Adjusting for bias introduced by instrumental variable estimation in the Cox proportional hazards models

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Overview

1. **Background/Introduction**
2. **Notation and Models**
3. **Proposed methodology**
4. **Monte Carlo simulations**
5. **Real world-application. The Vascular Quality Initiative dataset**
6. **Conclusions**

1. Background/Introduction (I)

In biomedical research is relevant to know the real [therapeutic] effect (average causal) of the procedures (treatments) on different type of outcomes [continuous, binary, time-to-event…]

Although, with this goal, randomized clinical trials (RCT) are the Gold Standard, they have some drawbacks

- Excessive patient selection [not dairy clinical practice]
- Complexity: expensive, logistic complications…
- Even, unethical.

1. Background/Introduction (II)

Observational studies (OS) are cheaper and depict the dairy clinical practice.

The presence of unmeasured confounders is the main handicap of estimations derived from OS.

In linear contexts, instrumental variable (IV) procedures have proved utility for dealing with unmeasured confounding in observational data and in RCTs with imperfect compliance.

1. Background/Introduction (III)

However, in **Cox proportional hazard models,** the capability of the existing IV procedures (particularly, 2SRI) for dealing with unmeasured confounders is unclear.

In practice,

1. There exists a number of large and valuable datasets with observational designs.
2. The use of the proportional hazard Cox regression models is overwhelming for reporting results from time-to-event outcomes.

1. Background/Introduction (IV)

Objective:

To study and improve the behavior of the 2SRI procedure in Cox proportional hazard (PH) regression models.

Motivation:

To estimate the impact on the mortality risk in carotid artery disease patients of the type of intervention: carotid endarterectomy [CEA] vs. carotid stenting [CAS] by using the data from the VQI registry.

2. Notation and models (I)

We have an standard right-censored framework:

1. $\{(t_i, \delta_i)\}_{i=1}^{N}$ [Sample, observed time]

Besides,

2. *X* [Treatment]
3. *Z* [Measured covariate]
4. *U, V* [Unmeasured covariates]
5. *W* [Instrument variable]

2. Notation and models (II)

The risk and the assignment models are:

Models

$$\lambda(t|X, \boldsymbol{Z}, \boldsymbol{U}) = \lambda_0(t) \cdot \exp\{\beta_X \cdot X + \boldsymbol{\beta}_Z^t \cdot \boldsymbol{Z} + \boldsymbol{\beta}_U^t \cdot \boldsymbol{U}\} \quad (1)$$

$$X = \alpha_0 + \boldsymbol{\alpha}_W^t \cdot \boldsymbol{W} + \boldsymbol{\alpha}_Z^t \cdot \boldsymbol{Z} + \boldsymbol{\alpha}_V^t \cdot \boldsymbol{V} + \epsilon \quad (2)$$

Our goal is to estimate $\boldsymbol{\beta}_X$.

2. Notation and models (III)

[If Y is the outcome] we assume:

C_1. $W \not\perp\!\!\!\perp (X|Z, U, V)$,

C_2. $W \perp\!\!\!\perp (Y|X, Z, U, V)$ (exclussion restriction assumption),

C_3. $W \perp\!\!\!\perp (V, U|Z)$ (randomization assumption).

2. Notation and models (IV)

That is (in words):

