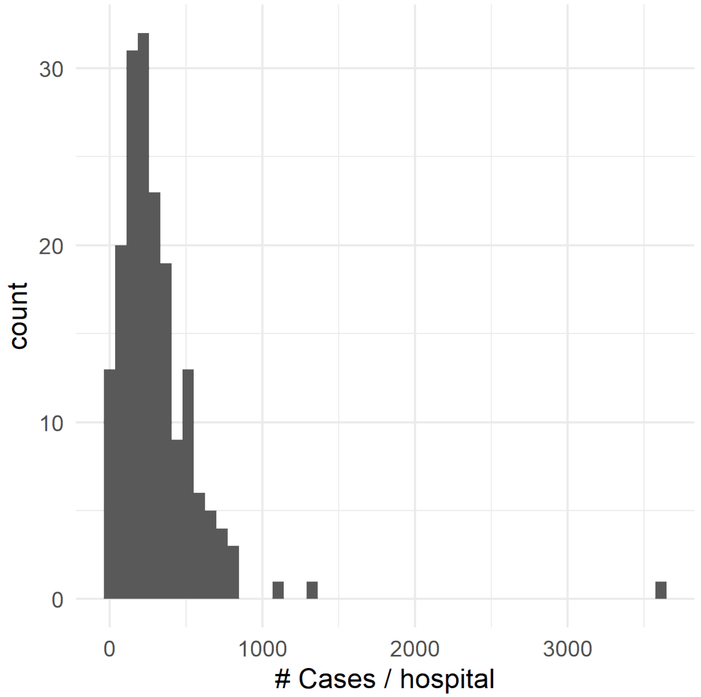
2. Include mortality as an adverse outcomes (332 cases)

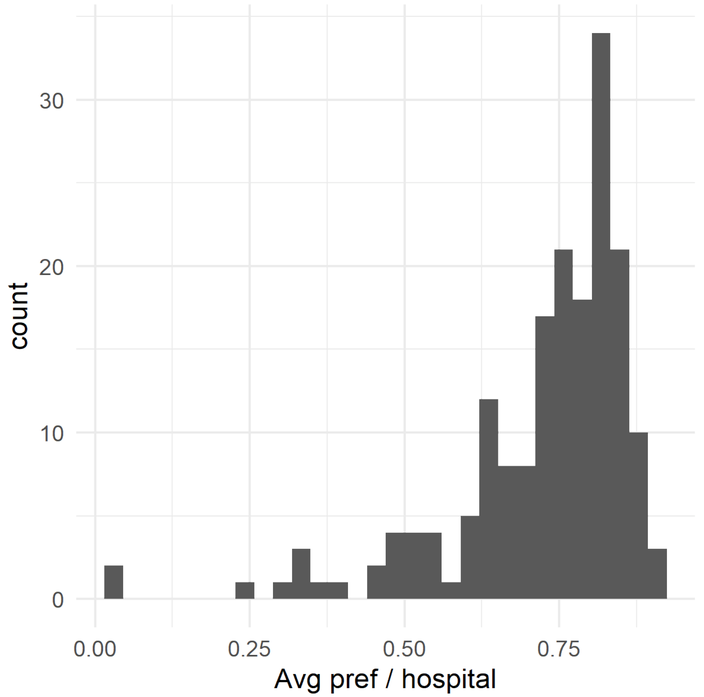
3. Together we have 5971 cases of adverse outcomes. (i.e., Prolonged LOS or mortality)

