Outcome

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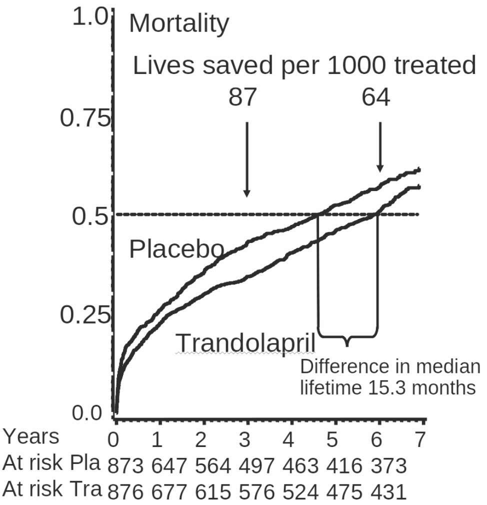
November 26, 2022

TRACE study - Hazard Ratio 0.78



Lancet 1999

Risk in observation study

Influence of Gender on Short- and Long-Term Mortality After Acute Myocardial Infarction

Lars Køber, MD, Christian Torp-Pedersen, MD, Michael Ottesen, MD, Susanne Rasmussen, MD, Mads Lessing, MD, and Knud Skagen, MD, on behalf of the TRACE study group

The aim of this study was to assess differences in short- and long-term mortality between male and female patients with acute myocardial infarction (AMI). The study population consisted of 6,676 consecutive patients admitted alive with an enzyme-confirmed AMI to 27 Danish hospitals from 1990 to 1992. Five patients were excluded because of missing information. Female patients (n = 2,170) were on average 5 years older than male patients (n = 4,501, p <0.001), had lower body mass index, and more often had diabetes, hypertension, and congestive heart failure. Left ventricular systolic function was the same for men and women. Women received thrombolytic therapy less often. The 1-year mortality for female patients was 28 ± 1% and for men 21 ± 1% (p <0.001). The unadjusted risk ratio associated with male gender in a proportional-hazards model was 0.76 (95% confidence intervals [CI] 0.70 to 0.83). Adjustment for age removed the importance of gender, and the risk ratio associated with male gender was 1.06 (95% CI 0.97 to 1.2, p = 0.2). An introduction of further variables in the model did not change this. Subdividing mortality into 6-day, 30-day, and late mortality demonstrated a significantly increased mortality in women in the short-term (6 and 30 days), with a risk ratio in men of 0.58 (95% CI 0.42 to 0.81) and 0.80 (95% CI 0.65 to 0.99), respectively. From day 30 onward there was an increased mortality in men with a risk ratio of 1.16 (95% CI 1.03 to 1.31, p = 0.01). Thus, women admitted alive to the hospital with an AMI have an increased long-term mortality that is explained by their older age. However, short-term mortality in women seems to increase independently of other risk factors, but is later followed by an increase in mortality in men.

(Am J Cardiol 1996;77:1052–1056)

Køber, Am.J.Cardiology 1996

TABLE I Patient Characteristics

Parameter	Women (n = 2,170)	Men (n = 4,501)	p Value
Age (yr)	72 (51–86)	67 (45–82)	<0.001
Body mass index	25 (18–33)	26 (21–32)	<0.001
Wall motion index	1.4 (0.8–2)	1.4 (0.7–2)	0.08
Creatinine (µmol/L)	91	102	<0.001
Max. CKB/CK-MB	49 (13–227)	53 (14–226)	0.003
Current smoker	44%	55%	<0.001
Angina	38%	36%	0.39
Previous AMI	19%	25%	<0.001
Diabetes mellitus	14%	9.3%	<0.001
Systemic hypertension (history)	28%	20%	<0.001
Electrocardiogram			0.13
Normal	12%	13%	
Non–Q-wave AMI	21%	20%	
Anterior Q-wave AMI	26%	26%	
Inferior Q-wave AMI	29%	32%	
Initial symptoms			0.001
Chest pain	65%	69%	
Dyspnea	6%	5%	
Dyspnea and chest pain	21%	20%	
Other symptoms	7%	5%	
Congestive heart failure	60%	50%	<0.001
Ventricular fibrillation	7.3%	7.1%	0.12
Delay from symptom to hospitalization	3.5 (0–48)	2.8 (0–38)	<0.001
Thrombolytic therapy	34%	44%	<0.001

AMI = acute myocardial infarction; CK = creatinine kinase.

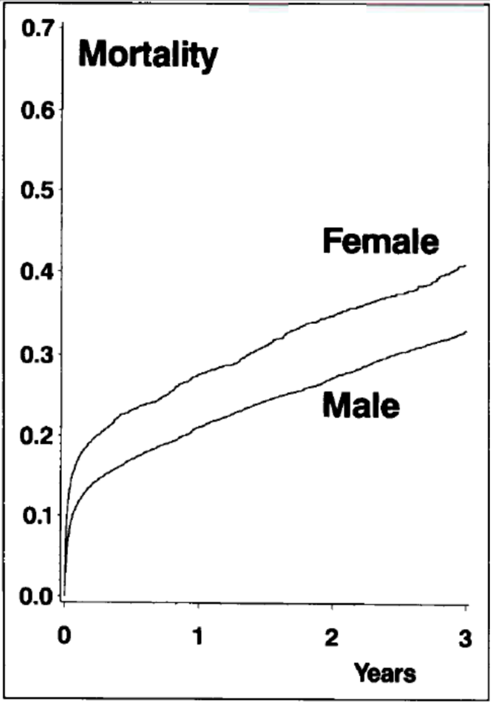

Mortality
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Female
Male
0
1
2
3
Years