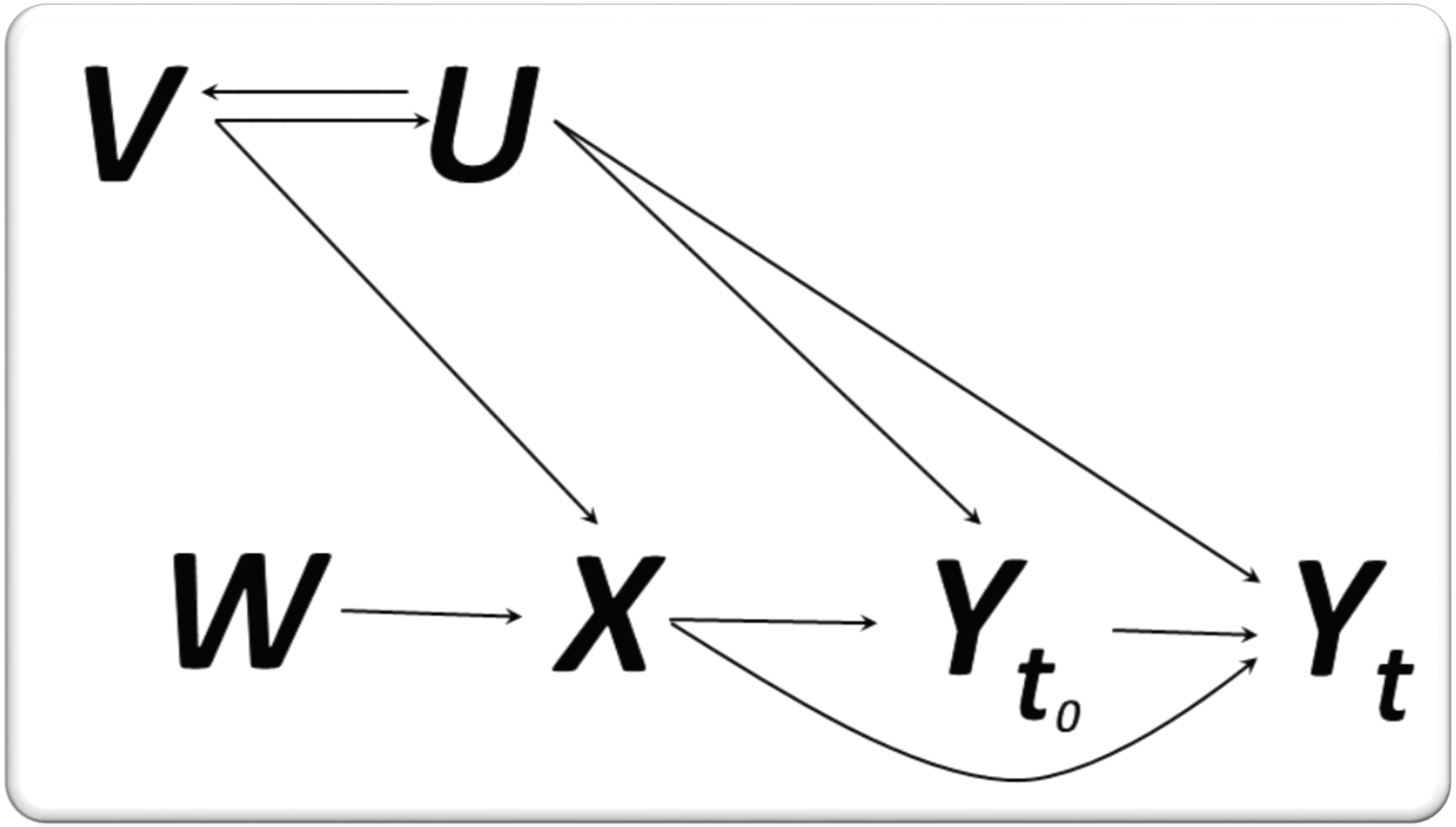
C_1. *W is related with X given Z, U and V.*

C_2. *W is independent of Y given X, Z, U and V.*

C_3. *W is independent of U and V given Z.*

2. Notation and models (V)

Figure 1. Directed acyclic graph, DAG, showing the unmeasured confounder *U*, treatment *X*, and the time-to-event outcome *Y* at t_0 and $t=t_0+e$, where *e* represents an arbitrarily small amount of time. If the independent variable *W* is related with Y_{t_0} and Y_t only through X, it is an instrumental variable.



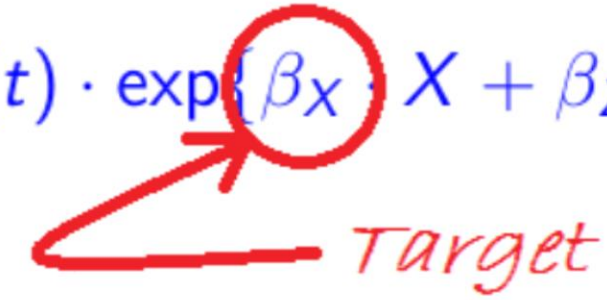
3. Proposed methodology (I)

