Demystifying causal inference in randomised trials

Lecture 3: Introduction to mediation and mediation analysis using instrumental variables

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Plan

1. Introduction to mechanisms evaluation
2. Treatment effect mediation using path diagrams
3. The Baron & Kenny (B&K) approach
4. Assumptions for B&K approach
5. Instrumental variable methods

2

Learning objectives

By the end of this session, you should be able to:

- Carry out a simple evaluation of mediation using the B&K approach, and be aware of the assumptions underpinning the method.
- Extend the above approach by incorporating confounder adjustments.
- Implement simple instrumental variable methods to allow for hidden confounding and measurement error.
- Appreciate the complexities and challenges of mediational mechanisms evaluation in practice.
- Critically appraise Efficacy and Mechanisms Evaluation (EME) trial data analysis plans with respect to mechanisms evaluation.

3

Focussing on the ME in EME trials

- Observational studies indicate that raised blood pressure is an important risk factor for stroke.
- Laboratory studies and clinical trials show that anti-hypertensive drugs such as β-blockers reduce blood pressure.
- Clinical trials also show that β-blockers reduce the risk of stroke.

- How do we know that the reduction of the risk of stroke is a result of lowering blood pressure?
- How much of the stroke risk reduction is explained by the lowering of blood pressure?
- Different anti-hypertensive drugs may have similar effects on blood pressure but vary in their effect on stroke reduction. Why?

4

Focussing on the ME in EME trials

- Observational studies indicate that raised low-density lipoprotein (LDL) or 'bad cholesterol' is an important risk factor for cardiovascular disease.
- Laboratory studies and clinical trials show that statins reduce blood LDL concentrations.
- Clinical trials also show that statins reduce the risk of cardiovascular disease.

- How do we know that the reduction of the risk of cardiovascular disease is a result of lowering LDL?
- How much of the stroke risk reduction is explained by the lowering of blood pressure?
- Statins are also known to be anti-inflammatory. Might this explain their clinical efficacy?

5

Focussing on the ME in EME trials

- In patients suffering from psychosis, high levels of worry are associated with more severe symptoms of paranoia.
- In a recent EME trial (Freeman et al., 2015), an intervention (a form of cognitive therapy) targeted on the reduction of worry has been found to reduce both levels of worry and the severity of paranoia.

- Has paranoia been lowered as a result of reducing worry?
- What proportion of the treatment effect on paranoia is explained by the effect of the intervention on worry?

6

A typical EME trial data analysis plan

- Demonstrate an intention-to-treat (ITT) effect on the primary clinical outcome.
- Demonstrate an ITT effect on the putative mediator (mechanism).
- Quite often, the proposed analysis terminates here. "It's scientifically obvious that the effect is working through the mediator, isn't it!"
  - **This is unsatisfactory.**
- Sometimes, investigators propose simply looking at the association or correlation between putative mediator and clinical outcome.
  - **This is still not good enough.**

7

An atypical EME trial data analysis plan!

- Demonstrate an intention-to-treat (ITT) effect on the primary clinical outcome.
- Demonstrate an ITT effect on the putative mediator (mechanism).
- Carry out a formal evaluation of mediation using a regression modelling approach.
  - This is an area relatively familiar to psychologists, social scientists and others involved in the evaluation of complex interventions in mental health and elsewhere.
  - Almost unheard of in mainstream medical research.
  - Modern methods for causal inference are increasingly being used.

