Propensity Scores for Control of Confounding

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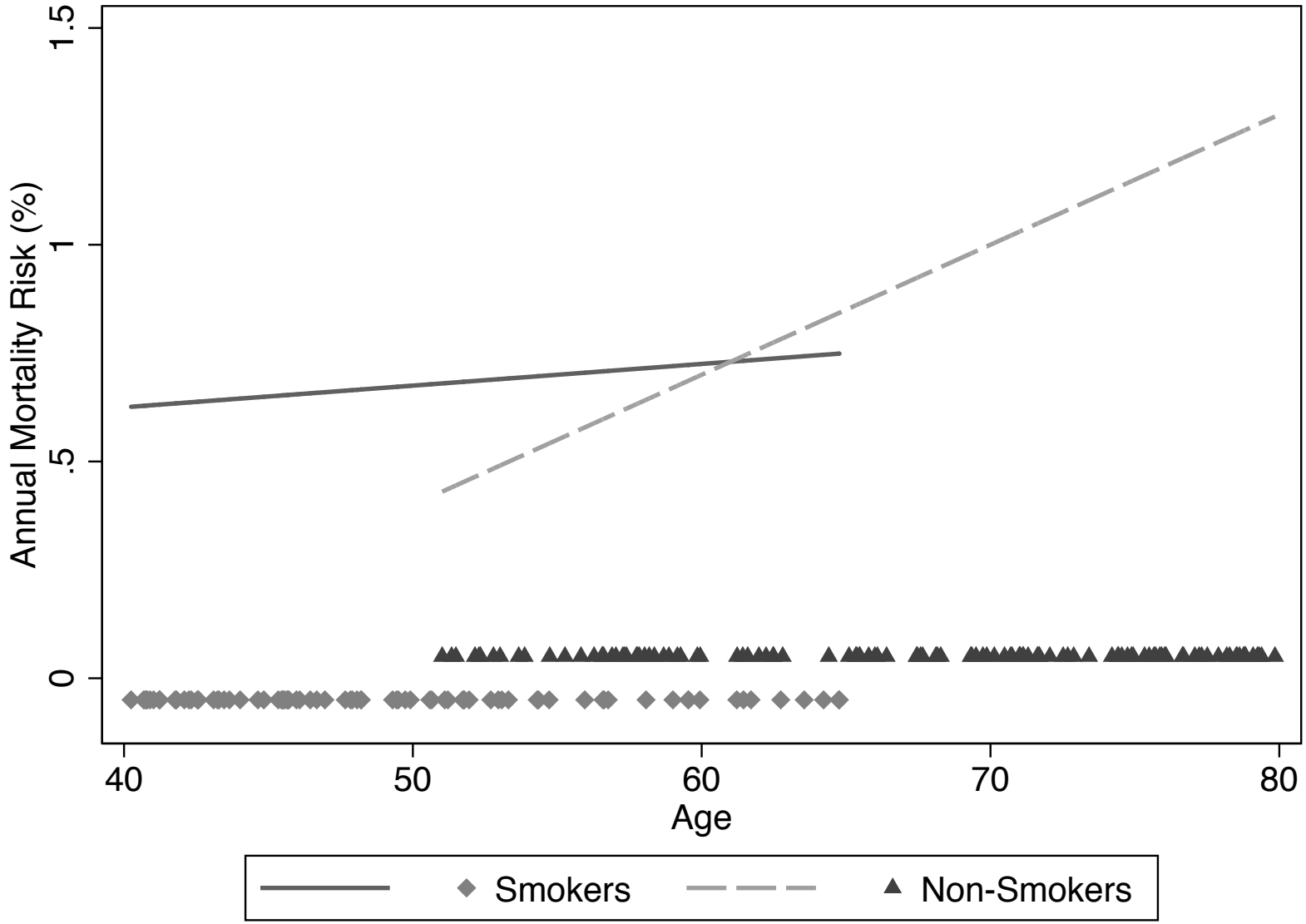
Biostatistics 210

Smoking and Mortality

- Compare mortality in a group of younger smokers v. older non-smokers?
- Suppose age is only confounder?
- How to estimate the causal OR or HR
- How to estimate the ACE?

What is Causal Effect?