First, we assume $V = \gamma_U \cdot U + \delta$, with $\delta \perp\!\!\!\perp U$. And then, the assigment treatment is

$$X = \alpha_0 + \alpha_W \cdot W + \alpha_Z \cdot Z + \alpha_U \cdot U + \epsilon + \delta.$$

Remember, the survival model is

$$\lambda(t|X, Z, U) = \lambda_0(t) \cdot \exp\{\beta_X \cdot X + \beta_Z \cdot Z + \beta_U \cdot U\}.$$



3. Proposed methodology (II)

2SRI method:

- Stage 1: Estimate

$$\hat{X} = \hat{\alpha}_0 + \hat{\alpha}_W \cdot W + \hat{\alpha}_Z \cdot Z,$$

and then,

$$\hat{R} = (\hat{X} - X)$$

$$= (\hat{\alpha}_0 - \alpha_0) + (\hat{\alpha}_W - \alpha_W) \cdot W + (\hat{\alpha}_Z - \alpha_Z) \cdot Z + \alpha_U \cdot U + \epsilon + \delta$$

0 (Hypothesis)

Who cares?

3. Proposed methodology (III)

- Stage 2: Estimate the model

$$\lambda(t|X,Z,R) = \lambda_0^*(t) \cdot \exp\{\beta_X^* \cdot X + \beta_Z^* \cdot Z + \beta_R \cdot R\}$$

Approximate the value of $\boldsymbol{\beta_X}$ by the estimation of $\boldsymbol{\beta_X^*}$

3. Proposed methodology (IV)

...Note that:

$$\mathcal{P}\{Y \geq t | X = x, U = u\} = \exp\{-\Lambda_0(t)\exp\{\beta_X \cdot x + \beta_U \cdot u\}\},$$

then the conditional distribution of the time-to-event given the exposure, X, and $R = X - \alpha_W \cdot W$ satisfies the Cox model with frailty term:

$$\begin{aligned}
&\mathcal{P}\{Y \geq t | X = x, R = r\} \\
&\quad = \mathcal{P}\{Y \geq t | X = x, \alpha_U \cdot U + \epsilon = r\} \\
&\quad = \mathbb{E}_\epsilon[\exp\{-\Lambda(t) \cdot \phi \cdot \exp\{\beta_X \cdot x + \beta_U \cdot \alpha_U^{-1} \cdot r\}\}]
\end{aligned}$$

where $\phi = \exp\{-\beta_U \cdot \alpha_U^{-1} \cdot \epsilon\}$ is the frailty term.

3. Proposed methodology (V)

We propose to include a univariate (parametric) frailty term in the second stage:

- Stage 2: Estimate the model

$$\lambda(t|X,Z,R) = \lambda_0(t) \cdot \phi \cdot \exp\{\beta_X \cdot X + \beta_Z^* \cdot Z + \beta_R \cdot R\}$$

Under the assumptions, the estimation of $\boldsymbol{\beta_X}$ is unbiased

4. Monte Carlo simulations (I)

First scenario:

Time: Weibull(1,2)

Expected censorship: 20%

Treatment model:

