Discussion of Sebastien Haneuse's Talk on Comparative Effectiveness Using Electronic Health Records

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Electronic Health Care Records for Comparative Effectiveness Research

- The promise (compared to randomized trials):
  - Expense
  - Speed
  - Large enough sample size to look at many subgroups
  - Real world effectiveness
- Challenges:
  - Selection bias due to missing data
  - Confounding bias

Sebastien's Talk

- Usual approach to missing data: There is one mechanism that leads a variable of interest to be not missing or missing.
- Sebastien's idea: In EHR, the process that leads a variable to be not missing or missing can be broken down into submechanisms:
  - Enrollment status
  - Treatment in multiple facilities and quality of EHR at facilities treated at
  - Encounters with the health system
  - Measurement of the variable
  - Structural changes over time in care and EHR recording

Nice Features of Breaking Down Missing Process into Submechanisms

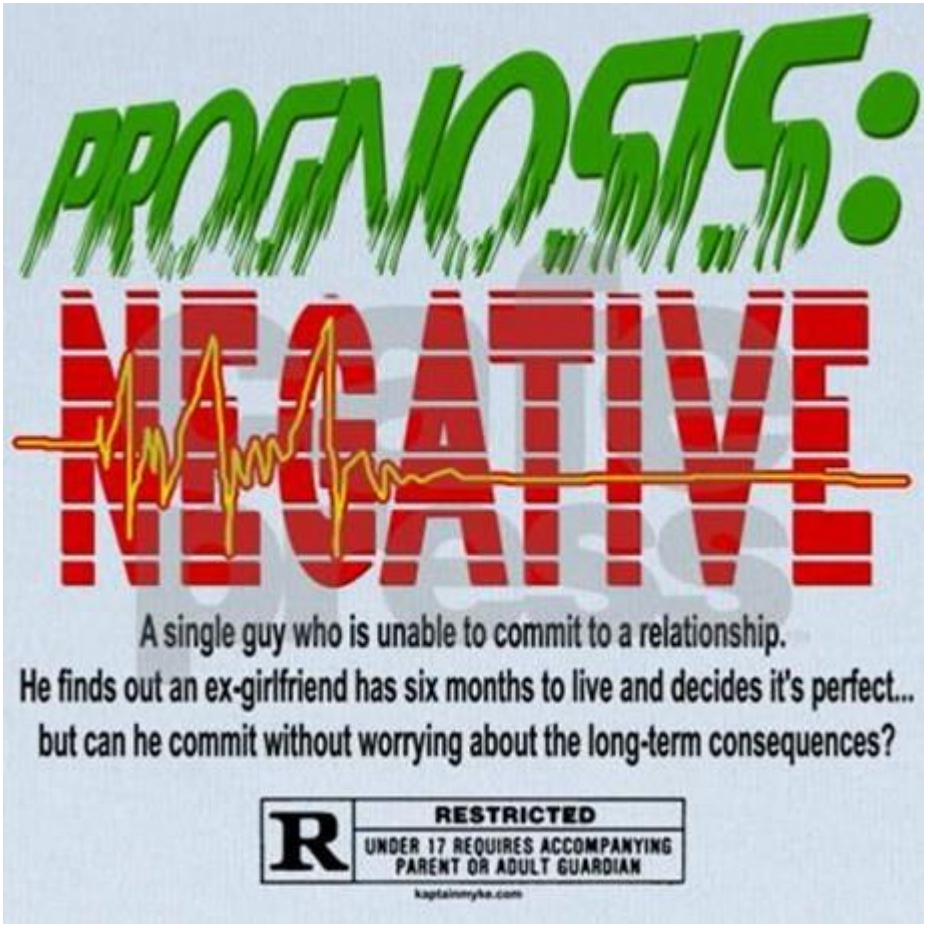
- Conquer and divide strategy.
- Greater understanding.
- More accurate modeling.
- Identification of subsets of the data where the missingness might be regarded as missing at random.
- Joffe et al. (2010), Selective Ignorability: One can obtain valid causal estimates by using g-estimating equations that only use those time points for a subject where data is plausibly missing at random.

Confounding Bias: The promise of EHR

- S. Begley, Scientific American, 2011:
- “Today’s pioneers in the use of health records for CER are well aware that they are conducting observational studies.
- But they have developed statistical and other methodologies to safeguard against the errors that can bedevil such investigations. The key step is to make sure that it was not something about the patient rather than the treatment that accounted for a given outcome, as was the case in the observational studies of hormone replacement.
- There is always the real possibility that people who get one treatment may be different in some ways from people who get another treatment,” Selby says. “To adjust for that, you need very detailed data, and Kaiser Permanente has it. It can tell you that patients [in the comparison groups] were identical for all practical purposes or allow you to adjust statistically for any remaining differences.”