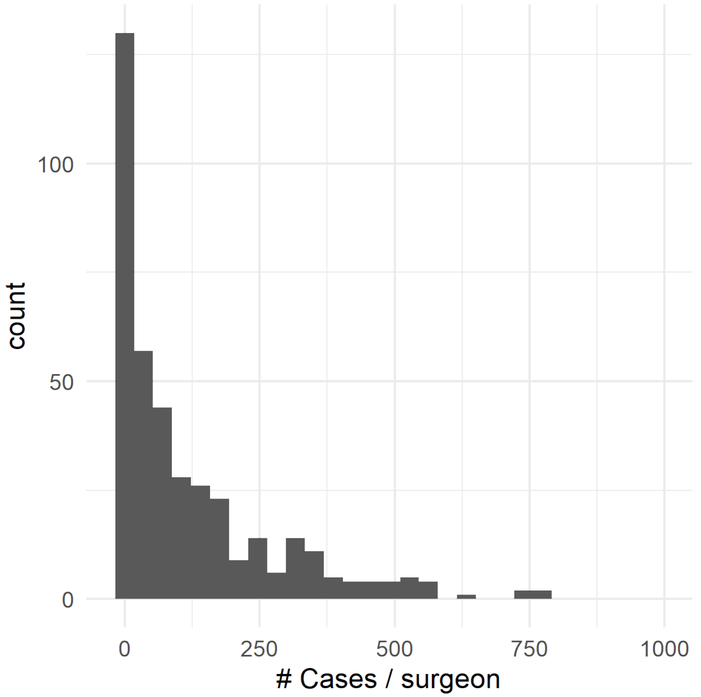
A.3 More description of the data

1. 181 unique hospitals and 397 unique surgeons.
2. IV strength varies between hospitals (approx 0.2~0.9)
3. Avg. preference per hospital varies (approx 0.03~0.90).
4. Covariates include 31 comorbidities based on Elixhauser indices, types of medical insurance, types of ethnicity (White, Black, Hispanic, and others), gender, the presence of sepsis, and disabilities. In addition to these binary variables, we also have the total number of comorbidities (count), the age of patients (continuous), and the surgeon's years of experience (continuous).

A.4 Cases per hospitals or surgeons







A.5 Definition of IVs

1. Relevance: $\mathbb{P}(A(1) = A(0)) \neq 1$
2. Exclusion restriction: $Y(z, a) = Y(a)$
3. Unconfounded IV: $Z \perp (A(z), Y(z)) \mid W$
4. Monotonicity: $\mathbb{P}(A(1) < A(0)) = 0$

A.6 Identification of LATE.

1. A valid IV (relevance, exclusion restriction, unconfounded IV)
2. **Monotonicity** (i.e., no defiers)
3. $0 < P(Z = 1 \mid W) < 1$ with prob. 1

$$E[Y(1) - Y(0) \mid \text{Complier}] = \frac{E[E[Y \mid Z = 1, W]] - E[E[Y \mid Z = 0, W]]}{E[E[A \mid Z = 1, W]] - E[E[A \mid Z = 0, W]]}$$

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Imbens and Angrist (1994)

$$E[Y(1) - Y(0) \mid \text{Complier}] = \frac{E[E[Y \mid Z = 1, W]] - E[E[Y \mid Z = 0, W]]}{E[E[A \mid Z = 1, W]] - E[E[A \mid Z = 0, W]]}$$

A.7 Identification of cond. LATE.

Let $V \subseteq W$ (the subset of covariates).

1. Valid IV* and 2. Monotonicity (i.e., no defiers).
   *Relevance needs to be strengthen.

3. $0 < P(Z = 1 \mid W) < 1$ with prob. 1.

Abadie (2003)

$$E_0[Y(1) - Y(0) \mid \text{Complier}, V = v]$$
$$= \frac{E_0[E_0[Y \mid Z = 1, W] \mid V = v] - E_0[E_0[Y \mid Z = 0, W] \mid V = v]}{E_0[E_0[A \mid Z = 1, W] \mid V = v] - E_0[E_0[A \mid Z = 0, W] \mid V = v]}$$

A.8 A nonparametric estimator of LATE.

$$\widehat{\psi_n} := \frac{n^{-1}\sum_{i=1}^{n}\phi_{n,1}(O_i;\widehat{\mu_n},\widehat{\pi_n})}{n^{-1}\sum_{i=1}^{n}\phi_{n,2}(O_i;\widehat{\lambda_n},\widehat{\pi_n})}$$

