Counterfactuals and Potential Outcomes Estimation

Dave Glidden
Biostatistics 210

BMD and Fracture Risk

- Cohort of older adults
- Have bone mineral density measured
- Followed for onset of fracture risk
- Risk of fracture associated level with BMD=x

Causal Question

- Many thing contribute to outcomes
- Want to manipulate the exposure
- How would outcome change?
- Observed differences in exposure don't approximate change in exposure

difference between "see" and "do"

Some Questions

- Kidney transplant
  better survival with living organ donation?
- Exercise benefit
  regular exercise control glucose in older women?
- Objective: causal inference or as close as well can come

What is a confounder?

What I learned….

A variable associated with the outcome and the exposure. One that leads to bias if it is not "controlled" for.

Not a rigorous definition

Now we use DAGs to identify adjustment sets

New Approaches

- Rigorous definitions
- Causal Inference
- Causal Estimands (targets)
- How to estimate targets
  which variables need to be controlled for?
- Interesting interplay with missing data

Some Notation

- $Y_{i:}$: observed outcome for the ith person
- $E_{i\,:}$ observed exposure for the ith person
  Exercise: binary, SOF: continuous
- $C_i=(C_{1i}\ldots.C_{pi})$ predictors associated Y_i, E_i

Potential Outcomes

- $Y_i(1)$: Glucose ith person who exercises
- $Y_i(0)$: Glucose ith person no exercise
- $Y_i(1)-Y_i(0)$: 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. $E[Y(1)] - E[Y(0)]$
  $= 1/n \sum Y_i(1) - Y_i(0)$
- Average causal effect
- Very elegant "target"
- Why is it causal?
  compares exposure in all i=1,…..,n
  the identical population

Table 9.1. Potential Outcomes Framework for the Effect of Exercise

Sub-Population	Person	$Y(1)$	$Y(0)$	$Y(1)$-$Y(0)$
C $=0$	1	94	99	-5
	2	98	99	-1
	3	99	98	1
	4	103	105	-2
	5	96	99	-3
C $=1$	6	95	94	1
	7	92	95	-3
	8	94	95	-1
	9	90	94	-5
	10	99	101	-2
Overall	Mean	96	98	-2

Fundamental Problem

- Only get to see actual exposure
  not potential outcome
- E_i: exposure in the ith person
- E_i: $_i$: associated w/ factor(s) C related to outcome
- E_i: -- confounder. Associated with exposure and outcome
- Distorts the observed difference in exposure groups

Table 9.2. Effect of Exercise Using Observed Data Only

Sub-Population	Person	$Y(1)$	$Y(0)$	Estimated Difference
C $= 0$	1		99	
	2		99	
	3		98	
	4		105	
	5	96		
C $= 1$	6	95		
	7		95	
	8	94		
	9	90		
	10	99		
Overall	Mean	94.8	99.2	-4.4

C=1: family history of diabetes, C=0: no family history of diabetes

Missing Data Problem

- What is mean of Y(1)?
- Missing in some people
  they were exposed to E_i=0
- Missingness associated with C
- C is associated with latent Y(1)
- Classic missing data problem

"Fundamental problem" is a missing data problem

Randomization Assumption

- E_i is independent of Y(1) and Y(0)
- If true can identify E[Y(1)] and E[Y(0)]
  estimate them rigorously
- Observed difference identifies causal effect
- Causal inference: without having counterfactuals

Why we love the RCT

Potential outcome is "missing completely at random"

No Confounders

- E_i is independent of $Y(1)$ and $Y(0)$
- If true can identify $E[Y(1)]$ and $E[Y(0)]$ *estimate them rigorously*
- Observed difference identifies causal effect
- Causal inference: without having counterfactuals

Why we love the RCT

Potential outcome is "missing completely at random"

Conditional Independence

- Relaxes this assumption
- If C is a confounder...
  - suppose within levels of C, E and $Y(1), Y(0)$ are not associated
  - exposure random within levels of the confounder
- Adjustment identifies effect within C
- Assumption behind "adjustment" for confounders

Conditional Independence

- Within levels of family hx diabetes
  - unconfounded effect of exercise
  - within levels exercise not associated with lipids if exercise or no exercise
- Then "see" reveals "do"
- Principle extends to complex confounders
  continuous or multiple confounders

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 Estimation

Glucose and Exercise

- $Y_i(1)$: Glucose ith person who exercises
- $Y_i(0)$: Glucose ith person no exercise
- $Y_i(1)-Y_i(0)$: causal effect in ith person
- Can't observe. Can estimate it's average $E\{Y(1)-Y(0)\}$
- Need to estimate: $E[Y(1)]$, $E[Y(0)]$