Caution: Confounding by Indication

- Confounding by indication: If doctors think Drug A is more effective than Drug B but has bigger side effects, then doctors are going to tend to prescribe Drug A to patients they think have worse prognosis.



Miettinen's Caution

- Miettinen, Statistics in Medicine, 1983:
- The need for randomization as a means of controlling confounders is accentuated in the study of intended effects (efficacy) as compared with unintended ones (toxicity).
- Basic reason: Whenever a rational indication for the intervention exists, it tends to constitute a confounder
- The indication, as applied in actual practice of health care, can be quite complex and subtle.

Miettinen's Caution Still Applies to EHR

- EHR and big data doesn't get around the confounding by indication problem.
- If two patients with the same observed covariates get different treatments, we need to ask why?
- We have to think that the reason is random to make causal inferences about the effect of the treatment.
- For reliable causal inferences:
  - Look for natural experiments embedded within the data.
  - Use quasi-experimental tools to test for hidden bias, e.g., multiple control groups, secondary outcomes that are known to be unaffected by treatment.

Constructing a Natural Experiment by Isolation

- Zubizarreta, Small and Rosenbaum (2014).
- Natural Experiment: Observational study in which treatment assignment, though not randomized, is haphazard.
- Traditionally, natural experiments have been found not built.
- There is scope for building natural experiments by *isolating* brief moments in time and aspects of treatment assignment that are haphazard, close to random.
- Like a laboratory in which a treatment is studied in isolation from disruptions.
- Isolation: Tool for constructing natural experiments that combines differential effects and risk set matching.

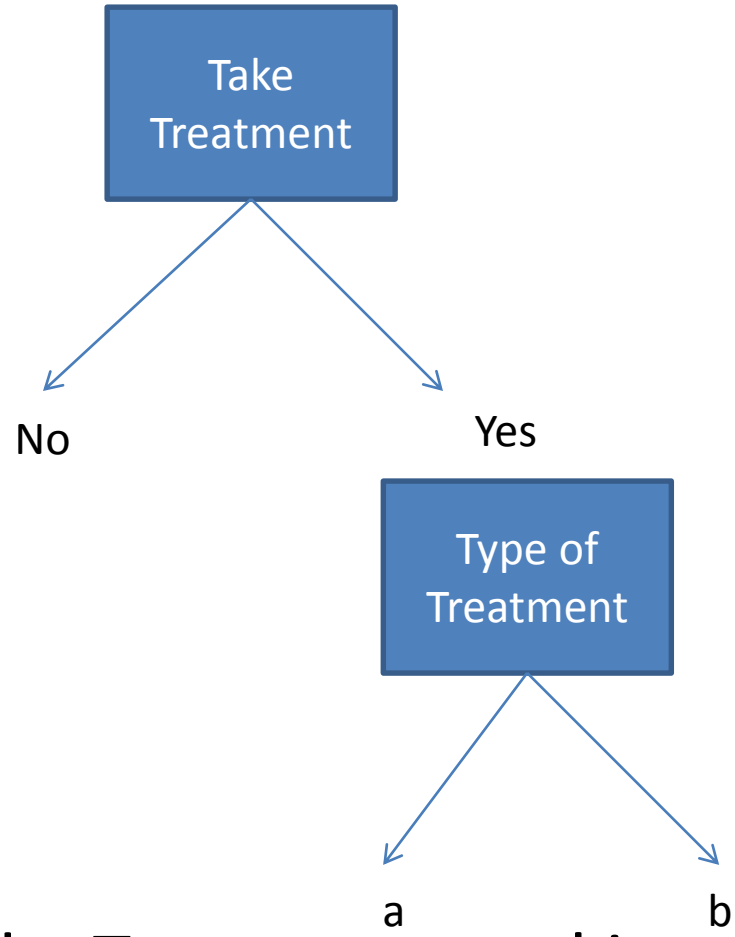
Example: Effects of Fertility on Workforce Participation

- Does having more children reduce a mother's participation in the workforce?
- The challenge of finding a natural experiment: Many decisions to have children are planned, not haphazard.
- Isolating a natural experiment (Based on Angrist and Evans, 1996):
  - Differential effect: Compare two women who are both having a child, but one has twins and one does not.
  - Risk set matching: Match two women -- one who had twins, one who did not -- who had similar covariates at the time before birth.

