Associating with DAGs can be beneficial:

A tour through counterfactuals, causal graphs, challenges and opportunities

Andrew Forbes
Monash University

Acknowledgements:
Dr Susan Shortreed, GHC, USA

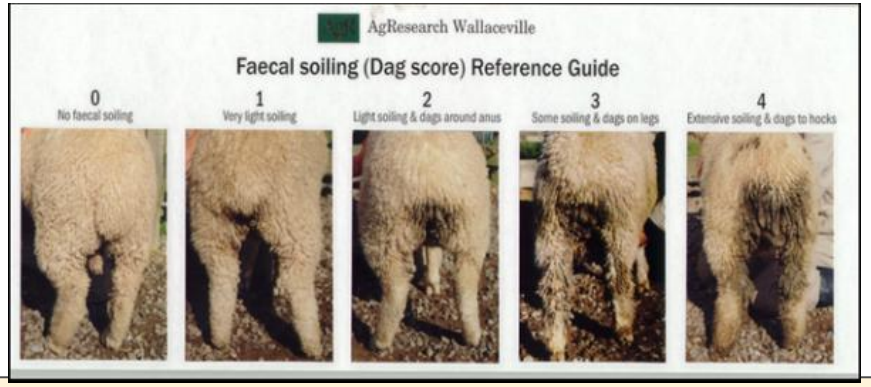
Outline

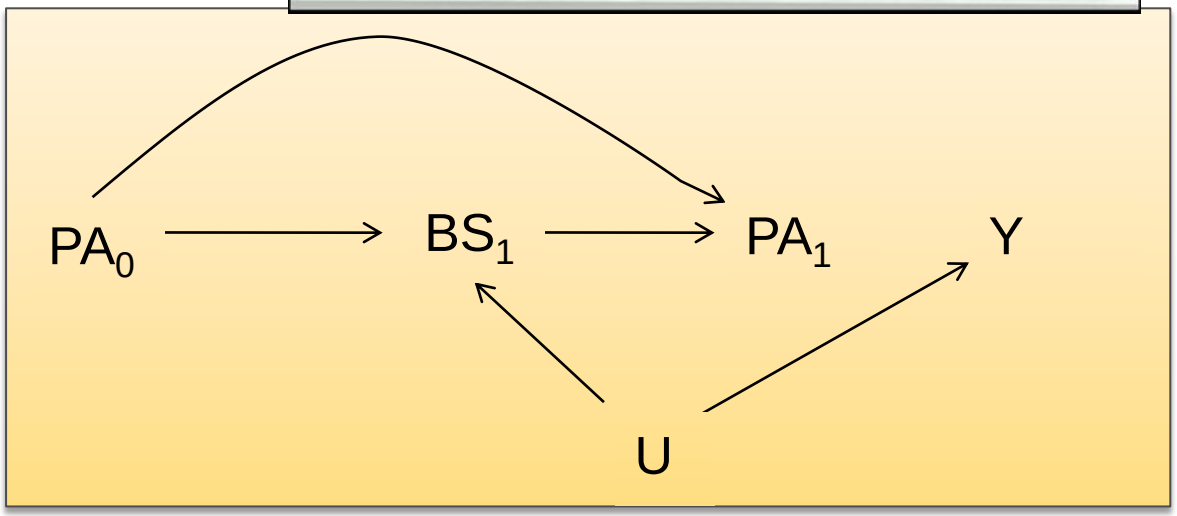
- Counterfactuals (potential outcomes)
- Defining causal effects
- Estimation, assumptions
- Causal graphs and longitudinal studies
- Mechanisms
- Comments
- Running example: Physical activity and CVD

DAG ?

Someone who *dresses* or *behaves*
in an unfashionable or unstylish manner

Wool on a sheep's rear quarters which is dirty with mud and excreta





Directed Acyclic Graph

Counterfactuals

[potential outcomes]

Neyman (1923)

Rubin (1974)

Rubin Causal Model

John has a headache

Will it help if he takes a Panadol?

He took a Panadol

Over the next 20 minutes …

Did the panadol *cause* his headache relief?

Outcome if he *didn't* take panadol ?

