Lecture 4

Extensions

Extension 1: advanced matching methods

- **Covariate-balancing propensity score** (Imai and Ratkovic, 2014)
  - Estimates Pscore to explicitly maximise balance
- **Entropy balancing** (Hainmueller and Xu, 2014)
  - Reweighting to maximise balance
- **Machine learning** approaches to pscore estimation (Lee et al 2010)
- **Cardinality matching** (Resa and Zubizarreta, 2016):
  - Maximises matched sample given balance constraints
- **Near/far matching** (Baiocchi et al. 2012)
  - Combines instrumental variables and matching

Extension 2: Sensitivity analysis:

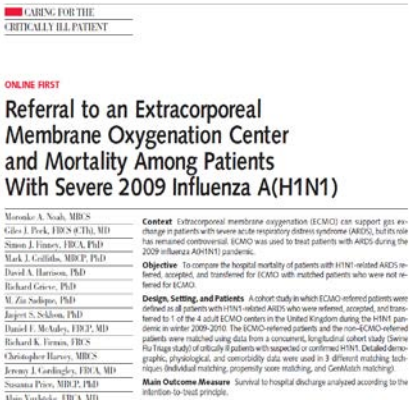
Considering the no unobserved confounding assumption

- Choices driven by 'the science' not statistical significance
- Theory, causal diagrams, empirics, experts can all help
- Good design is crucial: a rich set of measured covariates (Rubin 2007)
- Placebo tests (Jones 2007)
- Sensitivity analysis
- How strong does the unobserved confounding need to be, to invalidate conclusions? (Rosenbaum 2002)

Considering unmeasured confounding: example

Noah et al, 2011, JAMA

- Extracorporeal membrane oxygenation (ECMO) vs no ECMO
- H1N1, severe acute respiratory distress syndrome
- Matched cohort design for reducing selection bias
- Estimated relative risk of ECMO on mortality 0.47 (p=0.001)
- Sensitivity analysis to test robustness
  - Assumes unmeasured confounder, perfect correlation mortality
  - How large would relative prevalence of unobserved confounder in treatment versus controls need to be to change conclusions?
  - To conclude “no effect”, confounder would have to be relatively prevalent in ECMO vs no ECMO arm; odds ratio > 1.8
  - Highly imbalanced observed confounder; odds ratio=1.3



CARING FOR THE CRITICALLY ILL PATIENT

ONLINE FIRST

Referral to an Extracorporeal Membrane Oxygenation Center and Mortality Among Patients With Severe 2009 Influenza A(H1N1)

Extension 3: Population-adjusted indirect comparisons

- What if IPD available for one comparator, published data from other?
- For “anchored” indirect comparisons, can use propensity score methods
- Matching-adjusted indirect comparisons (MAIC) (IPW) (Signorovitch et al)
- To minimise bias must balance all prognostic variables that modify effect
- http://scharr.dept.shef.ac.uk/nicedsu/wp-content/uploads/sites/7/2017/05/Population-adjustment-TSD-FINAL.pdf
- See also Hartman et al 2010!

Extension 4: Time-varying treatments

- Interventions often administered over multiple time periods
- Clinicians update treatment decisions based on new prognostic information

Example 1: crossover in oncology trials

- Statistical adjustment to re-create control group with no access to treatment (Morden et al. 2011, Latimer et al., Ishak et al. 2014)
- Eg. Inverse probability of treatment weighting

Extension 4: Time-varying treatments

- Interest in evaluating the consequences of whole treatment sequences
- Dynamic treatment regimes (adaptive treatment, multi-stage treatment strategy)

Example 2: treatment of chronic conditions

- Biological drugs in rheumatoid arthritis: What is the optimal sequence?
- "Big data" can be used to emulate randomised trials (Hernan and Robins, 2016)
- Methods available to estimate "optimal" treatment sequences using patient-level data (e.g. inverse probability of treatment weighting, g-estimation)
- Strong assumption: "sequential randomisation"

References

- Noah M et al (2011). Extracorporeal membrane oxygenation for severe respiratory failure secondary to H1N1 Influenza A: a case-matched study. *JAMA* 206(15):1659-68.
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- Hartman E et al. From sample average treatment effect to population average treatment effect on the treated: combining experimental with observational studies to estimate population treatment effects. Journal of the Royal Statistical Society: Series A (Statistics in Society). 2015 Jun 1;178(3):757-78
- Latimer NR, et al. (2014) NICE DSU Technical Support Document 16: Adjusting survival time estimates in the presence of treatment switching. School of Health and Related Research, University of Sheffield, Sheffield, UK. 2014 Jul:b12.
- Hernán MA, Robins JM. Using big data to emulate a target trial when a randomized trial is not available. American journal of epidemiology. 2016 Mar 18;183(8):758-64.

Summary

- Impetus on RWE presents massive opportunities for HTA
- Big data and good design are necessary but insufficient
- Require analytical methods make realistic assumptions
- Matching methods reduce reliance on model specification
- Important to assess unobserved confounding
- 'Precision medicine' requires flexible analytical methods
  - estimate effects relevant individual patients
  - to evaluate dynamic treatment regimens