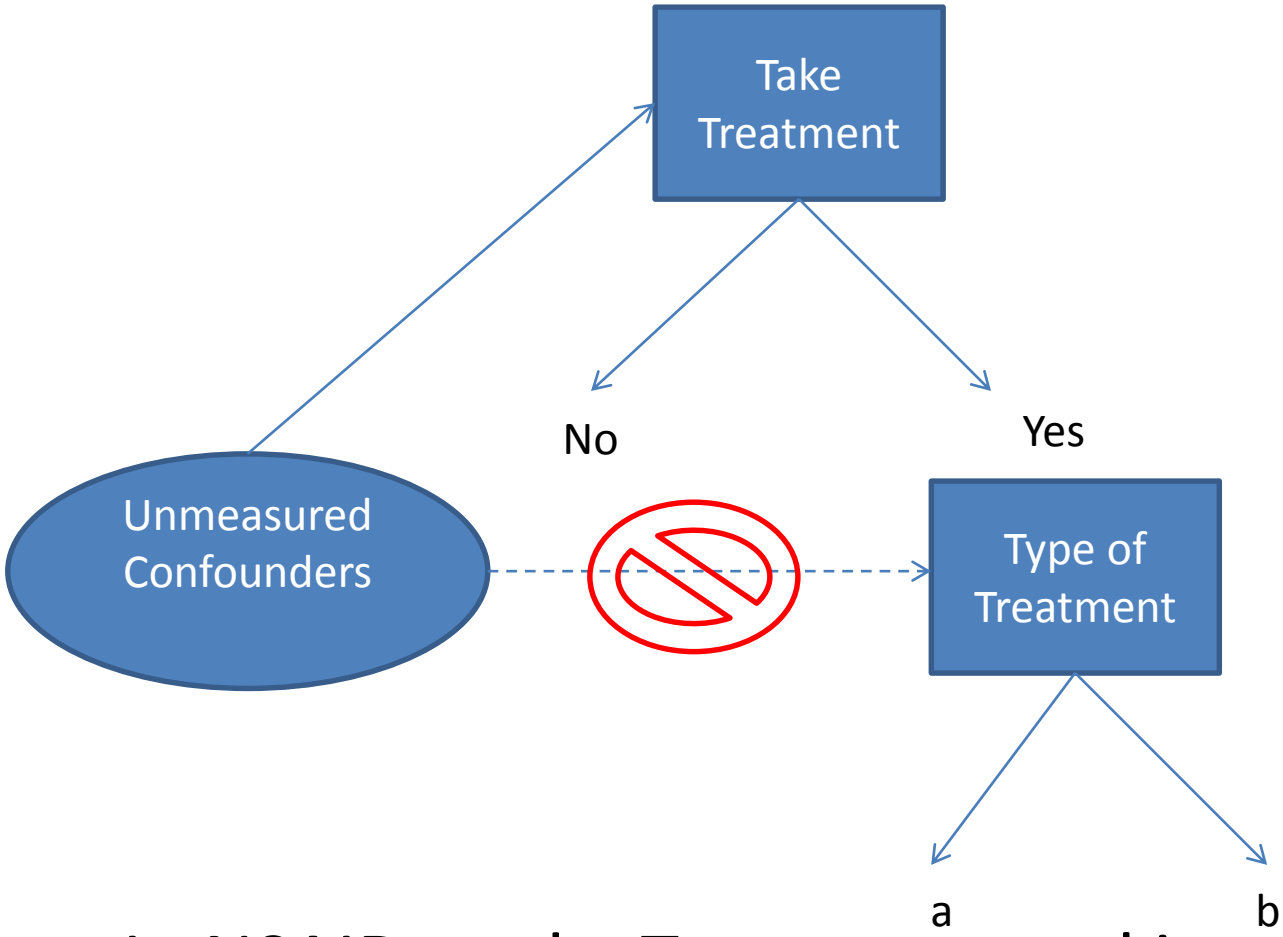
Differential Effects

- Receiving a treatment may be very biased by unmeasured covariates but among people receiving treatment, receiving treatment *a* in lieu of *b* may be less biased.
- Example (Anthony et al., 2000): There is a theory that taking NSAIDs (e.g., Advil) may reduce the risk of Alzheimer's.
- Confounding: People in early stage of Alzheimer's may be less aware of pain and less likely to take pain relievers like Advil.
- Differential effect: There are pain relievers that are not NSAIDs, e.g., Tylenol.