Where

$$\phi_{n,1}(O_i;\widehat{\mu_n},\widehat{\pi_n}) := \left\{\frac{Z_i}{\widehat{\pi_n}(W_i)} - \frac{1-Z_i}{1-\widehat{\pi_n}(W_i)}\right\}\left\{Y_i - \widehat{\mu_n}(Z_i,W_i)\right\} + \widehat{\mu_n}(1,W_i) - \widehat{\mu_n}(0,W_i)$$

$$\phi_{n,2}(O_i;\widehat{\lambda_n},\widehat{\pi_n}) := \left\{\frac{Z_i}{\widehat{\pi_n}(W_i)} - \frac{1-Z_i}{1-\widehat{\pi_n}(W_i)}\right\}\left\{A_i - \widehat{\lambda_n}(Z_i,W_i)\right\} + \widehat{\lambda_n}(1,W_i) - \widehat{\lambda_n}(0,W_i)$$

A.9 Delta method for influence functions.

We can combine multiple asymptotic linear estimators as follows:

$$
\begin{aligned}
& h\left(\widehat{\psi}_{n,1}, \widehat{\psi}_{n,2}\right) - h\left(\psi_{0,1}, \psi_{0,2}\right) \\
& \quad = \frac{1}{n} \sum_{i=1}^{n} \nabla h\left(\psi_{0,1}, \psi_{0,2}\right)^T \left[\phi^*_{0,1}(O_i), \phi^*_{0,2}(O_i)\right] + o_p(n^{-1/2}) \\
& \quad := \widetilde{\phi}^*_0(O_i)
\end{aligned}
$$

This is known as Delta method for influence functions.

We heavily use this property for $h(u, v) = u/v$.

A.10 Influence function for covariate profile

$$\mathbb{P}(I(V=v) \mid A(1) > A(0)) = \frac{E_0\left[I(V=v)\left\{E_0[A \mid Z=1,W] - E_0[A \mid Z=0,W]\right\}\right]}{E_0[E_0[A \mid Z=1,W] - E_0[A \mid Z=0,W]]}$$

$$\mathbb{P}(I(V=v) \mid A(1) = A(0) = 1) = \frac{E_0[I(V=v)E_0[A \mid Z=0,W]]}{E_0[E_0[A \mid Z=0,W]]}$$

$$\mathbb{P}(I(V=v) \mid A(1) = A(0) = 0) = \frac{E_0[I(V=v)E_0[A \mid Z=1,W]]}{E_0[E_0[A \mid Z=1,W]]}$$

A.11 Influence function for LATE.

$$\phi_1 := O \mapsto \left\{ \frac{Z}{\pi_0(W)} - \frac{1-Z}{1-\pi_0(W)} \right\} \left\{ Y - \mu_0(Z,W) \right\} + \mu_0(1,W) - \mu_0(0,W)$$

$$\phi_2 := O \mapsto \left\{ \frac{Z}{\pi_0(W)} - \frac{1-Z}{1-\pi_0(W)} \right\} \left\{ A - \lambda_0(Z,W) \right\} + \lambda_0(1,W) - \lambda_0(0,W)$$

$$\widetilde{\phi_0^*}(O;\mu_0,\lambda_0,\pi_0) := \frac{1}{\mathbb{E}_0[\phi_2(O)]} \left(\phi_1(O) - \psi_0 \phi_2(O) \right)$$

A simple consequence of Delta method

A.12 Nonparametric estimator for covariate profile

$$\phi_2 := O \mapsto \left\{ \frac{Z}{\pi_0(W)} - \frac{1-Z}{1-\pi_0(W)} \right\} \{A - \lambda_0(Z, W)\} + \lambda_0(1, W) - \lambda_0(0, W)$$

$$\frac{E_0\left[I(V=v)\{E_0[A \mid Z=1, W] - E_0[A \mid Z=0, W]\}\right]}{E_0[E_0[A \mid Z=1, W] - E_0[A \mid Z=0, W]]} = \frac{E_0 I(V=v)\phi_2(O)}{E_0\phi_2(O)}$$