Overlap and Positivity

- Average causal effect requires “overlap”
- Need exposed
- Un exposed
- Across all levels of confounders
- Previous example lacks that

Dilemma of Overlap

- Easy to assess with a single confounder
- In a 2 x 2 x 2 table, immediately evident
- Clear from smoking/age graph
- More complex with multiple variables
- Overlap not clear from regression:
  propensity offers some strategies

What if I lack overlap?

- Acknowledge it as a limitation
- Finesse the question: effect of smoking in middle aged men
- Could rely on extrapolation from regression
  heavily dependent on modeling choices

The modeling dilemma

- Handling non-linearities
- Interactions
- These are particular concerns with
  - small samples
  - poor overlap
- Extrapolation is fundamentally different use of regression

Potential Outcomes

- Pursues rigorous "causal" targets
- So-called "marginal" approach
- Comparing factors in standardized population
- Answer depends on confounder mix
- Doesn't assume homogeneous effect
- Model f(Y|C,E): familiar in that sense
- No clear generalization of hazard ratios

Counterfactuals

- $Y_i(1)$: survival if living kidney
- $Y_i(0)$: survival if cadaveric kidney
- $Y_i(1)$-$Y_i(0)$: causal effect in ith person
  would be rigorous to observe this!
- Only get to see one realization
  even in a randomized trial
  possible exception: crossover trials

Average Causal Effect

- Effect of exposure in population
- A.C.E. mean[Y(1)] - mean[Y(0)]
  $= 1/n \sum Y_i(1) - Y_i(0)$
- average causal OR or RR can also be defined
- Population is important here
- Causal inference: let estimate A.C.E.
  or a related quantity

Conditional Independence

- Core assumption of causal inference
- Synonymous with "no unmeasured confounders" beyond C
- Estimate effect of exposure with C
  and combine in some sense
- Basis of several methods
  regression, inverse weighting, propensity scores, potential outcomes estimation

Causal Effects from Regression

- Requires no unmeasured confounders
- Directly model exposure and confounders on outcome
- Not only tool for obtaining casual effects
  - propensity scores
  - stratification
  - inverse weight based methods

Propensity Scores

- A different approach to balance confounders
- Useful for binary exposures
- Modeling effort on the level of exposure
- Little modeling of effect on the outcome
- Can give rise to marginal and conditional effects

Example

- UNOS data
- Survival of pediatric kidney rx
- Effect of living v. cadaveric organ on survival
- 351 deaths
- Model on level of outcome (survival) or
- Model on level of propensity (txtype)

Flavor of Propensity Scores

- Two stage approach
- Very intuitive approach
- Has a feeling like randomized trial
  doesn't involve complex outcome model
- Can deal with confounding by matching
- Seems so direct -- more causal

Differences with regression more minor than major

What is the approach?

- Identify set of possible confounders
- Model exposure in terms of the confounders (e.g., logistic regression)
- Estimate predicted probability for each person (estimated propensity)
- Compared outcome by exposure within strata of the estimated propensity
- Alternative approach to controlling for confounders

Causal Inference

- Compare "like with like"
- Exposure holding confounder the same
- Propensity distills confounders into single continuous confounder
  - shows overlap
  - flexibility in outcome model
  - can be more careful about causal target

Basic Theorem

- f(C|propensity, Z) = f(C|propensity)
- Two people: one exposed, one not exposed have equal confounders on average
- Reduces confounding to single dimension
- Thing of propensity as our single confounder

Variables for Propensity

considerations identical to regression model

- No mediators or colliders
- Confounders must be included
- Don't include predictors of exposure which is not associated with outcome
- Strong predictor of outcome is OK
  can reduce residual variation -- no help for confounding

Adjusting for Instrument

- Predictor of exposure but not outcome
  hence, not a confounder
- Provide no protection against confounding
- Propensity will have less overlap
  and hence less efficiency
- Worst of both world:
  lose efficiency without helping confounding

Building Model for Propensity

- Outcome: exposure
- Ideal common exposure/rarer outcome
- Bias/Variance trade off tilts more toward to minimizing bias, less parsimonious
- Include splines and interactions
- Any binary model is OK
  extract the predicted probabilities

The steps

- Predictor Selection
- Build model for exposure
  calculate the prob. of exposure for each person
- Assess overlap/positivity
- Compare exposure by level of propensity
  quintiles, splines, matching