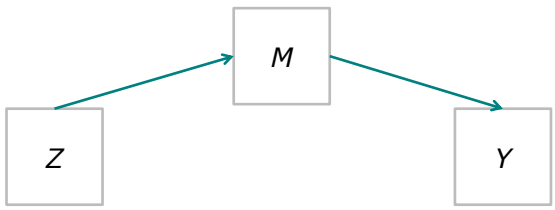
8

Mediation and mediators

- Baron and Kenny (1986) defined mediation as the "*generative mechanisms through which the focal independent variable is able to influence the dependent variable of interest*"
- A mediator (*M*) is a variable that occurs in the causal pathway from randomisation (*Z*) to an outcome variable (*Y*). It causes variation in the outcome and itself is caused to vary by the exposure variable.
  - This causal chain implies a temporal relation
    - *Z occurs before M and*
    - *M occurs before Y*
- Mediating variables are often called intervening or intermediate variables.
  - (They have also been called process variables; but we reserve this term for variables that measures aspects of the therapeutic process.)

Complete mediation

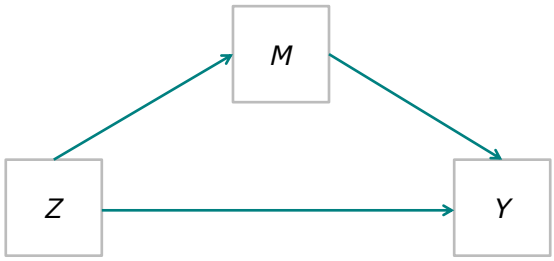
- To reflect the mediated effect we need a path from *Z* to *M* and a further path from *M* to *Y*.
- The following diagram illustrates complete mediation by *M*.



- Note that the diagram implies that *M* is the only mechanism by which *Z* can change *Y.*

"The mediation triangle"

- We might not want to rule out effects of *Z* on *Y* other than those operating by changing *M*.
- The following triangle illustrates partial mediation by *M*.



Direct and indirect effects

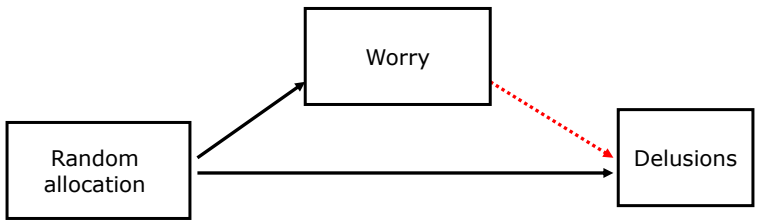
- Mediation investigations in trials aim to partition total (causal) treatment effects into
  1. effects that operate via changing the putative mediator – so called indirect treatment effects
  2. and non-mediated effects – so-called direct treatment effects.
- **Total effect = direct effect + indirect effect**
- Note that direct effects include effects via any mediating variable not included in the model.
  - So the meaning of a direct effect is always relative to the variable whose mediating effect is being modelled.

Are all mediators the same?

- Target intermediate variables:
  - Some treatments target a particular intermediate variable in order to bring about change in a clinical outcome.
  - An explanatory analysis of a trial would seek to establish that this is indeed the case; i.e. assess the mediated path.
- Nuisance mediators:
  - Sometimes treatments are intended to improve clinical outcome in more than one way, or an unexpected way.
  - It is then of interest to show that there is an effect on outcome that does not operate via changing a specific intermediate variable; i.e. assess the non-mediated path.
  - An intermediate variable that transmits the effect but is not of interest is referred to as a "nuisance" mediator.

"Target" Mediators

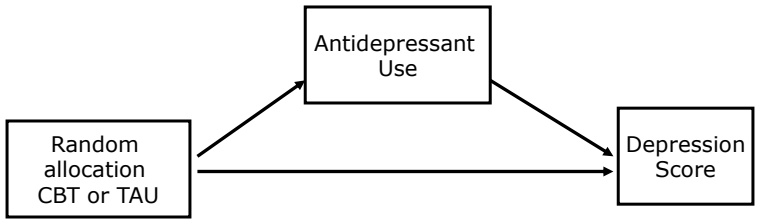
- **Does reducing worry improve delusions? (WORRY trial)**
  Does an intervention only targeting worry lead to an improvement in delusions in psychosis?