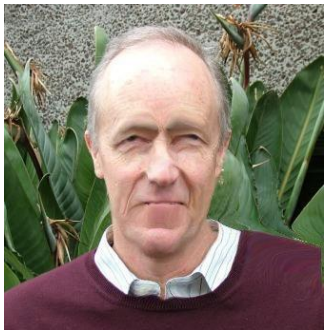
Potential outcomes Y(0), Y(1)

- Y(*a*) = potential outcome under *assignment* of 'treatment' A=*a* (0, 1)
- Causal effect = Y(1)-Y(0) = difference when *intervene*
- Observe Y(1) = Y = 1

- Y(0) unobserved

Y(0)=1 ??

OR



Y(0)=0 ??

Population (Average) Causal Effect

- E[Y(1) – Y(0)]
  - Average outcome if all 'treated' compared to all 'not treated'
- Can estimate in large perfectly conducted randomised trials
  - Control and treatment groups are 'exchangeable'
    - Trt groups alike wrt all factors apart from treatment
    - Control group represents outcome of treated group if had not been treated
    - P(Y(0)=1 | A=1) = P(Y(0)=1 | A=0) = P(Y(0)=1)
    - $Y(0) \perp A$ $Y(0), Y(1) \perp A$
  - Association in such RCT = Causation
- Observational studies ??
  - Exposed and unexposed not exchangeable [PA vs no PA]
  - How to mimic a randomised trial of exposure ?

Why are potential outcomes useful?

- Enables clear definition of causal effects
- Enables clear statement of assumptions required for causal inference
- Provides a framework for developing and assessing estimation methods
- *But causal framework not a 'magic pill' for inadequate data or design*
  - *- in best case is still based on untestable assumptions*

Assumptions for valid causal inference

Fundamental assumptions

- Consistency:
  - Observed outcome is one of the counterfactual outcomes [*consistent]*
  - Y=Y(A) : Potential outcome if observed exposure was assigned is the observed outcome
    links observed and counterfactuals
  - → No multiple versions of treatment/exposure
- Positivity
  - Every individual must be able in theory to have each exposure [a=0,1]
- Conditional exchangeability/randomisation given X
  - $Y(0), Y(1) \perp A \mid X$ = no unmeasured confounders
  - *Not testable - Design, design, design!!!*
- Correct functional form of models (no 'misspecification')

Randomised trials

- Consistency:
  - "We know what happens when the treated are assigned treatment"
  - Y=Y(A)
- Positivity: true by design $0<P(A=1)<1$
- Exchangeability: true by randomisation
- Models: none needed

Exch, Pos

Cons

$$E[Y(1)] = E[Y(1) \mid A=1] = E[Y \mid A=1]$$

Defining causal effects in observational studies ?

- Is Y(1) – Y(0) 'unambiguous' ?
- Non-randomised *treatments*
  - Can easily conceptualise assigning treatment or not
- *Exposures*:
  - eg Physical activity – a choice, action: can be intervened upon / manipulated
  - Body size – an attribute, biomarker (Hernan+Taubman 2008)
    - Potential outcomes ill-defined – will vary with manipulation for altering body size
    - Diet, starvation, gastric banding → "multiple versions"
    - Consistency violated
- "No causation without manipulation"

Estimation when assumptions hold:

- Exposure A= 0 or 1 Y binary
- E[Y(1) – Y(0)]
- X= all confounders : $Y(0), Y(1) \perp A \mid X$

Exch, Pos

$$E[Y(1)] = E_X(E[Y(1) \mid X]) = E_X(E[Y(1) \mid X, A=1])$$

Cons

$$= E_X(E[Y \mid X, A=1])$$

= (directly) standardised risk in A=1

= G-computation (Robins 1986)

Causal effect = Difference of standardized risks

Methods for confounding adjustment

Propensity scores, inverse probability weighting (IPW)

Propensity scores (Rosenbaum+Rubin 1983)

- Propensity score $e(X) = P(A=1|\underline{X})$
  - Regression model for treatment assignment mechanism
  - Exchangeability given $\mathbf{X}$ then exchangeability given scalar $e(X)$
  - Balance: $\underline{X} \perp A \mid e(X)$
  - Stratify, adjust, match using propensity score