$$X = W + Z + U + \epsilon$$

$W \sim N(0,1)$

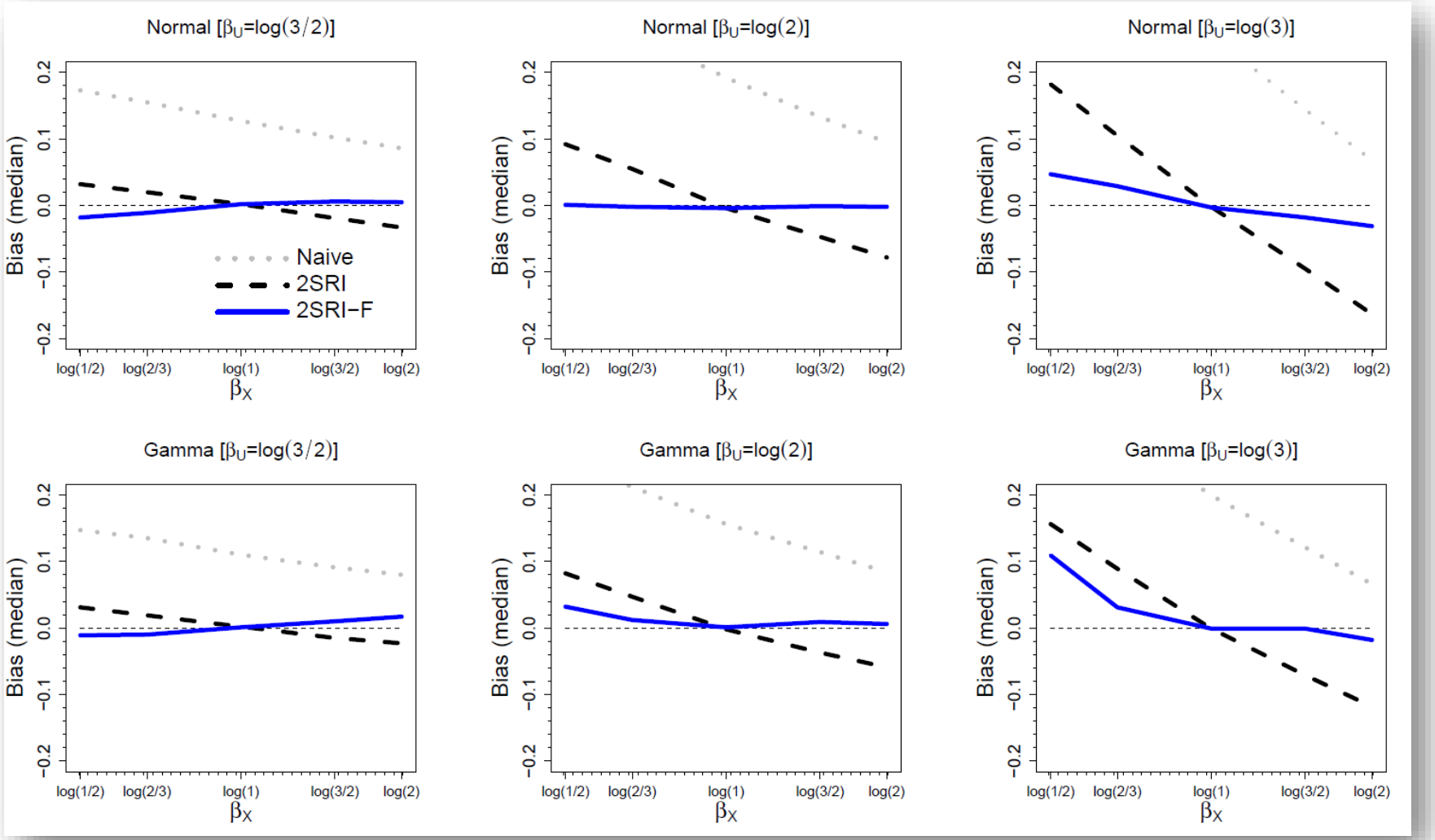
Z [measured] $\sim N(0,1)$

ϵ [unknown] $\sim N(0,1)$

U [unknown] $\sim N(0,1), \Gamma(1,1) - 1$

Survival model (risk):

$$\lambda(t) \cdot \exp\{\beta_X \cdot X + Z + \beta_U \cdot U\}$$



4. Monte Carlo simulations (II)

Second scenario:

Time: Weibull(1,2)

Expected censorship: 20%

Treatment model (binary):