  Compare Alzheimer's risk among people who take Advil vs. Tylenol.



- In NSAID study: Treatment = taking pain reliever, a=Advil, b= Tylenol
- In workforce participation study: Treatment = Having another child, a = Single birth , b = Twin birth



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Risk Set Matching

- We want to compare women, who prior to the birth, were similar.
- Such a comparison can be achieved by matching on measured covariates.
- We only want to match on covariates prior to the birth, not after the birth.
- For example, for two women giving birth at age 18, one who had a single birth, one who had twins, we want to match on education up to age 18, not education after age 18.
- Risk set matching: Matching that respects the temporal structure of treatment assignment in observational studies (Li et al., 2001; Lu, 2005).

Risk Set Matching for Workforce Participation Study

- Data from 1980 U.S. Census.
- Matched sets formed in temporal order, beginning with 2nd pregnancy, assuming no twins prior to 2nd pregnancy.
- First, mothers who had twins at their 2nd pregnancy were matched to five mothers who had single child at their 2nd pregnancy.
- Second, unmatched mothers who had twins at their 3rd pregnancy were matched to five unmatched mothers who had single child at their 3rd pregnancy.
- Third, unmatched mothers who had twins at their 4th pregnancy were matched to five unmatched mothers who had single child at their 4th pregnancy.

More on Risk Set Matching

- The matching at the 2nd pregnancy controlled for age and education at 1st and 2nd pregnancies but not at 3rd pregnancy.

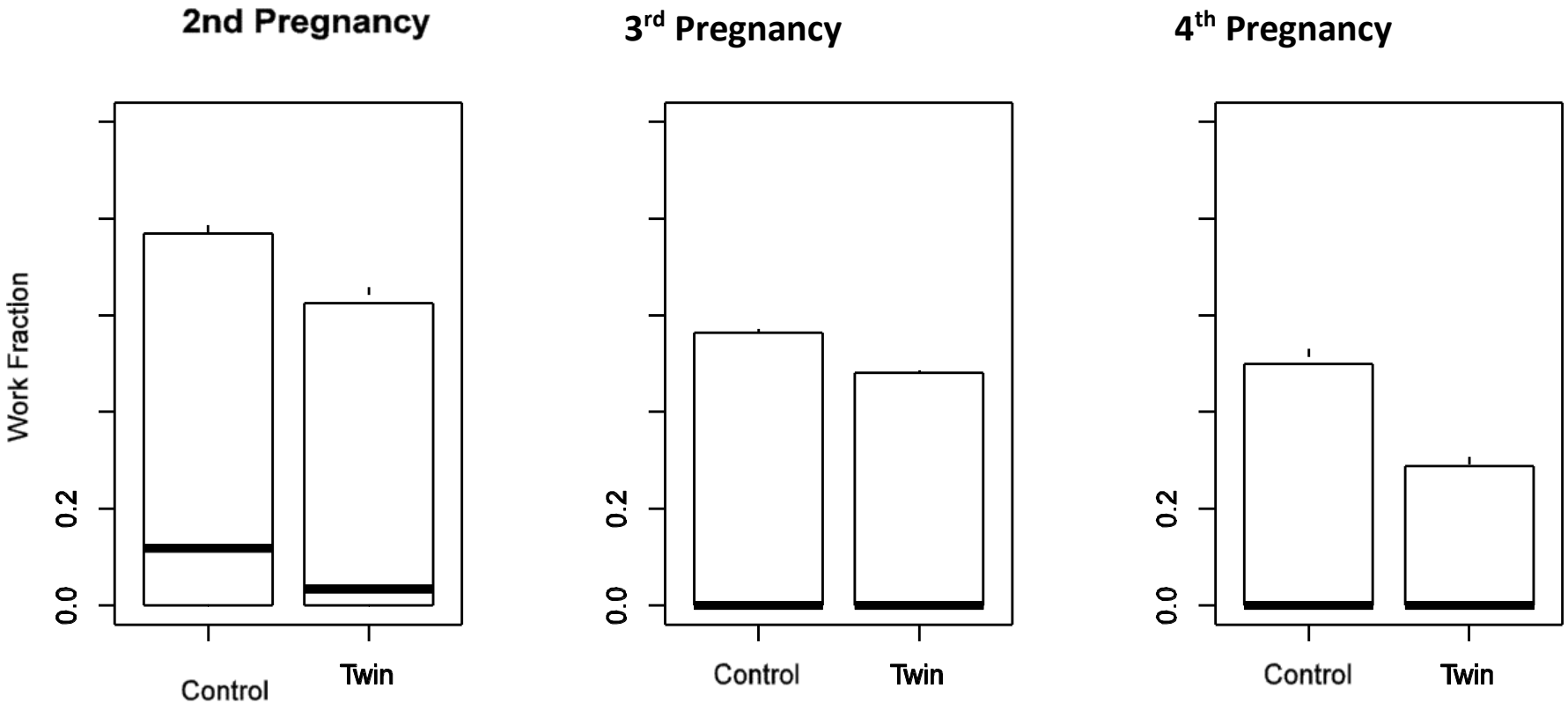
  The matching at the 3rd pregnancy controlled for age and education at 1st, 2nd and 3rd pregnancies but not 4th pregnancy.