- No 'magic' to propensity scores
  - With large enough sample size can do standardisation or regression model given $\underline{X}$ to estimate $E[Y(1) - Y(0)]$
  - Simply a useful method for "finite" samples

Inverse probability weighting (IPW)

- Sample surveys (Horvitz-Thompson)
- Example: Pr(Trt|Male) = 1/3 Pr(Trt|Female)=1/4
  - To estimate E[Y(1)] :
    Weight treated males by 3, treated females by 4
  - To estimate E[Y(0)] :
    Weight untreated males by 3/2, untreated females by 4/3

- Generally, estimate prob of treatment *actually received* as function of X = e(X) or 1-e(X)
  - Weight by reciprocal of this probability

- In weighted "*pseudo-population*" trt and X uncorrelated
- Can estimate E[Y(1) - Y(0)] using weighted analysis

- Other uses: Risk difference and ratio regression, odds ratios with propensity scores (Ukoumunne et al 2010, Forbes et al 2008)

Longitudinal studies and causal diagrams

Robins et al (1986+)

Pearl (2000+)

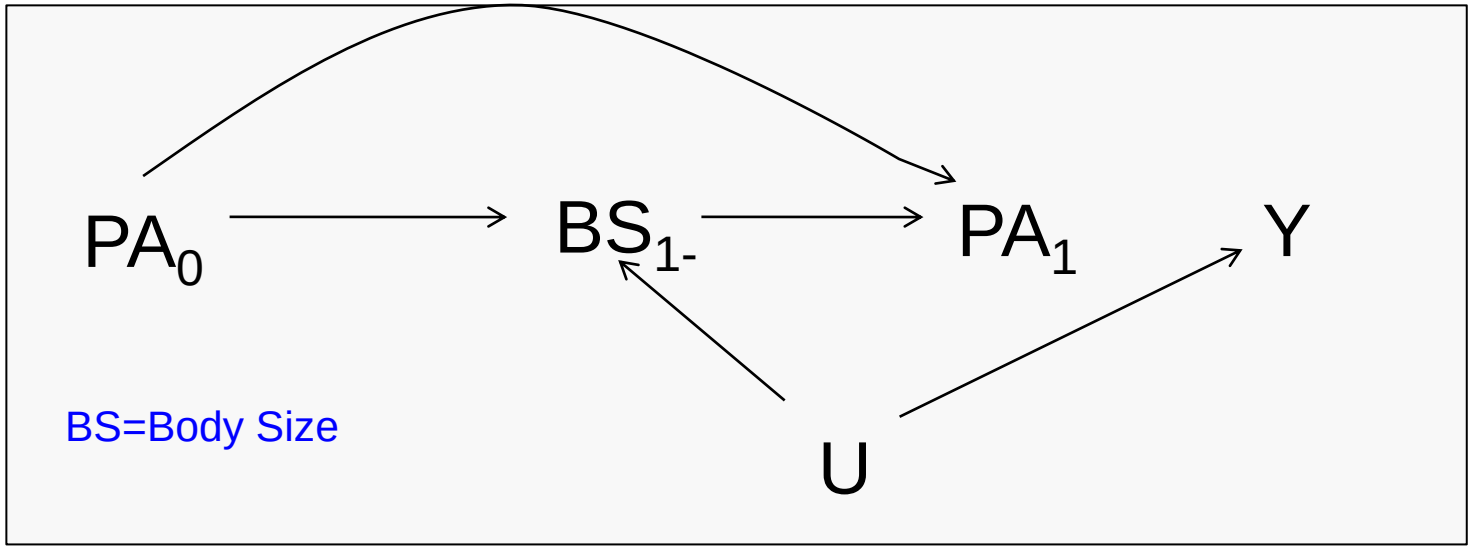
Hernan (2000+)

Longitudinal studies

- Exposure and covariates can vary over time
- Suppose 2 time points t=0, 1
- Assume single Y measured at end
- Potential outcomes – defined for each possible exposure sequence (a_0, a_1)
- Fixed/static exposure
  - Often interested in always versus never exposed (1, 1) vs (0, 0)
  - Average causal effect if $E[Y(1, 1)] \neq E[Y(0,0)]$