TABLE III Three Proportional-Hazards Models of Total Survival with Stepwise Addition of Variables

Variables	p Value	Risk Ratio	95% CI
	Model 1		
Male gender	<0.001	0.76	0.70–0.83
	Model 2		
Male gender	0.20	1.06	0.97–1.15
Age	<0.001	1.07	1.06–1.07
	Model 3		
Male gender	0.75	1.06	0.96–1.17
Body mass index	0.07	0.99	0.98–1.0
Previous AMI	0.77	1.0	0.9–1.1
Angina pectoris	0.001	1.2	1.1–1.3
Creatinine	<0.001	1.002	1.002–1.003
Congestive heart failure	<0.001	2.3	2.0–2.6
Diabetes mellitus	<0.001	1.3	1.1–1.4
Age	<0.001	1.04	1.04–1.05
Wall motion index	<0.001	2.5	2.3–2.8
Systemic hypertension	0.006	1.2	1.1–1.3
Thrombolytic therapy	<0.001	0.7	0.6–0.8

AMI = acute myocardial infarction; CI = confidence interval.

Counterfactual

Causal Inference

- Display causal consequences in observational studies
- Display observtional studies similar to randomised studies

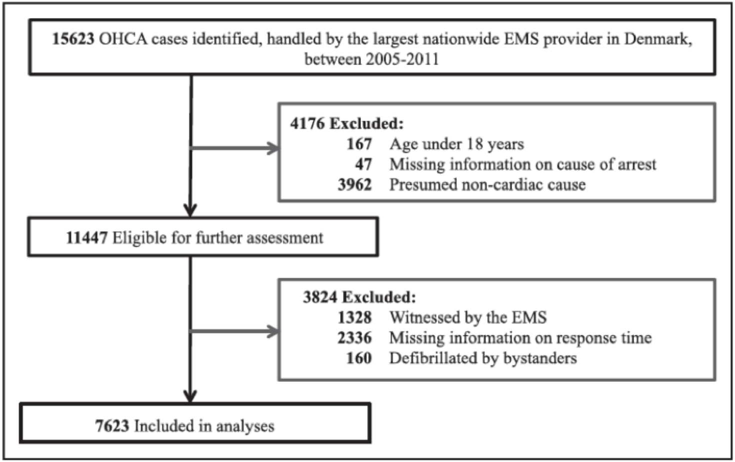
Causal assumptions

- Exchangeability
- Consistency
- Positivity

Practical options

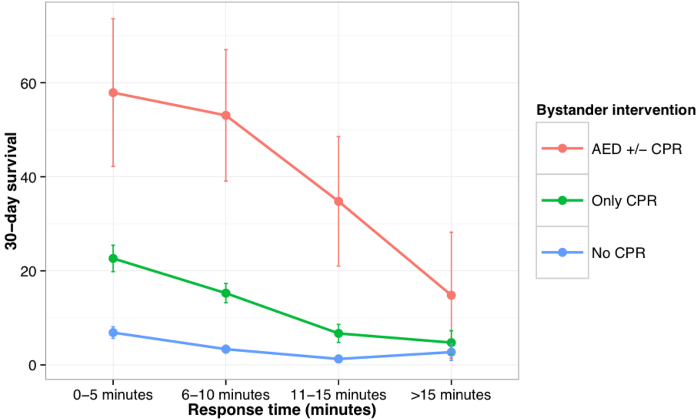
- g-model
- Propensity matching
- Inverse Probability Weighting
- Double Robust Methods

Is CPR important in cardiac arrest

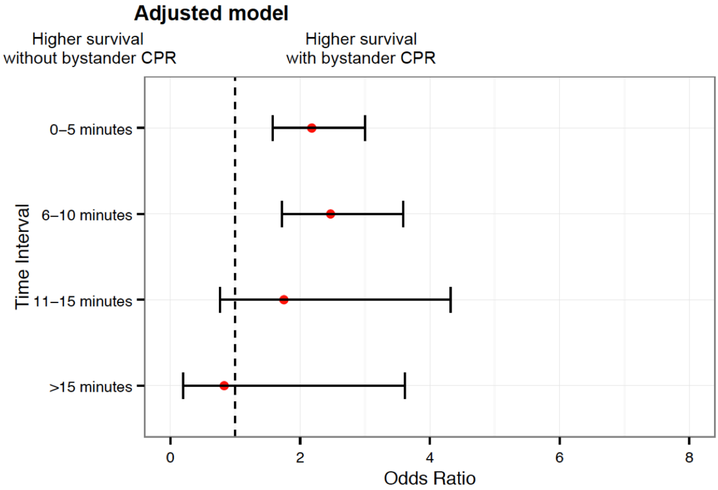


Rajan, Circulation 2016

Crude survival by time



Adjusted logistic regression

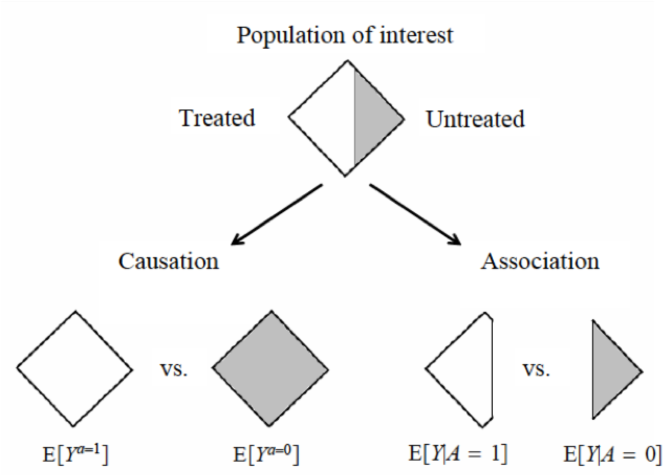


The model!