Table 9.2. Effect of Exercise Using Observed Data Only

Sub-Population	Person	$Y(1)$	$Y(0)$	Estimated Difference
C $= 0$	1		99	
	2		99	
	3		98	
	4		105	
	5	96		
C $= 1$	6	95		
	7		95	
	8	94		
	9	90		
	10	99		
Overall	Mean	94.8	99.2	-4.4

Potential Outcomes

- Estimate: E[Y(1)], E[Y(0)]
- Mean glucose in population
  E(Y(1)) if entire population exercises
  E(Y(0)) if entire population doesn't exercise
- Estimating is a missing data problem
- MAR with respect to variable C
  which is the two-level confounder

Major Methods

Model Outcome	Potential Outcomes/G-computation
Model Exposure	Inverse Weighting, Propensity Scores

all rely on no unmeasured confounders

The Means

	E=1	E=0	Diff
C=0	96	100.25	-4.25
C=1	94.5	95	-0.5

Weighting Population

- E(Y(x)) = P(C=1)*E(Y(x)|C=1)+P(C=0)*E(Y(x)|C=0)
- E(Y(1))= 5/10*96 + 5/10*94.5 = 95.25
- E(Y(0)) = 5/10*95 + 5/10*100.25 = 97.625
- E(Y(1)) - E(Y(0)) = - 2.4

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Sub-Population	Person	$Y(1)$	$Y(0)$	Estimated Difference
C $= 0$	1	96	99	
	2	96	99	
	3	96	98	
	4	96	105	
	5	96	100.25	
C $= 1$	6	95	95	
	7	94.5	95	
	8	94	95	
	9	90	95	
	10	99	95	
Overall	Mean	95.3	97.6	-2.4

Potential Outcome

- Step 1: Identify confounders: C
- Step 2: Regress Y given C and E
- Step 3: Set E_i=e, estimate $E(Y_i|E_i=e,C_i)$ mean, proportion, predicted survival
- Step 4: $E\{Y(e)\} = n^{-1}\sum_{i=1}^{n} E(Y_i|E_i = e, C_i)$

Fracture Data

Fracture Intervention Trial

- 2669 placebo participants in FIT
- Followed for mean of 3.9 years
- 523 new fractures of any kind
- 5.1/100 person year 0.95 CI (4.7 to 5.5)
- Baseline bone mineral density (BMD)
- estimate Y(e) where BMD = e
- confounders; age, body mass index

Relative Risk Regression

```
.  glm fracture blbmd bmi age, link(log) family(binomial) nolog eform

Generalized linear models                          No. of obs      =      2669
Optimization     : ML                              Residual df     =      2665
                                                   Scale parameter =         1
Deviance         =  2548.539609                    (1/df) Deviance =     .9563
Pearson          =   2653.92697                    (1/df) Pearson  =   .995845

Variance function: V(u) = u*(1-u)                  [Bernoulli]
Link function    : g(u) = ln(u)                    [Log]

                                                   AIC             =  .9578642
Log likelihood   = -1274.269805                    BIC             = -18476.87

------------------------------------------------------------------------------
             |                 OIM
    fracture | Risk Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       blbmd |   .6229577   .0338921    -8.70   0.000     .5599494    .6930559
         bmi |   1.015919   .0096703     1.66   0.097     .9971412     1.03505
         age |   1.017513   .0067336     2.62   0.009     1.004401    1.030797
       _cons |   .7162968   .4579807    -0.52   0.602     .2045775    2.508003
------------------------------------------------------------------------------
```

Potential Outcomes

$$E(Y(x_1)) = n^{-1} \sum_{i=1}^{n} \exp\{\beta_0 + \beta_1 x_1 + \beta_2 \mathrm{bmi}_i + \beta_3 \mathrm{age}_i\}$$

$$E(Y(x_0)) = n^{-1} \sum_{i=1}^{n} \exp\{\beta_0 + \beta_1 x_0 + \beta_2 \mathrm{bmi}_i + \beta_3 \mathrm{age}_i\}$$

Can calculate marginal summarizes based on comparison of x1 to x0

Margins Command

```
. margins, at(blbmd=(0.636 0.542)) post

1._at        : blbmd           =        .636

2._at        : blbmd           =        .542
------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
         _at |
E(Y(x1))   1 |   .1431981   .0084859    16.87   0.000     .1265662    .1598301
E(Y(x0))   2 |   .2298682   .0091738    25.06   0.000     .2118878    .2478485
------------------------------------------------------------------------------
```