$$X = I(W + Z + V + \epsilon > 0)$$

$W \sim N(0,1)$

Z [measured] $\sim N(0,1)$

ϵ [unknown] $\sim N(0,1)$

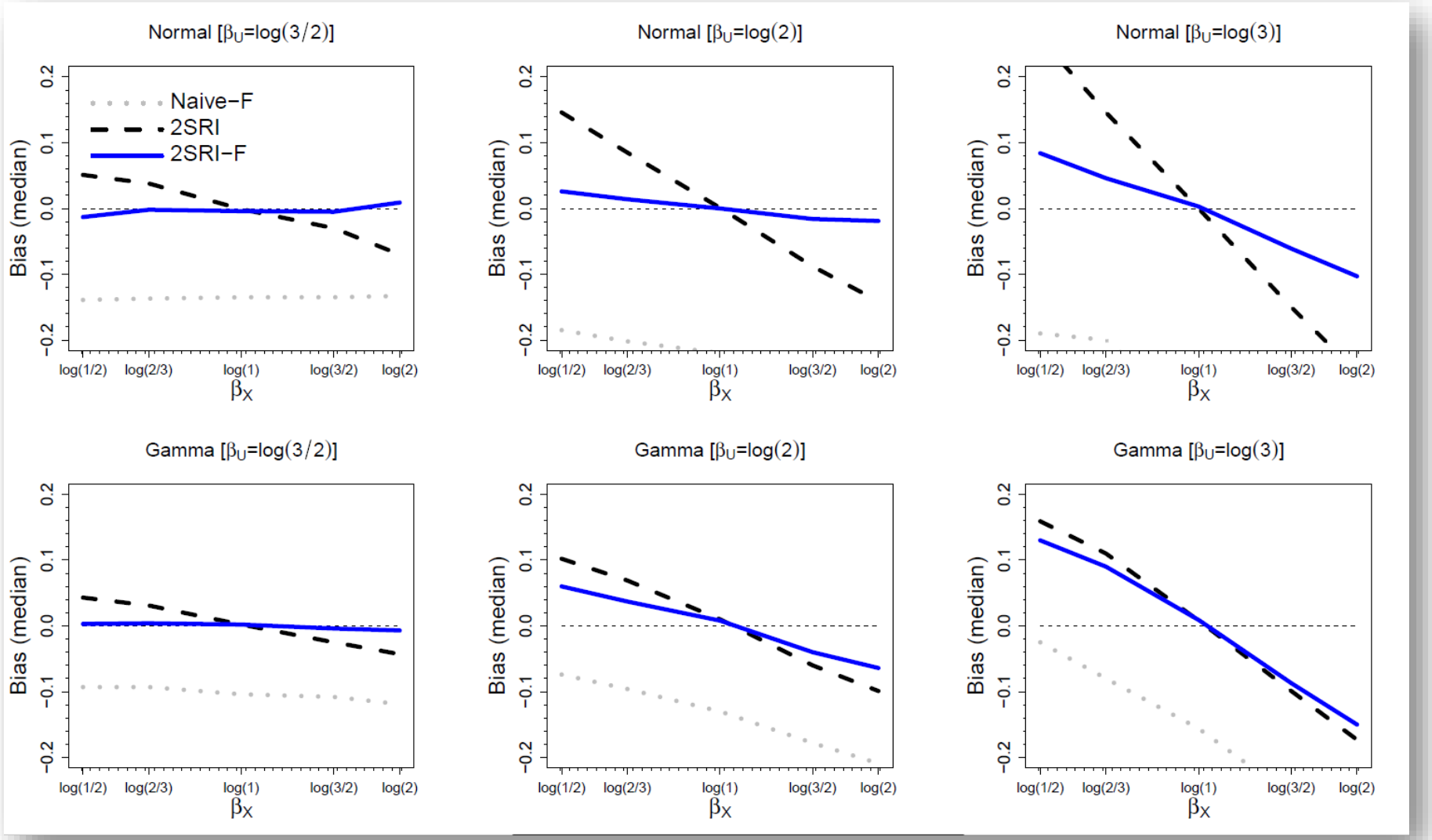
U [unknown] $\sim N(0,1), \Gamma(1,1) - 1$

V [unknown] $\sim N(0,1), \Gamma(1,1) - 1$

$$Cov(U, V) = 1/2$$

Survival model (risk):

$$\lambda(t) \cdot \exp\{\beta_X \cdot X + Z + \beta_U \cdot U\}$$



4. Monte Carlo simulations (III)

We conducted out more simulations in order to check the performance of the method under different situations:

- ✓Different covariance between *U* and *V*.
- ✓Different distributions for *U* (and *V*).
- ✓Different quality of the instrument variable.

4. Monte Carlo simulations (IV)

In general, results suggest,

1. The inclusion of the frailty term improve the results although do not remove “all” the bias (computational issue).
2. The procedure is robust respect to the frailty distributional shape.

5. Real-world application (I)

Objective:

Estimate the true therapeutic effect of endarterectomy (CEA) vs. carotid stenting (CAS) on all cause mortality of patients suffering from carotid artery disease using observational data

Data:

Vascular Quality Initiative (www.vascularqualityinitiative.org) and Medicare.