$$\log(\frac{p}{1-p}) = \beta_0 + \beta_1 sex + \beta_2 * age + \beta_3 * CPR + RCS(\beta_4 * time)$$

$$p = \frac{e^{\beta_0 + \beta_1 sex + \beta_2 * age + \beta_3 * CPR + RCS(\beta_4 * time)}}{1 + e^{\beta_0 + \beta_1 sex + \beta_2 * age + \beta_3 * CPR + RCS(\beta_4 * time)}}$$

G-model versus association



Herman Robins: Causal Inference

Modelling

$$\log(\frac{p}{1-p}) = \beta_0 + \beta_1 sex + \beta_2 * age + \beta_3 * CPR + RCS(\beta_4 * time)$$

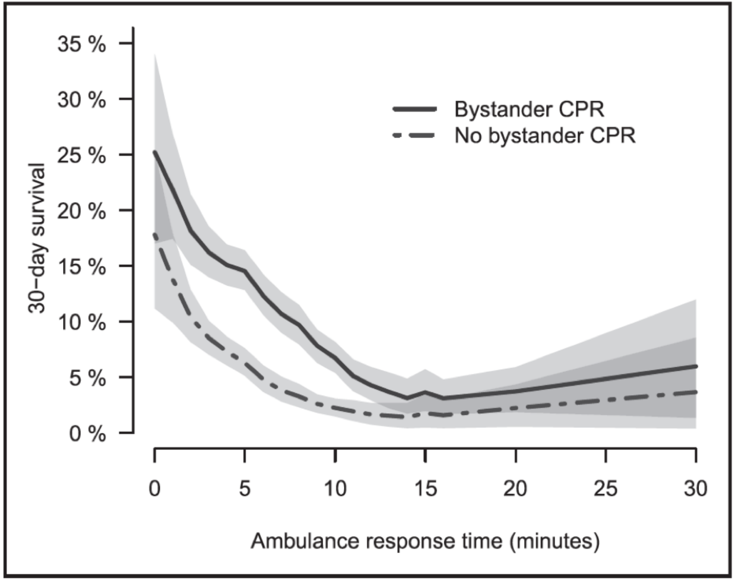
$$p = \frac{e^{\beta_0 + \beta_1 sex + \beta_2 * age + \beta_3 * CPR + \beta_4 * time}}{1 + e^{\beta_0 + \beta_1 sex + \beta_2 * age + \beta_3 * CPR + \beta_4 * time}}$$

```
fit <- glm(Surv30~sex+age+CPR+RCS(time),data=data,
    family=binomial(link=logit))
pred <- predictStatusProb(fit,newdata=data)
```

G-model

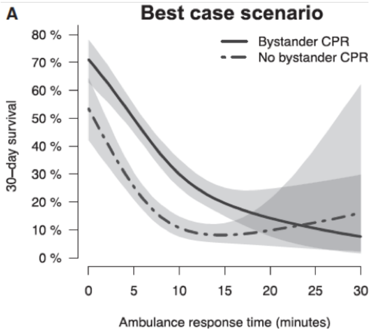
- Make 2 copies of the data
- Set CPR to 0 in one and 1 in the other
- Make predictions for each dataset
- Plot means for each dataset and each time
- Make 1000 bootstraps of the original dataset
- Repeat prediction as above
- find 5/95 percentiles from bootstraps

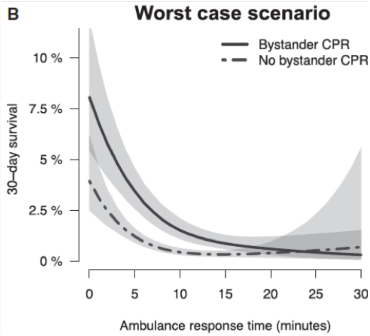
G-model



35 %
30 %
25 %
20 %
15 %
10 %
5 %
0 %
30−day survival
Bystander CPR
No bystander CPR
0
5
10
15
20
25
30
Ambulance response time (minutes)

Extreme cases





Age<65, no comorbidity

Age $\leq$ 65, $\geq$ 1 comorbidity

Smoking is good for you??

TRACE screening data[1]

- 6600 patients with AMI 1990-1992
- Follow up - 15 years
- 4000 cases with selected data and complete cases

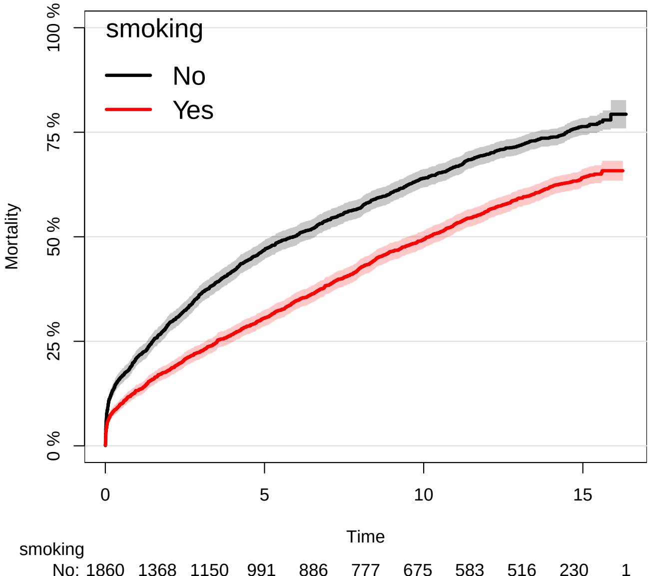
[1] European Heart Journal (2005) 26, 145–152