Propensity Fit: Example

- Splines for age, age of donor year
- Interactions of these with presence of previous transplant
- logistic txtype prevtx prevtx##c.yearsp* prevtx##c.agesp* prevtx##c.agedonsp* i.hla
- predict prop
- xtile group=prop, nq(5)

Quintile Overlap

5 quantiles of prop	txtype	
	Living	Cadaveric	Total
1	1,375	95	1,470
2	1,252	217	1,469
3	666	804	1,470
4	197	1,272	1,469
5	14	1,455	1,469
Total	3,504	3,843	7,347

Calculate Effect by Quintile

```
 cc death txtype, by(group)

5 quantiles of p |       OR        [95% Conf. Interval]   M-H Weight
-----------------+-----------------------------------------------
               1 |   2.139647       .7233504   5.240355     2.542857 (exact)
               2 |   1.350844       .6446765   2.618979     7.256637 (exact)
               3 |   1.436236       .8626344   2.431353     13.92245 (exact)
               4 |   1.390791       .6236271   3.654351     5.765827 (exact)
               5 |   .9183223       .1352256   39.42104     .9251191 (exact)
-----------------+-----------------------------------------------
           Crude |   1.604015       1.278398   2.018582              (exact)
    M-H combined |   1.450304       1.048069   2.006913
-------------------------------------------------------------------
Test of homogeneity (M-H)      chi2(4) =     1.00  Pr>chi2 = 0.9102
```

1st Quintile

death	txtype: Living	Cadaveric	Total
No	1,333	89	1,422
	96.95	93.68	96.73
Yes	42	6	48
	3.05	6.32	3.27
Total	1,375	95	1,470
	100.00	100.00	100.00

OR = 2.14, 95% Conf Int (0.7 to 5.2)

Survival if living recipients got a cadaveric organ

5th Quintile

death	txtype: Living	Cadaveric	Total
No	13	1,359	1,372
	92.86	93.40	93.40
Yes	1	96	97
	7.14	6.60	6.60
Total	14	1,455	1,469
	100.00	100.00	100.00

OR = 0.92, 95% Conf Int (0.14 to 39)

Survival if cadaveric recipients got a living organ

Stata Code

- logistic txtype *predictors*
- predict prop, p
- xtile group=prop, nq(5)
- cc death txtype, by(group)
- logistic death txtype i.group

Testing Interaction

- LR Test
- logistic death txtype##i.group
- est store A
- logistic death txtype i.group
- lrtest A

```
Likelihood-ratio test                                 LR chi2(4)  =      0.91
(Assumption: . nested in A)                           Prob > chi2 =    0.9229
```

Why Quintiles

- Overall
  - easily assessed
  - absent/variable effect in quintile
- Interactions
  - seamlessly checks for them
  - easy to calculate average causal effects

make it all transparent

Adjusting for Propensity

- Quintile: easy but residual confounding
- Linear: just. don't.
- Spline: flexible but hard to assess interaction
- Inverse Weight: causal rigorous, extreme weight, opaque method
- Matching: default, hard to construct

Matching

- Align on individual level based on propensity scores
- Needn't be 1-1
- Needn't be K-1
- Any matching can be wasteful
  has arbitrary element
- Extreme version of dialing up quintile to be a finer percentile
- Not a my preferred method

Spline

```
. mkspline prop_sp = prop, cubic nknots(7)

. logistic death txtype prop_sp*

Logistic regression                                     Number of obs   =       7347
                                                        LR chi2(7)      =      23.23
                                                        Prob > chi2     =     0.0016
Log likelihood = -1398.3454                             Pseudo R2       =     0.0082

------------------------------------------------------------------------------
       death | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     txtype |   1.399637   .2433085     1.93   0.053     .9955092    1.967821
    prop_sp1 |   144.3345   1024.966     0.70   0.484     .0001302    1.60e+08
    prop_sp2 |   9.0e-203   5.8e-200    -0.73   0.467            0           .
    prop_sp3 |          .          .     0.72   0.470            0           .
    prop_sp4 |   2.6e-213   1.8e-210    -0.71   0.478            0           .
    prop_sp5 |    4.36994    197.448     0.03   0.974     1.52e-38    1.26e+39
    prop_sp6 |   1.03e+67   1.47e+69     1.08   0.281     1.79e-55    5.9e+188
       _cons |   .0241336   .0161688    -5.56   0.000     .0064914    .0897228
------------------------------------------------------------------------------
```