A.13 Nonparametric estimator for covariate profile

$$\phi_2^{(0)} := O \mapsto \frac{1-Z}{1-\pi_0(W)} \left\{ A - \lambda_0(Z,W) \right\} + \lambda_0(0,W)$$

$$\frac{E_0[I(V=v)E_0[A \mid Z=0,W]]}{E_0[E_0[A \mid Z=0,W]]} = \frac{E_0 I(V=v)\phi_2^{(0)}(O)}{E_0 \phi_2^{(0)}(O)}$$

A.14 Nonparametric estimator for covariate profile

$$\phi_2^{(1)} := O \mapsto \frac{Z}{\pi_0(W)} \left\{ A - \lambda_0(Z, W) \right\} + \lambda_0(1, W)$$

$$\frac{E_0[I(V = v) E_0[A \mid Z = 1, W]]}{E_0[E_0[A \mid Z = 1, W]]} = \frac{E_0 I(V = v) \phi_2^{(1)}(O)}{E_0 \phi_2^{(1)}(O)}$$

A.15 Profiling with continuous RVs

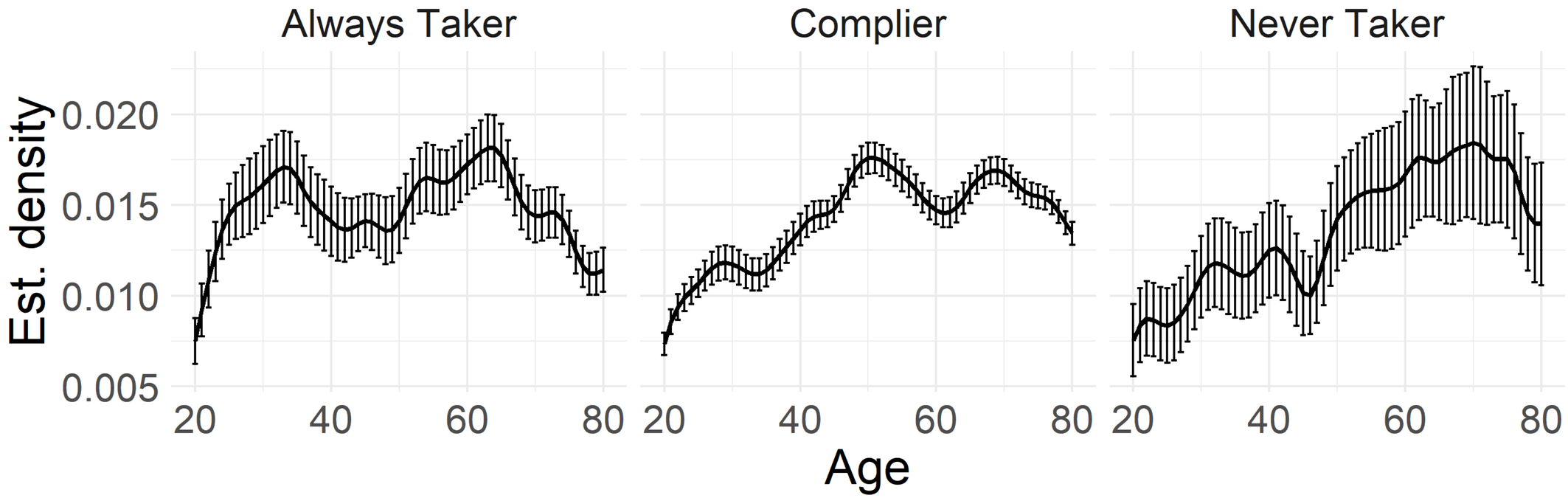

Fig: Estimated conditional density of age for each patient type. Vertical bars indicate pointwise 95% CIs.