Survival by smoking - syntax

```
fit <- prodlim(Hist(lifetime,status)~smoking,data=
    smoke)
plot(fit,type="cuminc")

# tip: Plotting options findes med:
help(plot.prodlim)
```

Survival by smoking



Descriptives by smoking - syntax

```
tab1 <- summary(univariateTable(smoking~DIGOX+ACE+
    killip+nyha+
    diur+sex+age+cereb_hx+TAMI+WMI,
    data=smoke,na.rm=TRUE,
    freq.format="count(x) (colpercent(x))"))
publish(tab1,org=TRUE)
```

Descriptives by smoking

Variable	Level	No (n=1860)	Yes (n=2200)	Total (n=4060)	p-value
DIGOX	No	1445 (77.7)	1947 (88.5)	3392 (83.5)	
	Yes	415 (22.3)	253 (11.5)	668 (16.5)	< 1e-04
ACE	No	1668 (89.7)	2067 (94.0)	3735 (92.0)	
	Yes	192 (10.3)	133 (6.0)	325 (8.0)	< 1e-04
killip	1	1521 (81.8)	1945 (88.4)	3466 (85.4)	
	2	253 (13.6)	195 (8.9)	448 (11.0)	
	3	25 (1.3)	23 (1.0)	48 (1.2)	
	4	61 (3.3)	37 (1.7)	98 (2.4)	< 1e-04
nyha	1	1091 (58.7)	1488 (67.6)	2579 (63.5)	
	2	559 (30.1)	564 (25.6)	1123 (27.7)	
	3	92 (4.9)	62 (2.8)	154 (3.8)	
	4	118 (6.3)	86 (3.9)	204 (5.0)	< 1e-04
diur	No	981 (52.7)	1529 (69.5)	2510 (61.8)	
	Yes	879 (47.3)	671 (30.5)	1550 (38.2)	< 1e-04
sex	Female	716 (38.5)	620 (28.2)	1336 (32.9)	
	Male	1144 (61.5)	1580 (71.8)	2724 (67.1)	< 1e-04
age	mean (sd)	70.6 (10.7)	62.5 (11.5)	66.2 (11.9)	< 1e-04
$cereb_{hx}$	No	1691 (90.9)	2074 (94.3)	3765 (92.7)	
	Yes	169 (9.1)	126 (5.7)	295 (7.3)	< 1e-04
TAMI	No	1388 (74.6)	1872 (85.1)	3260 (80.3)	
	Yes	472 (25.4)	328 (14.9)	800 (19.7)	< 1e-04
WMI	mean (sd)	1.5 (0.4)	1.6 (0.3)	1.6 (0.4)	< 1e-04

Old fashioned Cox - syntax

```
fit <- coxph(Surv(lifetime,status)~smoking+DIGOX+ACE+
       killip+nyha+diur+sex+age+ cereb_hx+TAMI+WMI,
       data=smoke)
fit <- regressionTable(fit)
plot(fit)
```

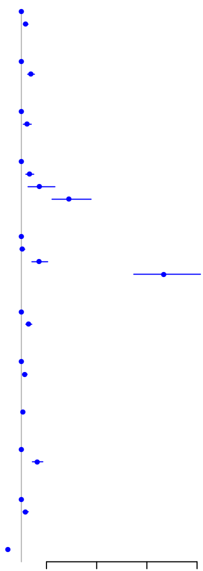
$$h(t) = \lim_{\delta t \to 0} \frac{\text{Observed deaths in}[t, t+\delta t]/N(t)}{\delta t}$$

$$h(t) = h_0(t) e^{smoking\beta 1 + sex\beta_2 + age\beta_3 \ldots\ldots}$$

$$hr_{smoking} = e^{\beta_1}$$

Old fashioned Cox

V1	Estimate (CI_{95})
smoking	
No	1.00 (1.00−1.00)
Yes	1.17 (1.08−1.27)
DIGOX	
No	1.00 (1.00−1.00)
Yes	1.38 (1.25−1.52)
ACE	
No	1.00 (1.00−1.00)
Yes	1.22 (1.08−1.40)
killip	
1	1.00 (1.00−1.00)
2	1.33 (1.18−1.49)
3	1.72 (1.26−2.34)
4	2.90 (2.22−3.78)
nyha	
1	1.00 (1.00−1.00)
2	1.04 (0.95−1.14)
3	1.70 (1.42−2.05)
4	6.68 (5.48−8.14)
diur	
No	1.00 (1.00−1.00)
Yes	1.29 (1.18−1.42)
sex	
Female	1.00 (1.00−1.00)
Male	1.13 (1.05−1.23)
age	
1 unit	1.06 (1.06−1.07)
cereb_hx	
No	1.00 (1.00−1.00)
Yes	1.63 (1.44−1.86)
TAMI	
No	1.00 (1.00−1.00)
Yes	1.16 (1.06−1.28)
WMI	
1 unit	0.46 (0.41−0.52)



Propensity stratification / matching

- Propensity is probability of smoking
- In propensity stratification analysis is stratified by multiple strata of this propensity to ensure that survival is compared for individual with similar propensity of smoking
- In propensity matching cases are matched with control that have similar probability of smoking. If it works nicely there is apparently a controlled trial.