Quintile

```
. logistic death i.txtype i.group

Logistic regression                                     Number of obs   =       7347
                                                        LR chi2(5)      =      23.85
                                                        Prob > chi2     =     0.0002
Log likelihood = -1398.0372                             Pseudo R2       =     0.0085

------------------------------------------------------------------------------
       death | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    1.txtype |   1.460813   .2433996     2.27   0.023     1.053823    2.024982
             |
       group |
          2  |   1.301893   .2544977     1.35   0.177     .8875235    1.909723
          3  |   1.274882   .2676887     1.16   0.247     .8447766    1.923968
          4  |    1.07496   .2522625     0.31   0.758     .6786397    1.702727
          5  |   1.480443   .3480316     1.67   0.095     .9338694    2.346915
             |
       _cons |   .0327919   .0048379   -23.16   0.000     .0245576    .0437872
------------------------------------------------------------------------------
```

Causal Effects

- p_0 = *Probability of death if everyone got living*
- p_1 = *Probability of death " " got cadaveric*
- Can be estimated by "margins" based on a particular model
- $p_1 - p_0$ = *ACE*
- p_1/p_0 = *Causal RR*
- $p_1 (1-p_0)/(1-p_1) p_0$ *Causal OR*

Marginal Effects

Margined Over Quintile

```
. margins txtype

------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
      txtype |
          0  |   .0386335   .0041469     9.32   0.000     .0305057    .0467613
          1  |   .0554319   .0046479    11.93   0.000     .0463223    .0645416
------------------------------------------------------------------------------

. margins, dydx(txtype)

------------------------------------------------------------------------------
             |            Delta-method
             |      dy/dx   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    1.txtype |   .0167985   .0072948     2.30   0.021     .0025008    .0310961
------------------------------------------------------------------------------
```

Code for ACE Risk Difference

- logistic death i.txtype i.group
  fits propensity model
- margins txtype
  calculate predicted
- margins dxdy(txtype)
  calculate different

Code for Causal RR

- logistic death i.txtype i.group
  could be any model for the data
- *margins txtype, post*
  post saves some key results
- nlcom (RR: _b[1.txtype] / _b[0.txtype])
  SE can a little off
- nlcom (logRR: log(_b[1.txtype]) - log(_b[0.txtype]))
  then exponentiate -- always better SE/CI

Causal RR -- Quintile Fit

```
logistic death i.txtype i.group
margins txtype, post

 nlcom (risk_ratio: _b[1.txtype]/_b[0.txtype] )

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  risk_ratio |   1.434816    .228147     6.29   0.000     .9876558    1.881976
------------------------------------------------------------------------------


logistic death i.txtype i.group
margins txtype, post
. nlcom (logRR: log(_b[1.txtype]) - log(_b[0.txtype]))

       logRR:  log(_b[1.txtype]) - log(_b[0.txtype])

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       logRR |   .3610364   .1590079     2.27   0.023     .0493867    .6726861
------------------------------------------------------------------------------
```

marginal RR = 1.43 (1.05, 1.96)

Causal OR -- Quintile Fit

```
logistic death i.txtype i.group
margins txtype, post
. nlcom (OR: (_b[1.txtype]*(1-_b[0.txtype])) / (_b[0.txtype]*(1-_b[1.txtype])) )

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          OR |   1.460333   .2433062     6.00   0.000     .9834615    1.937204
------------------------------------------------------------------------------
```

```
logistic death i.txtype i.group
margins txtype, post
nlcom (OR: log(_b[1.txtype])+log(1-_b[0.txtype])-log(_b[0.txtype])-log(1-_b[1.txtype]) )

  ------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
          OR |   .3786644   .1666101     2.27   0.023     .0521146    .7052142
------------------------------------------------------------------------------
```

marginal OR = 1.46 (1.05, 2.02)