A.16 An algorithm for LATE

Step 1: Use sample-splitting to construct machine learning estimators: $\widehat{\mu_n}$, $\widehat{\lambda_n}$, $\widehat{\pi_n}$.

Step 2: Plug-in to the (uncentered) influence functions: $\{\phi_{n,1}(O_i; \widehat{\mu_n}, \widehat{\pi_n})\}_{i=1}^n$ and $\{\phi_{n,2}(O_i; \widehat{\lambda_n}, \widehat{\pi_n})\}_{i=1}^n$.

Step 3: Return $\widehat{\psi_n} := \dfrac{n^{-1}\sum_{i=1}^n \phi_{n,1}(O_i; \widehat{\mu_n}, \widehat{\pi_n})}{n^{-1}\sum_{i=1}^n \phi_{n,2}(O_i; \widehat{\lambda_n}, \widehat{\pi_n})}$.

Step 4: 95%-CI is given by $\left[\widehat{\psi_n} \pm 1.96\sqrt{Var\,\widetilde{\phi}_n^*/n}\right]$ where $\widetilde{\phi}_n^*$ is an estimate of the influence function.

A.17 An algorithm for cond. LATE

Step 1: Use sample-splitting and construct machine learning estimators: $\widehat{\mu}_n$, $\widehat{\lambda}_n$, $\widehat{\pi}_n$.

Step 2: Plug-in to the (uncentered) influence functions: $\{\phi_{n,1}(O_i; \widehat{\mu}_n, \widehat{\pi}_n)\}_{i=1}^n$ and $\{\phi_{n,2}(O_i; \widehat{\lambda}_n, \widehat{\pi}_n)\}_{i=1}^n$.

Step 3: Regress $\{\phi_{n,1}(O_i; \widehat{\mu}_n, \widehat{\pi}_n)\}_{i=1}^n$ and $\{\phi_{n,2}(O_i; \widehat{\lambda}_n, \widehat{\pi}_n)\}_{i=1}^n$ on V using (nonparametric) regression.

Step 4: Return $\widehat{\psi}_n(v)$ as the estimates of $\dfrac{\widehat{E}_0[\phi_{n,1}(O) \mid V = v]}{\widehat{E}_0[\phi_{n,2}(O) \mid V = v]}$.

A.18 Properties of LATE estimator

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1. Our estimator is root-n consistent.

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$$n^{1/2}\left(\widehat{\psi_n} - \psi_0\right) \xrightarrow{d} N\left(0, Var\widetilde{\phi_0^*}(O; \mu_0, \lambda_0, \pi_0)\right)$$

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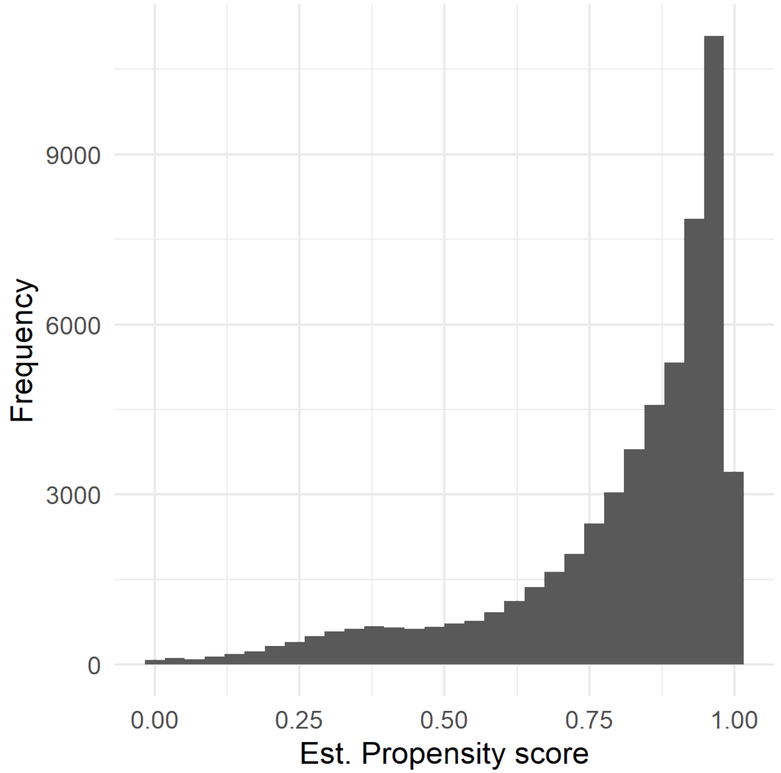
2. It possesses *double-robustness.*