- **Mediation by design**

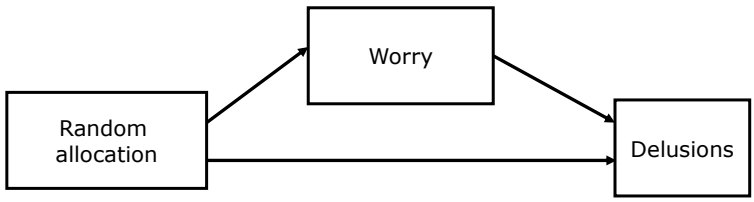
"Nuisance" mediators

- Variables measured post-randomisation that we may wish to rule out having a mediated effect - essentially we want to estimate the residual direct effects and find a small indirect effect.
- **Use of concomitant medication**
  (SMaRT; PROSPECT trials)
  Does psychotherapy improve compliance with medication which, in turn, leads to better outcome? What is the direct effect of psychotherapy?



"Target" or "Nuisance" Mediators

- What makes these variables 'mediators'?
  - We are interested in all three pathways in the diagram, and the effect decomposition:



- Requirements for mediation:
  1. Aim is to estimate the size of the indirect effect, and
  2. The mediator is measured in both arms.

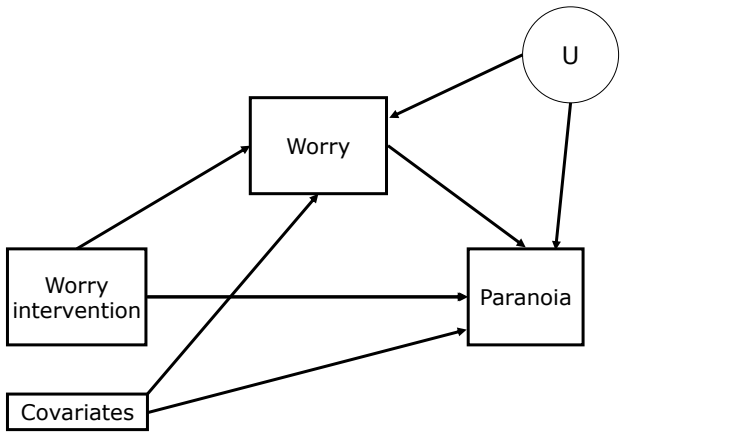
Challenges for establishing mediation

- Possible confounding of the effect of mediator on outcome (the omitted variables problem).
- Mediator measured with error.
- Data structure: e.g. serial assessments of both mediator and clinical outcome, or serial assessments of the mediator and a survival time for the outcome.
- Possibility of multiple mediators working in parallel.

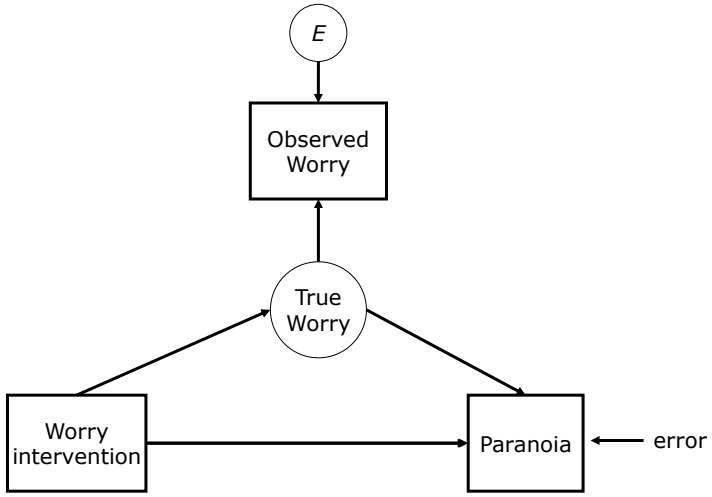
17

Hidden confounding - the omitted variables problem

U – the unmeasured confounders



Measurement error in the mediator (E)