Causal Directed Acyclic Graphs

- Encodes causal assumptions
- Nodes are random variables
- Arrows reflect (direct) causal effects, absence=strong assumption
- Common causes of two variables must be included
- Here no direct or indirect effect of exposure (PA) on CVD



Note: Well defined interventions only needed for nodes of causes of interest

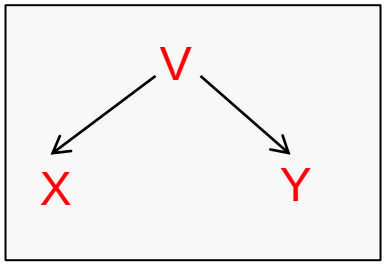
DAGs and usefulness

- Substantive concept map
  - intuitive
- Source of biases (Hernan et al)
  - Confounding
  - Selection bias
  - Measurement error
- Analysis approaches
- Direct effects / mediation
- Correspondence with counterfactuals
  - Theorem in DAGs = theorem in counterfactuals (Pearl 2000, 2009)

DAG Background

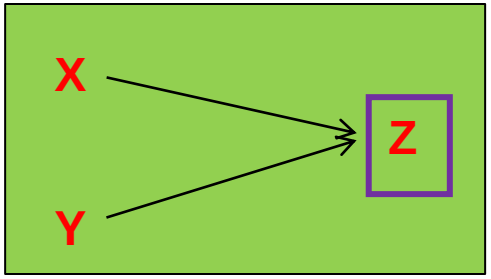
An observed association between two random variables X and Y can be due to:

- Chance
- X causes Y or Y causes X
- X and Y share a common cause (confounding)
- A third variable was conditioned on which is a consequence of both X and Y (ie a common effect of X and Y)



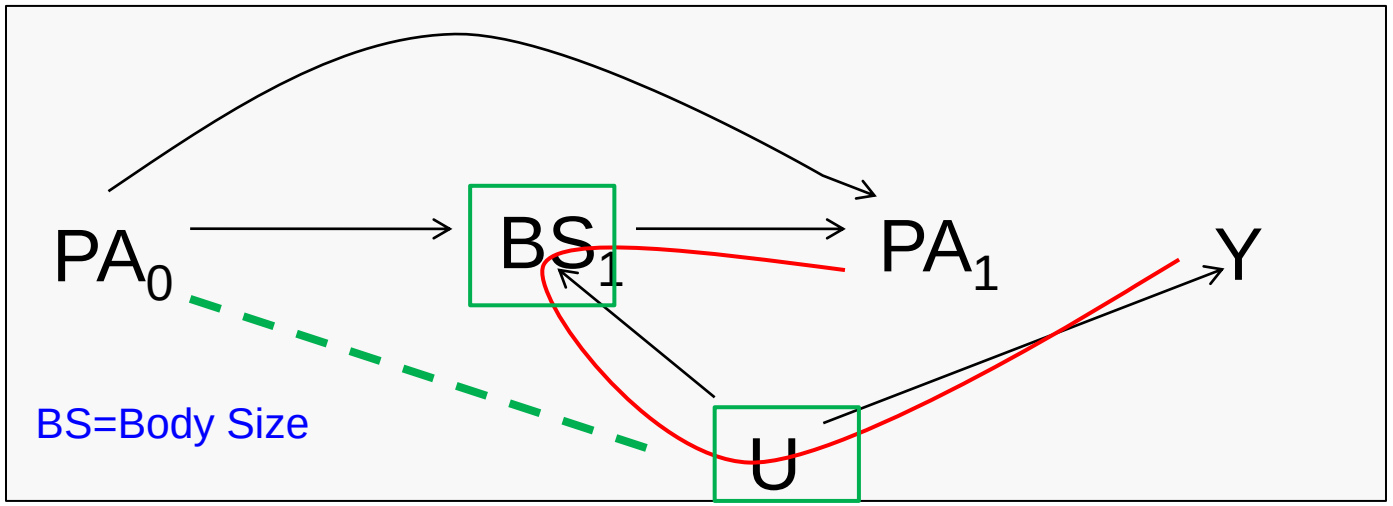
Height and speed: basketball prowess

- X = height, Y = speed, Z = pro basketball player (=1)
- short pro players must be very fast! → -ve assoc b/w X and Y