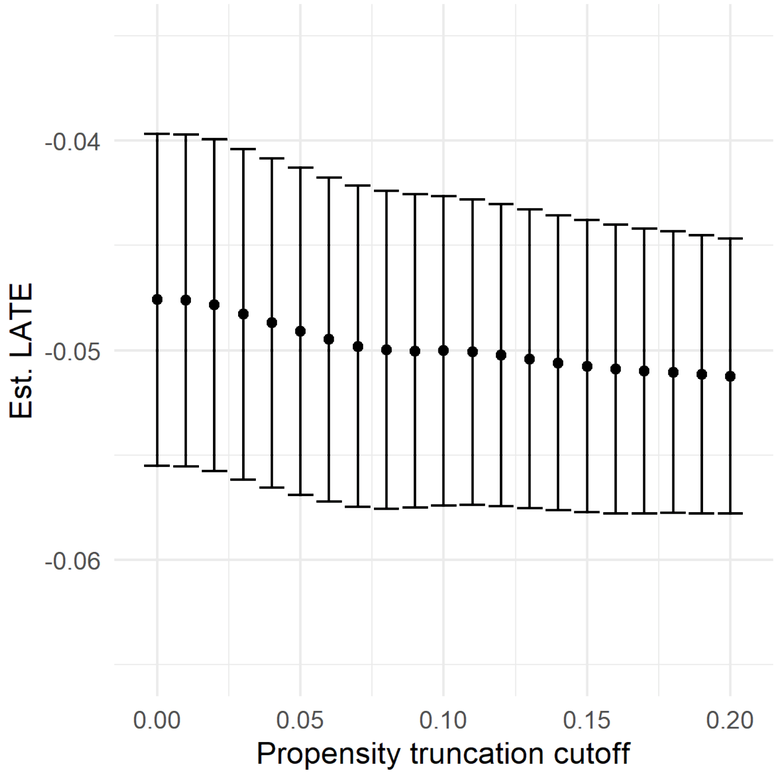
$\widehat{\psi_n}$ is root-n consistent if

$$\|\widehat{\pi_n} - \pi_0\|_2 \left(\|\widehat{\lambda_n} - \lambda_0\|_2 + \|\widehat{\mu_n} - \mu_0\|_2\right) = o_P(n^{-1/2})\,.$$

A.19 Positivity violation



Distribution of est. propensity scores



Est. LATE at different truncation values of propensity

A.20 F-test for relevance

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1. Regress A on Z and W
2. Regress A on constant and W
3. Perform F-test on the nested model

A.22 Exclusion restriction

$Y(0,a) \neq Y(1,a)$ where $Y(z,a)$ is POs for both IV and trt.

$$E[Y(1) - Y(0) \mid \text{Complier}] \in \left[\psi_0 - \frac{\delta_1\delta_2}{\delta_3}, \psi_0 + \frac{\delta_1\delta_2}{\delta_3}\right]$$

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$\delta_1 := 1 - P(\text{Complier})$

$\delta_2 := E[Y(1,a) - Y(0,a) \mid \text{Always taker} \cup \text{Never taker}]$

$\delta_3 := P(\text{Complier})$