Causal Effect of a Single Variable

29 Oct 2013
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Biostatistics 210

Four General Problems

for which regression is useful

1. Developing a Model for Prediction/ Stratification
2. Adjusted Effect of Single Variable
3. Identifying Multiple Predictors of Outcome
4. Adjustment to Improve Efficiency in RCT

Predictor of Primary Interest

- RCT with non-compliance
  taking FTC/TDF prevent HIV infection?
- Urinary incontinence
  incontinence promote falls/fractures?
- Kidney transplant
  better survival with living organ donation?
- Objective: causal inference or as close as well can come

Causal Inference

raises foundational issues

- If we could modify the exposure how would the outcome change?
- How might we modify those exposures?
- Can we consider manipulating those exposures: sometime easy, sometimes not.

suppose treatment for incontinence has side effect like somnolence or dizziness

Counterfactuals

- $Y_i(1)$: Fracture if incontinent
- $Y_i(0)$: Fracture if not incontinent
- $Y_i(1)$-$Y_i(0)$: 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

Fundamental Problem

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

Randomization Assumption

- e is independent of Y(1) and Y(0)
  BMD is not associated with incontinence
- 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

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

- 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
- Not only tool for obtaining casual effects
  - propensity scores
  - stratification
  - inverse weight based methods
- How to use regression?

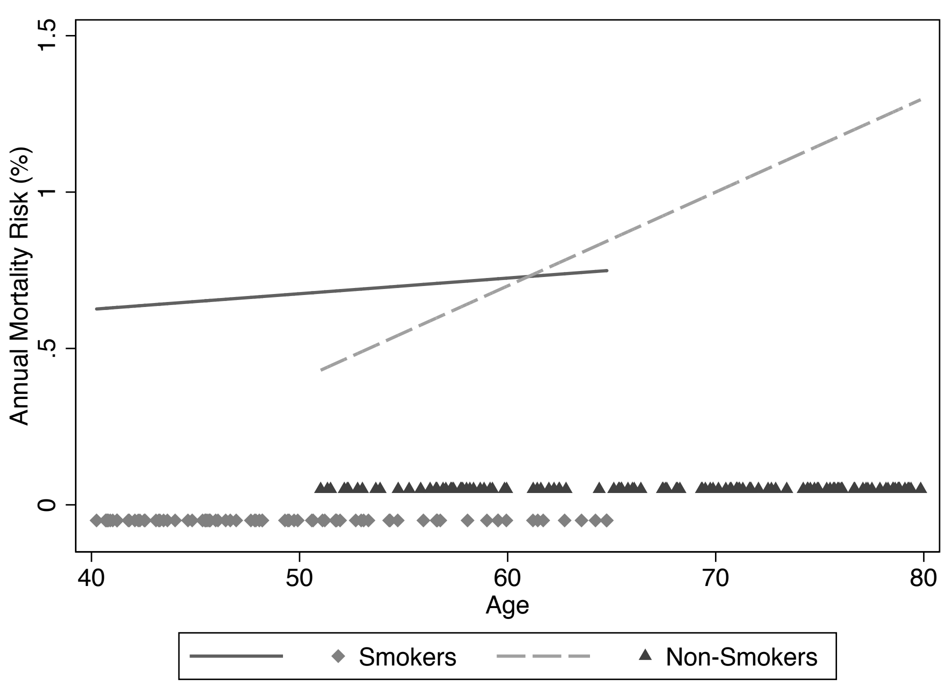
Regression for Causal Inference

- Model outcome as a function of the exposure and confounders
- Coefficient for exposure interpreted as causal
- Regression coefficient *not always* the ACE
- Requires correct specification of the model
  linearity, model family, interactions
  implicitly assumes constant causal effect

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 understand:
  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

Predictor Selection

- Issue is the same across models: Cox, linear, logistic, etc
- Rule out confounding as persuasively as possible
- Include factors from previous studies
- Use substantive grounds: causal diagram
- Use empirical confounders

Do Not Adjust List

- Alternative measures of the outcome
  diabetes in a model for glucose
- Alternative measures of the predictor
- Mediators
- Don't worry about collinearity among adjusting variables

Face Validity

- My least favorite term
- Other people can't see your data
  "they didn't adjust for age...."
- But not everything associated with outcome must be adjusted for
- Objective: persuasive adjustment

Empirical Selection

- Need to be conscious of limitations on # predictors
- Use a backward selection approach
- Look for association with predictor and exposure
- Backwards with $p < 0.20$
- Issue: p is not synonymous with confounding

Gold Standard for Confounding

- Adjusting for it changes the effect of the primary predictor
- Provided it's not on the do not adjust list...
- How much is a change: we say 10% change in coefficient: *very sensitive to context*

Sample Size

- Adequate sample size does not make confounding less likely
- Pet peave: suggesting an observation study (NHS/PHS) just because the sample size is large
- But large sample sizes has some pays off