- Z is called a **"collider":** arrows collide at Z: X→Z←Y

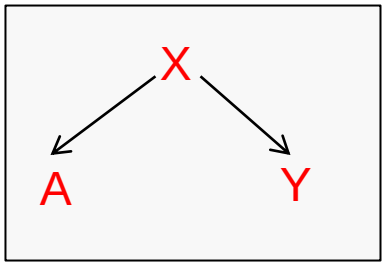
Paths and observed associations



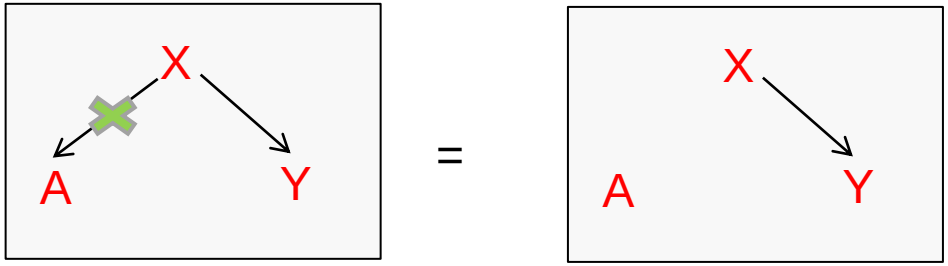
- Observed associations arise from transmission along paths
- A *"backdoor"* path exists from PA_1 to Y: $PA_1 \leftarrow BS_1 \leftarrow U \rightarrow Y$
  - → Observed association b/w PA_1 and Y
  - Confounding by U (common cause)
- Conditioning on a non-collider blocks the path
- Associations are not transmitted across colliders, unless the collider is conditioned on eg $PA_0 \rightarrow BS_1 \leftarrow U$

Aside: DAGs and IPW

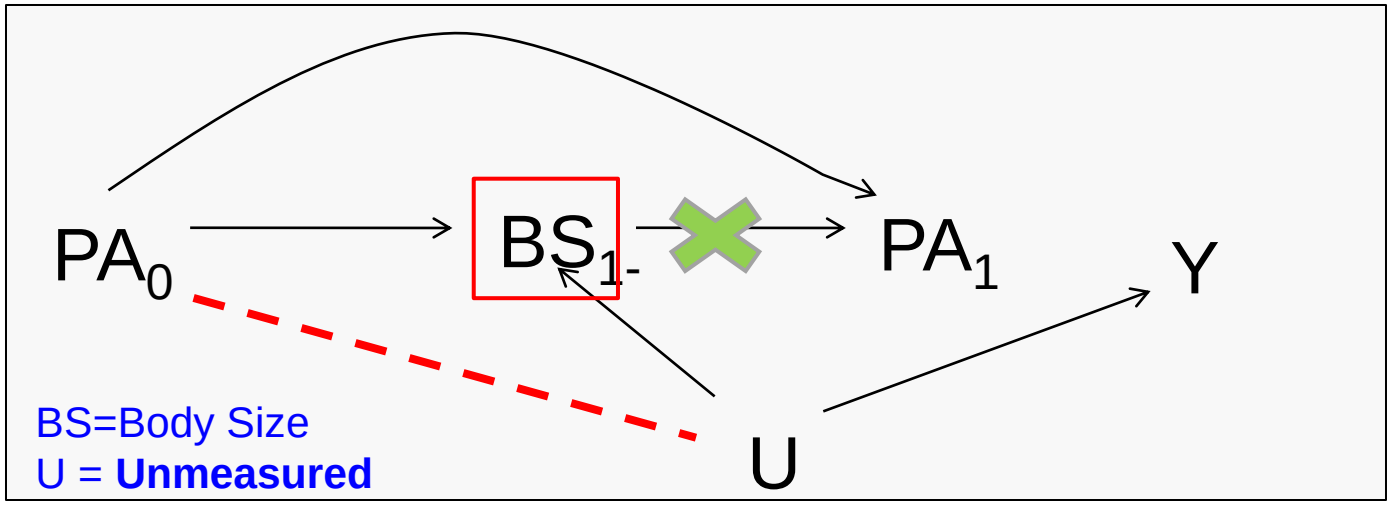
- IPW creates pseudopopulation where X is balanced between exposure groups
- Initially