Propensity matching - syntax - naive

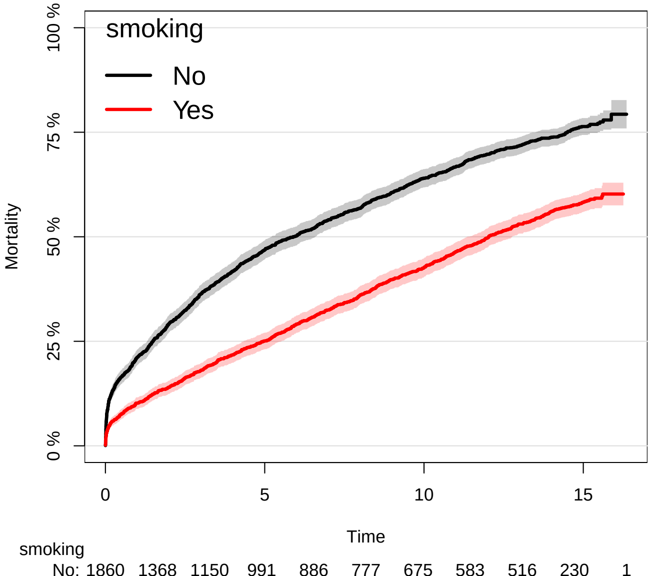
$$\text{Propensity}_{\text{smoking}} = P(\text{smoking}|\text{sex}, \text{age}, \dots)$$

Propensity score matching sensible if

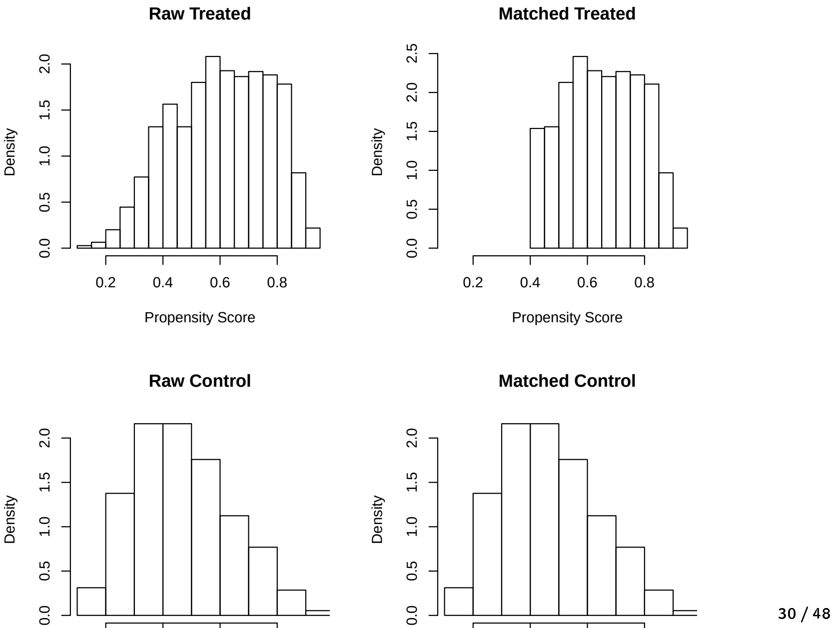
- Exchangeability conditioned on propensity
- Practically: The covariates must predict smoking

```
m.smoke = matchit(smokingn~DIGOX+ACE+killip+
    nyha+diur+sex+age+cereb_hx+TAMI+WMI,
    data = smoke, method = "nearest",
    distance="logit",ratio = 1)
smoke.m <- match.data(m.smoke)
```