RR = E(Y(x1)) / E(Y(x0)) = 0.143/0.230 = 0.62

Marginal Relative Risk

log RR = log (E(Y(x1))/E(Y(x0)))

```
. nlcom (logRR: log(_b[1._at]) - log(_b[2._at]))

       logRR:  log(_b[1._at]) - log(_b[2._at])

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       logRR |  -.4732766   .0544051    -8.70   0.000    -.5799087   -.3666445
------------------------------------------------------------------------------
```

```
. dis exp( -.4732766)
.62295774

. dis exp(-.5799087)
.55994949

. dis exp( -.3666445)
.69305598
```

Identical to the relative risk from the conditional model

Logistic Regression

```
. logistic fracture c.bmdsp*##c.bmi##c.age

Logistic regression                               Number of obs   =       2669
                                                  LR chi2(11)     =      99.27
                                                  Prob > chi2     =     0.0000
Log likelihood =  -1270.831                       Pseudo R2       =     0.0376

------------------------------------------------------------------------------------
            fracture | Odds Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
---------------------+--------------------------------------------------------------
              bmdsp1 |   .0060128   .0640367    -0.48   0.631     5.17e-12     6990156
              bmdsp2 |   .4289443   5.758955    -0.06   0.950     1.60e-12    1.15e+11
                 bmi |   .6878283   1.707098    -0.15   0.880     .0053078    89.13511
                     |
      c.bmdsp1#c.bmi |   1.091443   .4809919     0.20   0.843     .4601316    2.588929
                     |
      c.bmdsp2#c.bmi |   1.117461   .5956207     0.21   0.835     .3931258    3.176388
                     |
                 age |   .7869287    .665148    -0.28   0.777     .1501278    4.124865
                     |
      c.bmdsp1#c.age |   1.054416   .1593224     0.35   0.726     .7841428    1.417845
                     |
      c.bmdsp2#c.age |   1.024268   .1990111     0.12   0.902     .6998882     1.49899
                     |
         c.bmi#c.age |   1.003063    .035319     0.09   0.931     .9361739    1.074732
                     |
c.bmdsp1#c.bmi#c.age |   .9992013   .0062572    -0.13   0.898     .9870123    1.011541
                     |
c.bmdsp2#c.bmi#c.age |    .997932   .0077008    -0.27   0.788     .9829522     1.01314
                     |
               _cons |   1.17e+10   6.97e+11     0.39   0.698     1.87e-41    7.32e+60
------------------------------------------------------------------------------------
```

Margins After Logistic

```
. margins, at(blbmd=(0.636 0.542)) post

1._at        : blbmd           =        .636

2._at        : blbmd           =        .542
-------------------------------------------------------------------------------
             |            Delta-method
             |     Margin   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+-----------------------------------------------------------------
         _at |
E(Y(x1))  1  |   .1414725   .0094845    14.92   0.000     .1228833    .1600618
E(Y(x0))  2  |   .2359769   .0120128    19.64   0.000     .2124323    .2595215
-------------------------------------------------------------------------------
```

RR = E(Y(x1)) / E(Y(x0)) = 0.141/0.236 = 0.60

Marginal Relative Risk

log RR = log (E(Y(x1))/E(Y(x0)))

```
. nlcom (logRR: log(_b[1._at]) - log(_b[2._at]))

       logRR:  log(_b[1._at]) - log(_b[2._at])

------------------------------------------------------------------------------
             |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       logRR |  -.5116282   .0791684    -6.46   0.000    -.6667954   -.3564609
------------------------------------------------------------------------------
```