  The matching at the 4th pregnancy controlled for age and education at 1st, 2nd, 3rd and 4th pregnancies.
- In addition to age and education up to kth pregnancy, we matched for race/ethnicity and region.
- We used a robust Mahalanobis distance and carried out optimal matching to minimize this distance. We used mipmatch in R (Zubizarreta, 2012) to do the matching.

Covariate	2nd birth		3rd birth		4th birth	
	Twin	Control	Twin	Control	Twin	Control
	Sample Size					
# of mothers	3380	16900	1358	6790	302	1510
	Mother's Age in Years, mean					
At the Census	30.4	30.4	30.7	30.7	31.6	31.6
At 1st birth	20.4	20.4	19.5	19.5	18.8	18.8
At 2nd birth	23.5	23.4	21.8	21.8	20.7	20.7
At 3rd birth			25.1	25.1	23.5	23.4
At 4th birth					26.7	26.6
	Mother's Education in Years, mean					
At 1st birth	11.9	12.0	11.4	11.4	10.8	10.9
At 2nd birth	12.2	12.2	11.6	11.6	11.0	11.1
At 3rd birth			11.6	11.6	11.1	11.2
At 4th birth					11.1	11.2
	Mother's Education at 1st Birth, %					
High school	43	43	42	42	32	33
Some college	19	19	14	14	15	14
BA or more	09	09	05	05	03	03
	Mother's Education at 2nd Birth, %					
High school	47	47	48	48	39	40
Some college	20	20	15	15	16	15
BA or more	11	11	06	06	04	04
	Mother's Education at 3rd Birth, %					
High school			48	48	41	41
Some college			16	16	16	16
BA or more			06	06	05	05
	Mother's Education at 4th Birth, %					
High school					41	41
Some college					16	16
BA or more					05	05

Matching created balance on covariates prior to treatment (birth).

Outcomes



Outcome is Work Fraction = % of 40 hour work week worked.

Inferences

- Permutation test to check whether treatment (having twins) is independent of putative potential outcome for workforce participation under hypothesized treatment effect.
- We estimated that having twins decreased hours worked by 8% with a lower 95% confidence bound of 6%.

Isolating a Natural Experiment

- In a process that exhibits both thoughtful planning and confounding with unmeasured covariates, there may be brief moments when aspects of the process are decided nearly at random.
- Isolation means focusing on those aspects and those moments:
  - Using differential effects to focus on those aspects (single birth vs. twin births)
  - Using risk set matching to focus on particular moments when some haphazard event occurs.
- Example of another potential application: Effect of incarceration on subsequent criminal activity (Nagin and Snodgrass, 2013):

  Committing a crime is not haphazard nor is a judge's decision about whether to incarcerate a person

  Differential effect: Consider people who have committed a crime. Compare those people who committed a crime and were tried by a lenient judge to those people who committed a crime and were tried before a strict judge.

Summary

- EHR and other big data sources: Potential for improving causal inferences.
- But old problems of selection bias and confounding bias still need to be attended to.
- Sebastien's good idea: For selection bias, break down the process of missing data into submechanisms which can be better understood than whole process at once.
  - Conquer and divide strategy.
  - Offers potential for identifying subsets of the data where selection bias is not as much of a problem.
- Confounding bias: Try to isolate natural experiments.

References

- Miettinen, O.S. “The need for randomization in the study of intended effects,” *Statistics in Medicine*, 1983.
- Joffe, M.M., Yang, W.P. and Feldman, H.I. “Selective ignorability assumptions in causal inference”, *International Journal of Biostatistics*, 2011.
- Zubizarreta, J.R., Small, D.S. and Rosenbaum, P.R., “Isolation in the Construction of Natural Experiments,” *Annals of Applied Statistics*, 2014.