Number of Events

- Regression is sensitive to the bias/variance trade off
- Increases the chances of overlap
- Makes modeling choices less ambiguous
- Permits adjustment for more potential confounders
- Many large databases have few predictors

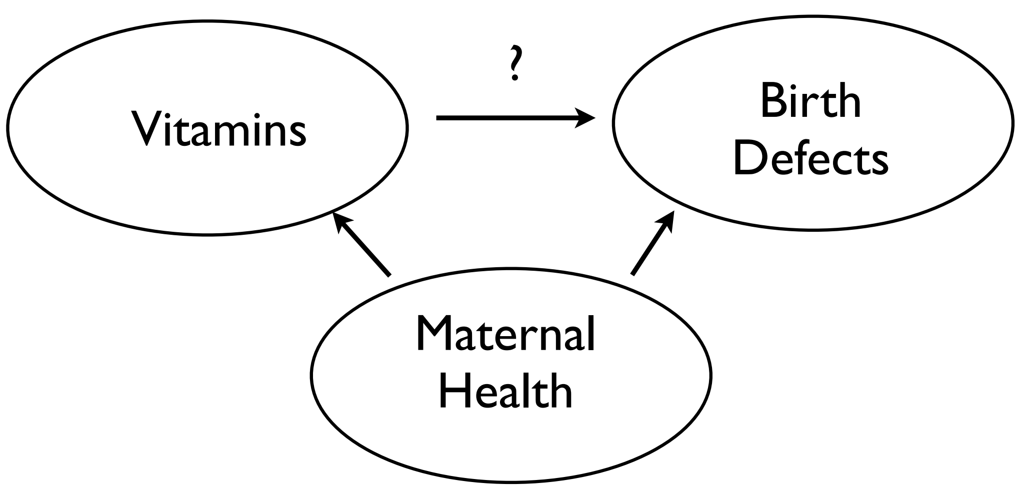
Incontinence and Falling

- Does urinary incontinence lead to falling? hasty bathroom trips at night
- Used backward selection $p < 0.20$
- Looked at other models
- Adjusted for 12 variables
- Interactions

Directed Acyclic Graphs

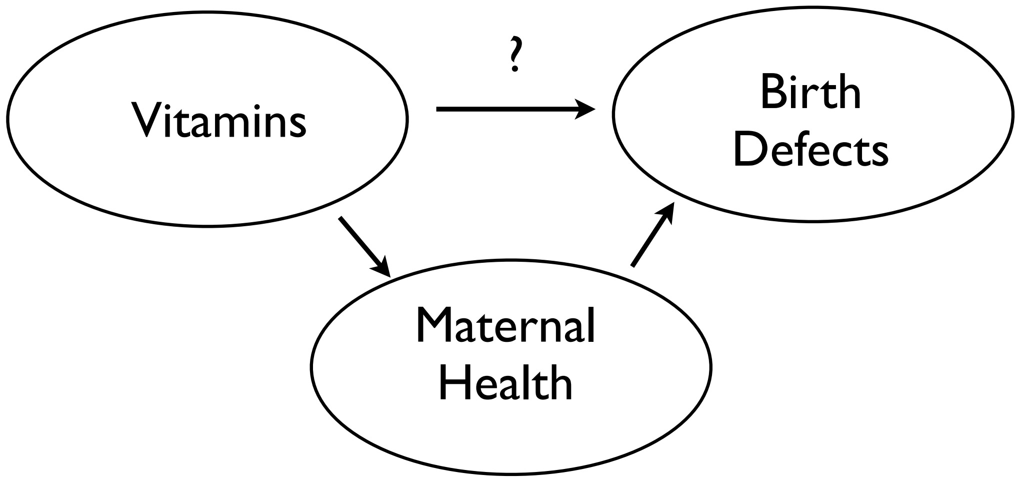
- Draws hypothesized causal relationships
- Shows what's causally related
  direction of arrows is important
- Yields principled control of confounding
- Confounder, Mediator, Collider

Confounder



Classic confounding: healthy women use vitamins more. Their better health decreases birth defects by other pathways (pre natal care)