Usual Regression

Basic Model

```
. logistic death txtype prevtx year age age_don i.hla

Logistic regression                                     Number of obs   =       7347
                                                        LR chi2(11)     =     109.57
                                                        Prob > chi2     =     0.0000
Log likelihood = -1355.1776                             Pseudo R2       =     0.0389

------------------------------------------------------------------------------
       death | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     txtype |   1.352607   .2104378     1.94   0.052     .9971076    1.834852
     prevtx |   1.025545    .148438     0.17   0.862     .7722383    1.361941
       year |   .8667789   .0149232    -8.30   0.000     .8380179    .8965269
        age |   .9693932   .0102048    -2.95   0.003     .9495972     .989602
    age_don |   .9976164   .0042928    -0.55   0.579     .9892381    1.006066
            |
     hlamat |
          1 |   1.118378   .2534091     0.49   0.621     .7173287     1.74365
          2 |   .9684949   .2219639    -0.14   0.889     .6180381    1.517677
          3 |   .8122357   .1911163    -0.88   0.377       .51215    1.288151
          4 |   .8067894   .2186669    -0.79   0.428     .4743032    1.372348
          5 |   .9442997   .3425764    -0.16   0.874     .4637757    1.922701
          6 |     .89599   .3324897    -0.30   0.767     .4329461    1.854268
```

Usual Regression

Spine/Interaction Model

```
 logistic death txtype prevtx prevtx##c.yearsp* prevtx##c.agesp* prevtx##c.agedonsp* i.hla

Logistic regression                                     Number of obs   =       7347
                                                        LR chi2(32)     =     162.11
                                                        Prob > chi2     =     0.0000
Log likelihood = -1328.9077                             Pseudo R2       =     0.0575

------------------------------------------------------------------------------
       death | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     txtype |   1.472337   .2414501     2.36   0.018     1.067623    2.030471
     prevtx |   6.5e+189   3.3e+192     0.86   0.389     1.8e-242           .
    yearsp1 |    .975281   .1156388    -0.21   0.833     .7730419    1.230429
    yearsp2 |   1.058858   .8618707     0.07   0.944     .2147788    5.220161
    yearsp3 |   .2970671    1.00785    -0.36   0.721     .0003846    229.4555
    yearsp4 |   3.538337   15.02097     0.30   0.766     .0008615    14531.97
            |
prevtx#c.yearsp1 |
          1  |   .8033063   .2045974    -0.86   0.390     .4876241    1.323358
            |
prevtx#c.yearsp2 |
          1  |   3.321273   6.292198     0.63   0.526     .0810385    136.1187
            |
```

and more!

20 Strata

```
xtile group3=prop, nq(20)
logit death txtype, i.group3

 logistic death txtype i.group3

Logistic regression                                     Number of obs   =       7347
                                                        LR chi2(20)     =      50.29
                                                        Prob > chi2     =     0.0002
Log likelihood = -1384.8183                             Pseudo R2       =     0.0178

------------------------------------------------------------------------------
       death | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
     txtype |   1.427705   .2478669     2.05   0.040      1.01592      2.0064
            |
     group3 |
          2 |    .326775   .1705254    -2.14   0.032     .1175046    .9087467
          3 |   .7250355    .292959    -0.80   0.426     .3284139    1.600653
          4 |   1.137948   .4122547     0.36   0.721     .5594356    2.314701
          5 |   1.500861   .5153622     1.18   0.237      .765697    2.941874
          6 |   .8503287   .3286302    -0.42   0.675     .3986753    1.813654

ETC
```

Models

Model	Risk Diff	Marginal OR	Cond. OR
Prop: Quint	0.017	1.46	1.46
Prop: Spline	0.015	1.4	1.4
Reg: Simple	0.014	1.35	1.35
Reg: Spline+Int	0.017	1.47	1.46

Regression	Propensity Score
assess confounding	assess confounding
draw DAG	draw DAG
assess predictor size	assess predictor size
select confounders	select confounders
model for outcome	model exposure
check overlap	check overlap
	check for interaction
	compare outcome exposure adjusted for propensity

Major Differences

- Propensity scores (PS) only useful for binary exposure
- Model size can be very different
  PS great for rare outcome/common exposure
- PS involves less modeling of the outcome
- More choices for controlling for propensity
- PS involves many ad-hoc choices

Final Recommendations

- Useful for binary variable
  or possibly ordinal variable
- Switches modeling to exposure
  rather than outcome
  - Advantage if exposure is common,
    outcome is rare
- Makes overlap transparent
- Analysis for like "randomized trial"
  less modeling of the outcome
- Often similar results