	CEA N=28,712	CAS N=8,117
Age	70.2±9.4	69.1±10.3
Gender, male	59.8%	63.1%

5. Real-world application (II)

In crude unadjusted analyses, CEA is much better (HR: 0.72, 95% CI (0.67-0.78)). However, CEA patients are also healthier and this likely contributes to unmeasured confounders. Adjusted HR: 0.69 (0.63-0.76).

What happen with unmeasured confounding?

5. Real-world application (III)

IV: The proportion of CEA performed in the hospital the 12-months (rolling window) before the current patient CEA/(CEA+CAS)

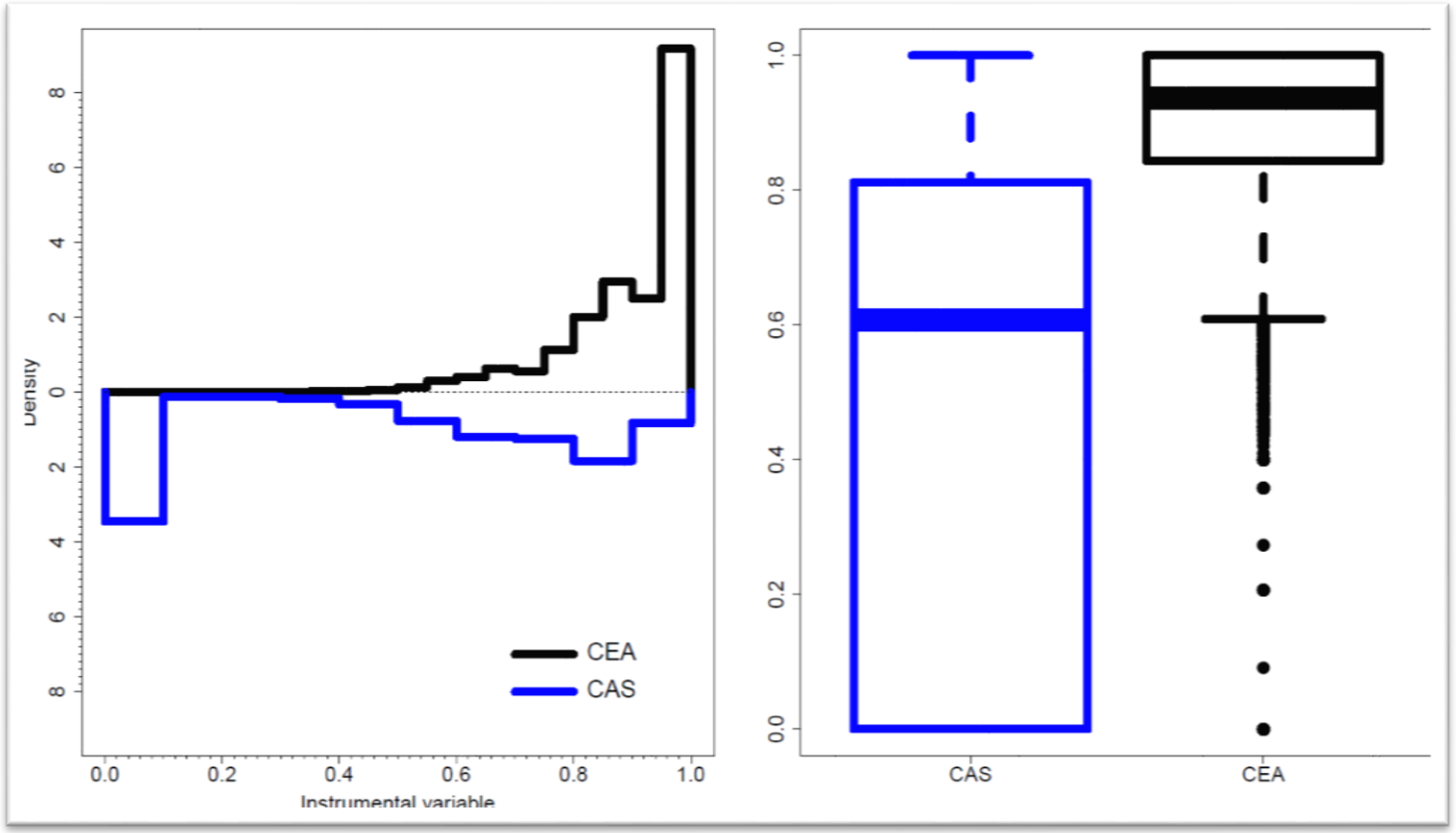


Figure 4. Histogram and box-plot for the instrumental variable by groups.

