



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)

Murako A. Noah, MBS
Giles J. Park, FRCR & The MD
Simon J. Timmes, FRCR, PhD
Mark J. Goldacre, MRCGP, PhD
David A. Harrison, PhD
Richard Grieve, PhD
W. Zia Nadeem, PhD
Jagjit S. Nadeem, PhD
Daniel J. McAdam, FRCR, MD
Richard K. Evans, FRCR
Christopher Barnes, MBS
James J. Galloway, FRCR, MD
Susanna Price, MRCGP, PhD
Dina Vekic, PhD & The MD

Context Extracorporeal membrane oxygenation (ECMO) can support gas exchange in patients with severe acute respiratory distress syndrome (ARDS), but its role has remained controversial. ECMO was used to treat patients with ARDS during the 2009 influenza A(H1N1) pandemic.

Objective To compare the hospital mortality of patients with H1N1-related ARDS referred, accepted, and transferred for ECMO with matched patients who were not referred for ECMO.

Design, Setting, and Patients A cohort study in which ECMO-referred patients were defined as all patients with H1N1-related ARDS who were referred, accepted, and transferred to 1 of the 4 adult ECMO centers in the United Kingdom during the H1N1 pandemic in winter 2009–2010. The ECMO-referred patients and the non-ECMO-referred patients were matched using data from a concurrent, longitudinal cohort study (Severe Flu Trial) of critically ill patients with suspected or confirmed H1N1. Detailed demographic, physiological, and comorbidity data were used in 3 different matching techniques (individual matching, propensity score matching, and GenMatch matching).

Main Outcome Measure Survival to hospital discharge analyzed according to the intention-to-treat principle.



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.
- Signorovitch JE, et al. (2012) Matching-adjusted indirect comparisons: a new tool for timely comparative effectiveness research. *Value in Health*. 2012 Oct 31;15(6):940-7.
- 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