- IPW: regress A on X
  - X and A unassociated in weighted population



Estimation of PA effect (1,1) vs (0,0)



- Effect of PA_1 on CVD : need to control for U
  → obtained by conditioning on BS_1
- Conditioning on BS_1 induces assoc b/w PA_0 and U !
- → Adjust or not, conventional methods biased
- Remedy – don't condition on BS: use IPW of PA_1 on BS_1 to break path $BS_1 \rightarrow PA_1$

Marginal structural models

- Extension of IPW to longitudinal setting
- Weights are reciprocal of probability of observed exposure *history* conditional on past covariate history
  - Creates pseudopopulation where exposure not confounded at any time ["sequential randomisation"]
- "Structural" outcome model for single counterfactual exposure history
  - eg $E[Y(a_0,a_1)] = g(a_0, a_1)$
  - Weighted regression, robust SEs

Framingham Heart Study: Effect of PA

Shortreed+Forbes 2012

- National Heart Institute enrolled 5,209 men and women for longitudinal study of CVD in 1948
- Risk factors collected every 2 years
  - Physical activity collected 3 times, 16 years apart
- 40 years of follow-up
- Interested in effects of "long term" PA

Physical Activity and covariates

- Interested in active versus inactive
  - Create binary PA based on Aust recommendations
    - derived from # of hours spent at different activity levels

- 3 categories of PA history at time t
  1. Always Inactive up to t
  2. Always Active up to t
  3. Mixed Activity Levels up to t

- Set of covariates included in analysis: (2 years prior to PA)
  - sex, type of job, education, birth country, BMI at age 25, age, BMI, comorbidity (arthritis, LVH, ankle edema, pulmonary disease, diabetes, cancer), smoking status, hypertension status, marital status, alcohol use, blood glucose level

Estimating "lifetime" PA effect

- Standard time dependent Cox model biased for lifetime PA
- Use marginal structural model

- **Weights at t:** PA history at time t as function of past PA and all covariates
  - Also include model for missing data and loss to followup
  - Pseudo popn with no confounding and no missing data and no loss to followup

- **Structural Cox model:**

( ) ( )

e^{β} = HR for always vs never active

Estimation by weighted Cox regression [pooled logistic]

Results: CVD Mortality

Model	HR [95% CI]
Cox_{adj} Lifetime PA -CC	0.76 [0.63, 0.91]
MSM – CC	**0.75 [0.60, 0.94]**
MSM – censoring model	**0.65 [0.43, 0.97]**

CC=complete case

- Little difference in CC: time dependent confounding perhaps not major problem!
- *OR: Time dept confounding is swamped by unmeasured confounding!*
  - *Model decision to be physically active ??*
- Generalisable to other lifestyle exposures??
- *PA measurement error?*
- How handled missing data had greater effect than handling confounding!

More than ‘total’ effect: Mechanisms of action

Mechanisms

So far: Total causal effects

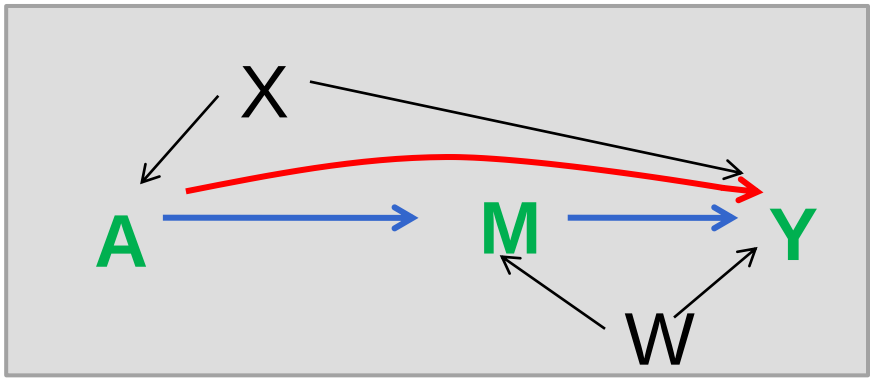
- No examination of mechanism

Mechanisms:

- Often substantively interesting
- "Direct" and "indirect" effects, mediation
- Eg Indirect: PA → BMI (2 years later) → CVD
  Direct: PA → CVD directly

Mechanisms and direct effects

- Direct effect of A on Y "Standard" approach: (Baron+Kenny 1986, 18000 cites)
  - regress Y on A, then Y on A and M
- DAG rules can help
  - Eg Here M a collider, so need to control for W
  - If W a consequence of A then no good!



- Implicit is ability to intervene on M
  - "Controlled" and "natural" direct effects (IPW, G-comp)
  - Sequential conditional exchangeability assumptions needed + more! (Petersen 2006)

When M is an attribute

- eg BMI - manipulation ill-defined
- Principal stratification approach (Frangakis+Rubin 2002)
  - Regard BMI as counterfactual outcome – not intervened upon
  - eg *effect of PA on CVD for people who would have high BMI if don't exercise*

    E (Y(1) | BMI(0) = H) vs E(Y(0) | BMI(0) = H)
  - *Not identified! Needs assumptions to provide bounds.* *(Joffe 2007, Sjolander 2009)*

- Similar issues: "Complier Average Causal effect" ,"Truncation by death"
- Varying approaches for identifiability
  - which ones make sense for practice?

- Conclusion: Mechanisms are difficult to estimate!!
  - Much more than multiple regression!

Conclusions: opportunities

- Causal framework has provides lots of new avenues for work
- Always challenging! Needs sensible assumptions to enable practical use

In ViCBiostat program:

- Measurement error in exposures
- Dynamic interventions in longitudinal data: G-computation extensions
- Principal stratification – RCTs and obs studies

General:

- New methods, sensitivity to assumptions
- Maths-heavy or applied: needs more application papers !
- Mechanisms! Alternative approaches?
- Many subject matter areas to apply methods

References

- Neyman 1923: Translation: On the Application of Probability Theory to Agricultural Experiments. Essay on Principles. Section 9. *Statistical Science* 1990;5(4):465-72.
- Rubin DB. Estimating causal effects of treatments in randomized and nonrandomized studies. *Journal of Educational Psychology; Journal of Educational Psychology* 1974;66(5):688.
- Robins J, Hernan M. Causal Inference book: http://www.hsph.harvard.edu/faculty/miguel-hernan/causal-inference-book/
- Hernan MA, Taubman SL. Does obesity shorten life? The importance of well-defined interventions to answer causal questions. *Int J Obes* 2009;32(S3):S8-S14
- Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika* 1983;70(1):41-55.
- Ukoumunne O et al. Confounder-adjusted estimates of the risk difference using propensity score-based weighting. *Statistics in Medicine* 2010;29(30):3126-36.
- Forbes AB , Shortreed S. Inverse probability weighted estimation of the marginal odds ratio. *Statistics in Medicine* 2008;27(26):5556-59.
- Pearl J. Causality. 2nd edition, 2009.
- Robins J A New Approach to Causal Inference in Mortality Studies with a Sustained Exposure Period - Application to Control of the Healthy Worker Survivor Effect. *Mathematical Modelling* 1986;7(9-12):1393-512.
- Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11(5):550-60.
- Shortreed S, Forbes AB: Estimating the effect of long-term physical activity on cardiovascular disease and mortality: evidence from the Framingham Heart Study. Submitted
- Petersen M. et al. Estimation of direct causal effects. *Epidemiology* 2006;17(3):276-84.
- Frangakis CE, Rubin DB. Principal stratification in causal inference. *Biometrics* 2002;58(1):21-29.
- Joffe M. et al Defining and estimating intervention effects for groups that will develop an auxiliary outcome. *Statistical Science* 2007;22(1):74-97.
- Sjölander A et al. Sensitivity Analysis for Principal Stratum Direct Effects, with an Application to a Study of Physical Activity and Coronary Heart Disease. *Biometrics* 2009;65(2):514-20.