5. Real-world application (IV)

This IV seems reasonable,

1. It is independent of the patient characteristics [at least, the measured ones]
2. It seems that the patients survival should not depend on this variable conditioning by the received surgery.
3. The relationship with mortality is (just) through the received procedure.

5. Real-world application (V)

Table 1. HR and 95% confidence intervals for the different models.

	HR (95% CI)
Crude	0.72 (0.67-0.78)
Adjusted	0.69 (0.63-0.76)
2SRI	0.90 (0.74-1.00)
2SRI-F (Gaussian)	0.89 (0.72-1.09)
2SRI-F (Gamma)	0.88 (0.72-1.09)

5. Real-world application (VI)

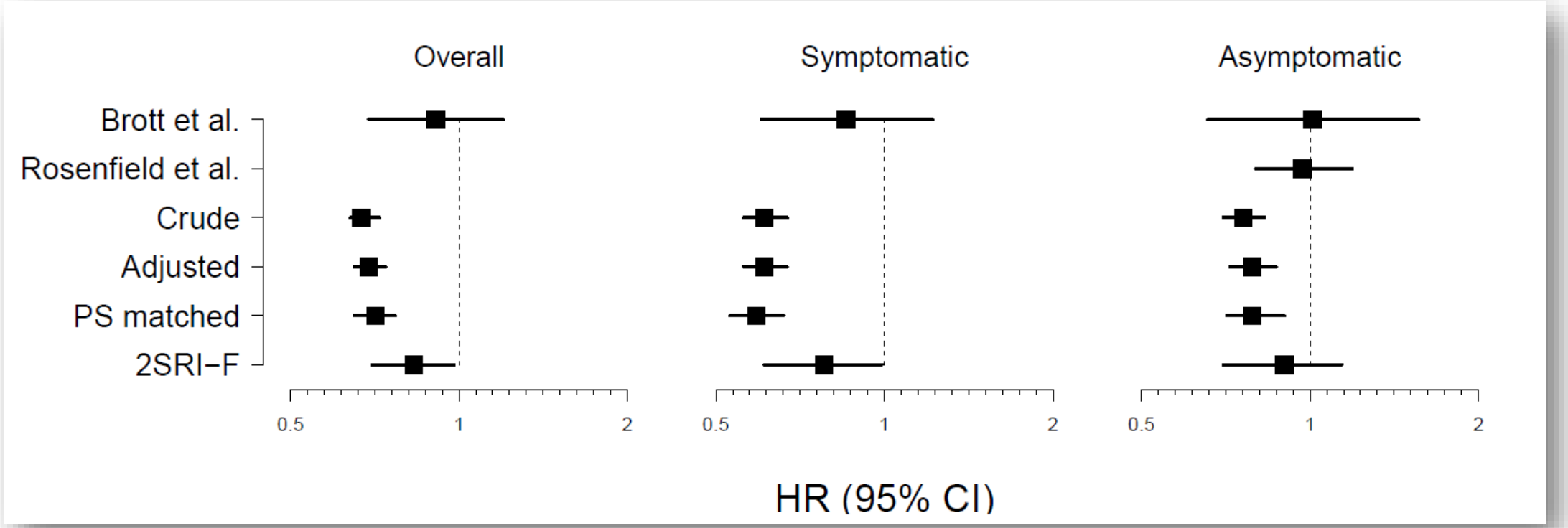


Figure 5. HRs for two RCT, unadjusted, adjusted and propensity score matched HRs and 2SRI-F for the overall sample and in two different subgroups.

6. Conclusions (I)

The estimation provided by the proposed procedure, 2SRI-F, is:

1. Unbiased under theoretical assumptions
2. Robust respect the frailty distributional assumption
3. Better than the 2SRI (without “F”).
4. Observed real results suggest good compliance between 2SRI-F and RCT.

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Thanks for the attention!

Questions?