Propensity matching



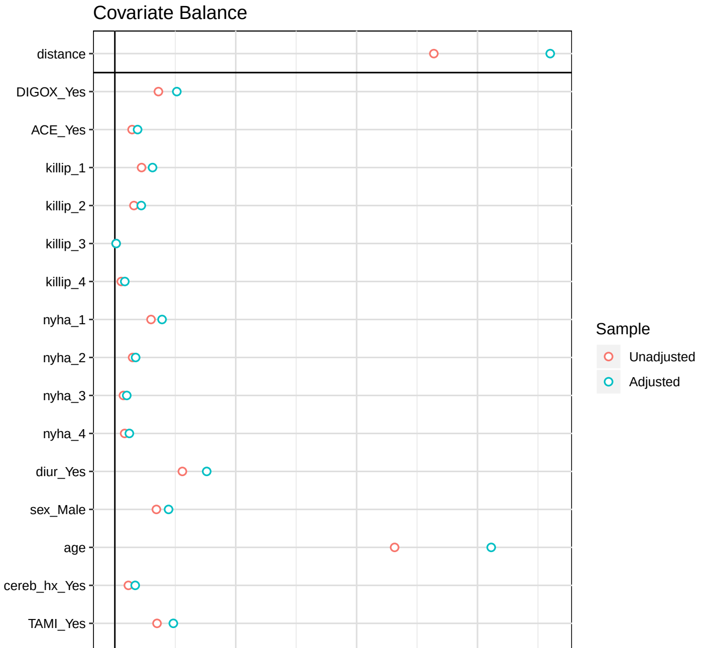
Propensity plot



Descriptives by propensity

Variable	Level	No (n=1860)	Yes (n=1860)	Total (n=3720)	p-value
DIGOX	No	1445 (77.7)	1731 (93.1)	3176 (85.4)	
	Yes	415 (22.3)	129 (6.9)	544 (14.6)	< 1e-04
ACE	No	1668 (89.7)	1773 (95.3)	3441 (92.5)	
	Yes	192 (10.3)	87 (4.7)	279 (7.5)	< 1e-04
killip	1	1521 (81.8)	1695 (91.1)	3216 (86.5)	
	2	253 (13.6)	131 (7.0)	384 (10.3)	
	3	25 (1.3)	19 (1.0)	44 (1.2)	
	4	61 (3.3)	15 (0.8)	76 (2.0)	< 1e-04
nyha	1	1091 (58.7)	1309 (70.4)	2400 (64.5)	
	2	559 (30.1)	463 (24.9)	1022 (27.5)	
	3	92 (4.9)	37 (2.0)	129 (3.5)	
	4	118 (6.3)	51 (2.7)	169 (4.5)	< 1e-04
diur	No	981 (52.7)	1405 (75.5)	2386 (64.1)	
	Yes	879 (47.3)	455 (24.5)	1334 (35.9)	< 1e-04
sex	Female	716 (38.5)	468 (25.2)	1184 (31.8)	
	Male	1144 (61.5)	1392 (74.8)	2536 (68.2)	< 1e-04
age	mean (sd)	70.6 (10.7)	59.8 (10.1)	65.2 (11.7)	< 1e-04
cereb_{hx}	No	1691 (90.9)	1785 (96.0)	3476 (93.4)	
	Yes	169 (9.1)	75 (4.0)	244 (6.6)	< 1e-04
TAMI	No	1388 (74.6)	1658 (89.1)	3046 (81.9)	
	Yes	472 (25.4)	202 (10.9)	674 (18.1)	< 1e-04
WMI	mean (sd)	1.5 (0.4)	1.6 (0.3)	1.6 (0.3)	< 1e-04

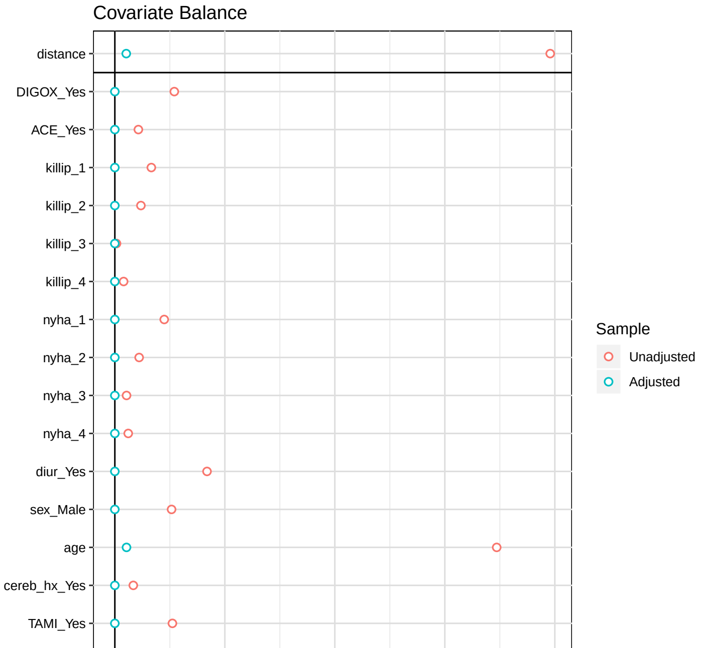
Love plot


Covariate Balance
distance
DIGOX_Yes
ACE_Yes
killip_1
killip_2
killip_3
killip_4
nyha_1
nyha_2
nyha_3
nyha_4
diur_Yes
sex_Male
age
cereb_hx_Yes
TAMI_Yes
Sample
Unadjusted
Adjusted

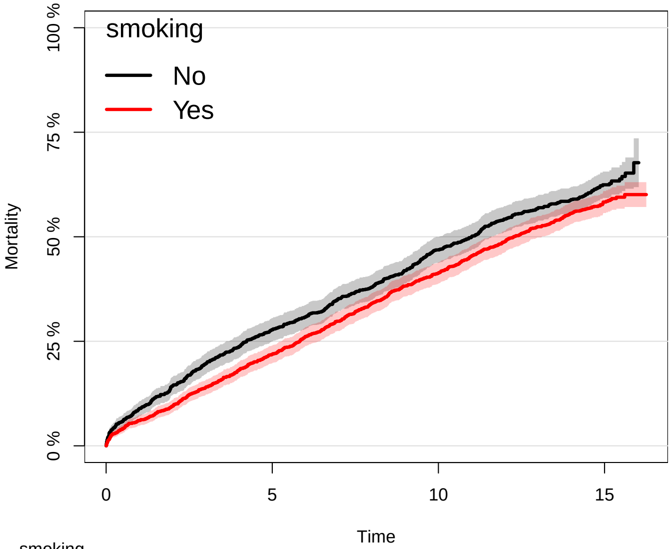
Another matching - course exact matching

```
m2.smoke = matchit(smokingn~DIGOX+ACE+killip+nyha+diur
    +sex+age+
     cereb_hx+TAMI+WMI, data = smoke, method = "cem")
smoke.m2 <- match.data(m2.smoke)
love.plot(bal.tab(m2.smoke))
```