Mediator

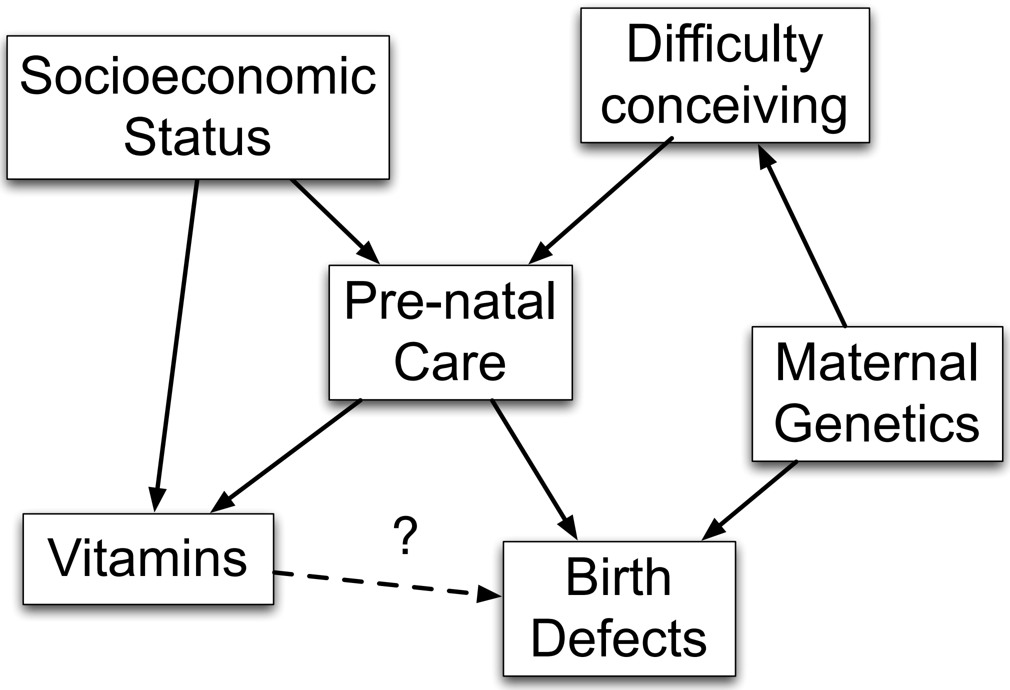


Mediation: Vitamins increase health (e.g., nutritional status). This better health decreases birth defects.

Don't Adjust for Mediator

- What question does it answer?
  How much association of vitamins not reflected in post-supplement nutrition
- That is analysis of mediation
- Does address causal question
- Part of the reason we don't adjust for post-baseline variables in RCTs

More Complete DAG



Backdoor Path

- Path not originating from exposure
  arrow doesn't not point out of exposure
- Connecting exposure and outcome
- Mediation is not considered backdoor bath
  arrow points out of exposure for mediation

Four Backdoor Paths

1. Vitamin use ← pre-natal care → birth defects
2. Vitamin use ← SES → pre-natal care → birth defects
3. Vitamin use ← pre-natal care ← difficulty conceiving ← maternal genetics → birth defects
4. Vitamin use ← SES → pre-natal care ← difficulty conceiving ← maternal genetics → birth defects

what variable is in the middle of all four paths?

Confounding and Backdoor Paths

- Confounding is controlled by including one variable from the path
- Need variable(s) that block all path
- Complicated by a collider
  let's look at path #4

Collider

- In path #4, prenatal care is a *collider*
- It is a common effect of SES and difficultly conceiving
- If we condition on prenatal care, induces association between them
- Opens a new backdoor path
- Sufficient to adjust for one more variable
  either SES or prenatal care

Collider

- Collider Bias
- Suppose X and Y are independent
  difficulty conceiving and SES
- Conditioning on their common effects induces association
- Stratification or regression can cause this
- Selection biases are collider biases

Models Which Control for Confounding

- Prenatal + SES
- Prenatal + difficulty conceiving
- Prenatal + difficulty conceiving + SES
- Prenatal + maternal genetics + SES
- Prenatal + difficulty conceiving + SES + maternal genetics
- Prenatal + difficulty conceiving + maternal genetics

Using DAGs to Select Model

- Draw DAG
- Algorithms can select sufficient adjustment sets
- Maybe be multiple choices
- Idea is to select a small, plausible model which controls confounding
- *dagitty.net* can spit out possible models

Using DAGs in Practice

- Identify variables don't need to adjust for
- Mediators: very sensible
- Colliders: helpful (their not always easy to recognized) but usually an issue when we adjusting for few variables
- Exception: the "M DAG" set up
  see VGSM 10.2.5.3

Use of DAGs

- Develop a coherent selection if associations known
  big DAGs often have uncertain arrows
  absent arrows especially important
  those are ones which suggest non-adjustment
- How to synthesize this uncertainty?
- Hard to argue you don't need to adjust some something

Non-Adjustment

- Colleagues may not understand DAGs
- Colleague may have a different DAGs explicitly or implicitly
- DAG: Elegant approach
  -- not easy to synthesize uncertainty
  -- not always convincing to others either on issues of fact or doubt

Recommendations

- Assess permissible predictor number
- Prioritize based on empirical associations
  no mediators, surrogates of outcome/exposure
- Then face validity
- Then consider insights from DAG
- DAG have place but limited
  useful for insights on relationships
  great for dialog but predictor selection
- Look at interactions, modeling, overlap