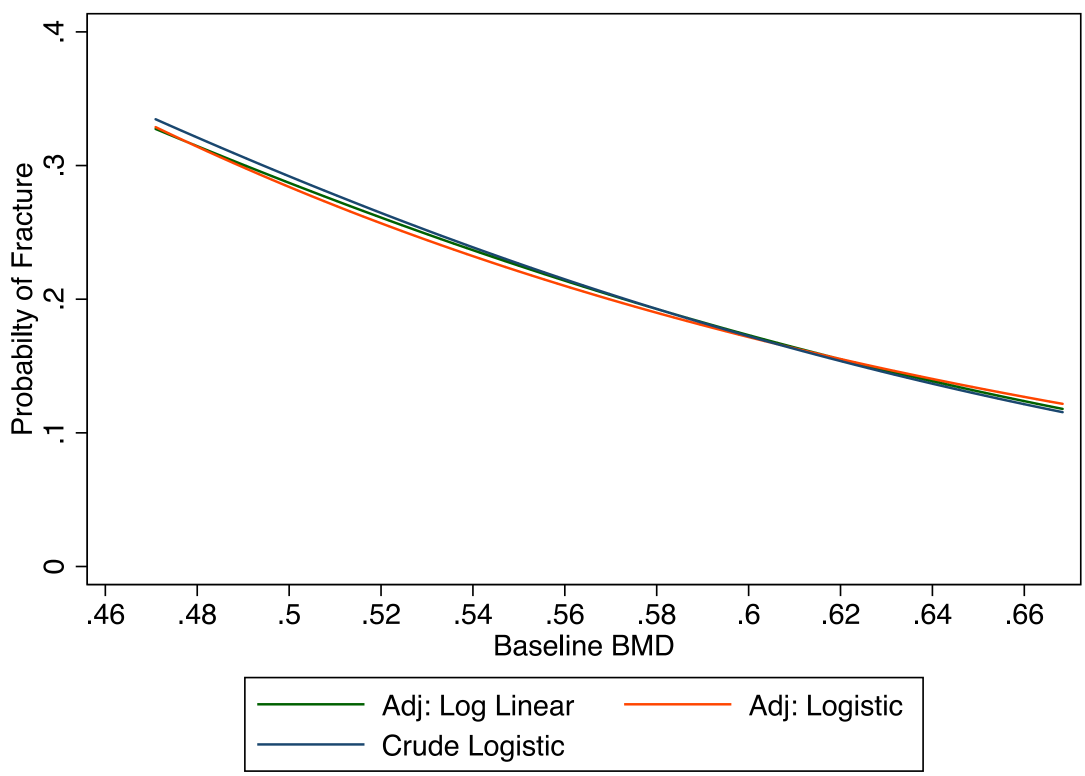
```
. dis exp( -.5116282)
.59951865

. dis exp(-.6667954)
.51335103

. dis exp(-.3564609)
.70014985
```

Rather similar results

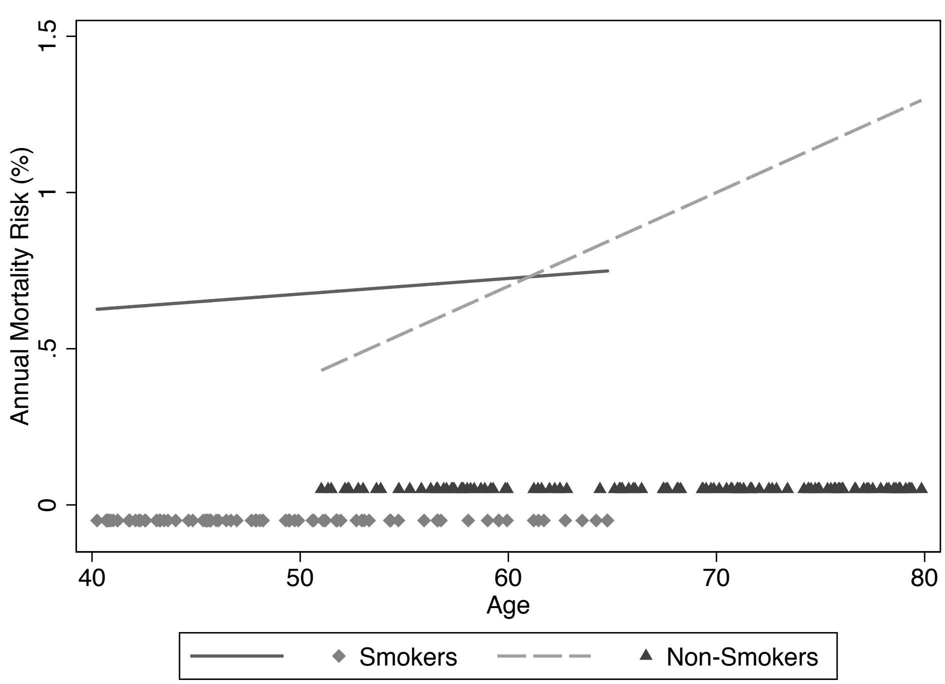
Fracture Risk by BMD



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

- Positivity: for every covariate combination there is a change of exposure and non-exposure. *Property of the population.*
- Overlap: there are obs with exposure and non exposure in all covariate combination. *Property of the data.*

Dilemma of Positivity

- 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

Consider Interactions

- Quantitative v. qualitative interaction
- Absence can aid credibility:
  effect doesn't vary with study site
- Presence can aid understanding:
  effect more pronounced in young people
- Limit number of interactions:
  false positive
- Consider most plausible ones first

No Unmeasured Confounders

- Essential
  particularly important for weak effects
- Unverifiable
  fundamental dilemma of causal inference
- A surrogate can stand in for unmeasured confounder
- Value for an adjusted effect even if it is not completely free of confounding

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