Course Exact Matching



Survival by CEM-matching

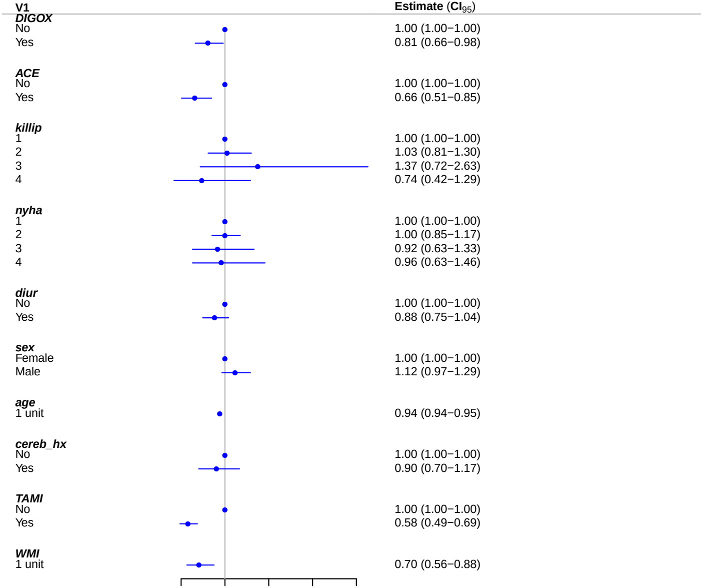


smoking
No: 1001 876 788 722 671 606 534 473 426 220 0

Descriptives by CEM

Variable	Level	No (n=1001)	Yes (n=1462)	Total (n=2463)	p-value
DIGOX	No	927 (92.6)	1396 (95.5)	2323 (94.3)	
	Yes	74 (7.4)	66 (4.5)	140 (5.7)	0.0032658
ACE	No	991 (99.0)	1449 (99.1)	2440 (99.1)	
	Yes	10 (1.0)	13 (0.9)	23 (0.9)	0.9481526
killip	1	969 (96.8)	1428 (97.7)	2397 (97.3)	
	2	29 (2.9)	32 (2.2)	61 (2.5)	
	3	0 (0.0)	0 (0.0)	0 (0.0)	
	4	3 (0.3)	2 (0.1)	5 (0.2)	NA
nyha	1	770 (76.9)	1174 (80.3)	1944 (78.9)	
	2	223 (22.3)	281 (19.2)	504 (20.5)	
	3	4 (0.4)	4 (0.3)	8 (0.3)	
	4	4 (0.4)	3 (0.2)	7 (0.3)	0.1989648
diur	No	768 (76.7)	1210 (82.8)	1978 (80.3)	
	Yes	233 (23.3)	252 (17.2)	485 (19.7)	0.0002614
sex	Female	281 (28.1)	359 (24.6)	640 (26.0)	
	Male	720 (71.9)	1103 (75.4)	1823 (74.0)	0.0564162
age	mean (sd)	67.2 (10.4)	62.2 (10.9)	64.2 (11.0)	$< 1e-04$
$cereb_{hx}$	No	983 (98.2)	1443 (98.7)	2426 (98.5)	
	Yes	18 (1.8)	19 (1.3)	37 (1.5)	0.4062322
TAMI	No	862 (86.1)	1317 (90.1)	2179 (88.5)	
	Yes	139 (13.9)	145 (9.9)	284 (11.5)	0.0030339
WMI	mean (sd)	1.7 (0.2)	1.7 (0.2)	1.7 (0.2)	0.9361005

Determinants of smoking

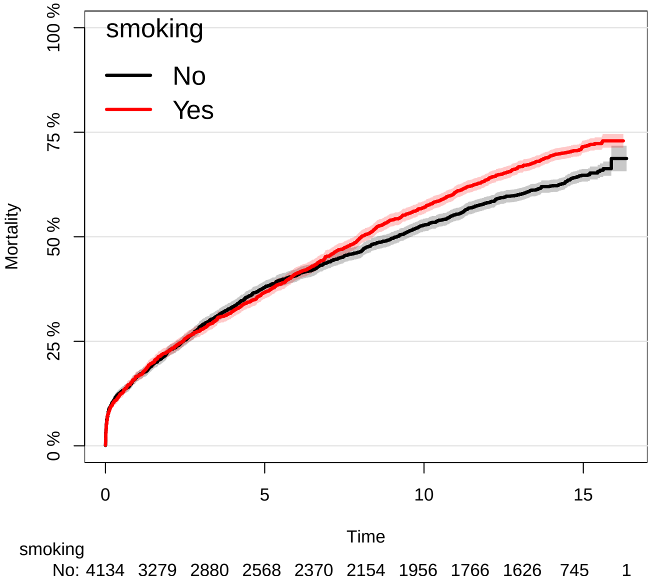


Inverse probability score - syntax

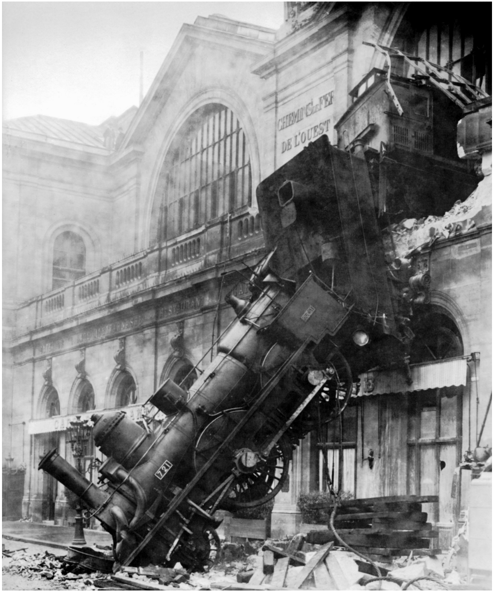
```
smoke.l <- glm(smoking~sex+age+DIGOX+TAMI+ACE+WMI,
 family= binomial(link="logit"),data=smoke)
prob <- predict(smoke.l,newdata=smoke,type="response")
smoke.p <- cbind(smoke,prob)
smoke.p$inv <- 1/smoke.p$prob
smoke.p$inv[smoke.p$smokingn==0] <- 1/(1-smoke.p$prob[
    smoke.p$smokingn==0])

fit.i <- prodlim(Hist(lifetime,status)~smoking,
  caseweights=smoke.p$inv,data=smoke.p)
plot(fit.i)
```

Inverse probability score - result



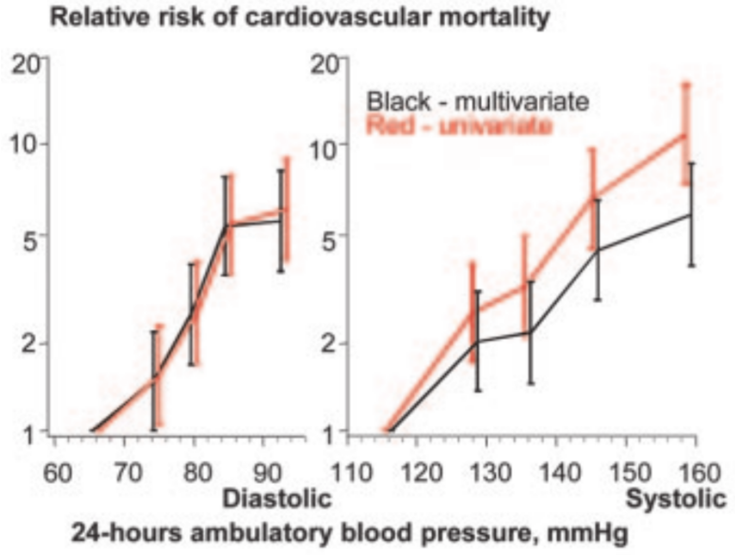
Navigate with care!



Matching?

- Beware of propensity scores
- Do use matching, but select carefully
- Consider not smoking

Cardiovascular death and ambulatory blood pressure



Hansen, Hypertension 2005

Hazard ratio of blood pressure

Variables	Univariate	Adjusted
Ambulatory blood pressure		
Systolic 24-h	1.39 (1.26–1.54)‡	1.18 (1.06–1.31)†
Systolic daytime	1.36 (1.23–1.50)‡	1.15 (1.04–1.28)†
Systolic nighttime	1.36 (1.24–1.49)‡	1.19 (1.08–1.30)†
Diastolic 24-h	1.18 (1.09–1.28)‡	1.18 (1.09–1.28)‡
Diastolic daytime	1.16 (1.08–1.25)‡	1.16 (1.08–1.26)‡
Diastolic nighttime	1.18 (1.10–1.27)‡	1.16 (1.08–1.25)‡
Office blood pressure		
Systolic	1.24 (1.15–1.33)‡	1.05 (0.96–1.14)
Diastolic	1.08 (1.01–1.16)*	1.06 (0.99–1.14)

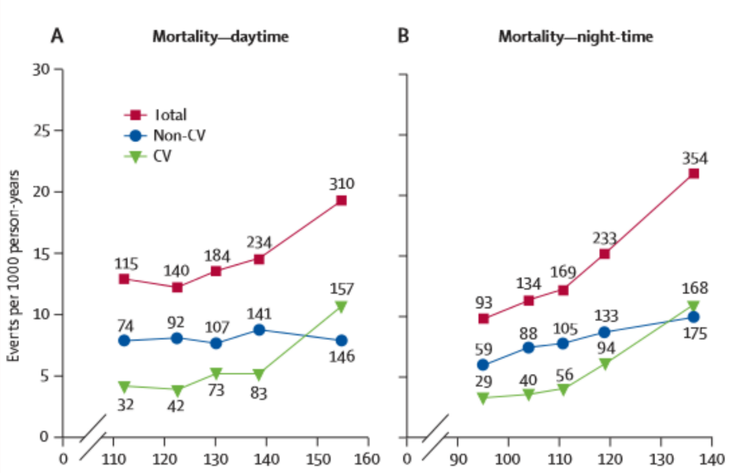
In multivariate analysis adjusted for age, smoking status, alcohol consumption, and physical activity.

*$P<0.05$.

†$P<0.01$.

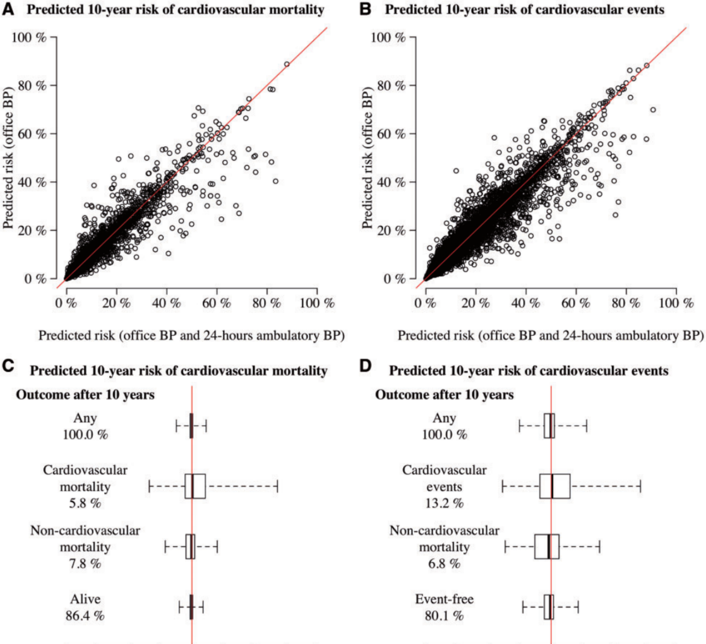
‡$P<0.0001$.

Metaanalysis of night time blood pressure



Systolic Blood Pressure Boggia, Lancet 2007

Added predictive value of ambulatory blood pressure



Area under receiver operator curve