Implications of randomisation

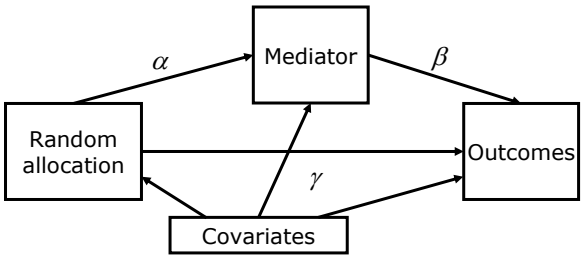
- No confounding between treatment allocation (or receipt) and intermediate outcome (potential mediator).
- No confounding between treatment allocation (or receipt) and final outcome.
- **BUT**, still the possibility of confounding between mediator and final outcome (because we do not have experimental control of either of these outcomes).
- **AND,** confounding of the effect of the mediator on the final outcome **ALSO** implies confounding of the direct effect of treatment on outcome.

20

Traditional regression approach

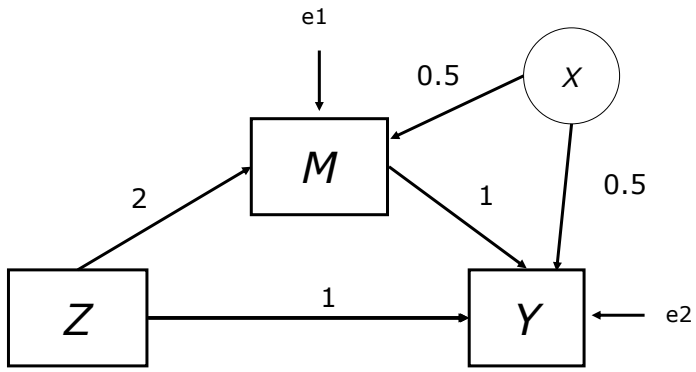
- The traditional regression approach popular in the social and behavioural sciences was first mentioned in Hyman (1955), and further proposed by Judd and Kenny (1981) and Baron and Kenny (1986).
- It is based on two regression models:
  - Model for mediator (*M*): $E[M|Z,X] = \mu + \alpha Z + \delta X$
  - Model for outcome (*Y*): $E[Y|Z,M,X] = \tau + \gamma Z + \beta M + \varphi X$
  - (**X** are baseline covariates that act as observed confounders.)

Baron and Kenny approach with covariates



1. Demonstrate that randomisation has an effect on outcome;
   - Regress outcome on randomisation and covariates; check if it is significant.
2. Demonstrate that randomisation has an effect on the mediator;
   - Regress mediator on randomisation and covariates; check if α is significant.
3. Demonstrate that the mediator has an effect on outcome, after controlling for randomisation.
   - Regress outcome on randomisation, covariates AND mediator; check β is significant and γ reduced in magnitude compared to total effect.

Example: mediation using simulated data



Total effect	**= direct effect**	+	**indirect effect**
	= 1	+	2*1
	= 1	+	2
	= 3		

Exercise: B&K using simulated data

- Focussing on the parameters of interest: what should happen to the estimated coefficients in the following pairs of models?
  - regress y z
  - regress y z x
  - regress m z
  - regress m z x
  - regress y m z
  - regress y m z x

24

Example: Baron and Kenny stage 1

```
. regress y z

      Source |       SS           df       MS      Number of obs   =     2,000
-------------+----------------------------------   F(1, 1998)      =   3752.69
       Model |  4423.89284         1  4423.89284   Prob > F        =    0.0000
    Residual |  2355.35806     1,998  1.17885789   R-squared       =    0.6526
-------------+----------------------------------   Adj R-squared   =    0.6524
       Total |   6779.2509     1,999  3.39132111   Root MSE        =    1.0858

------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           z |    2.97506   .0485651    61.26   0.000     2.879816    3.070303
       _cons |   .5114539   .0346654    14.75   0.000     .4434698    .5794381
------------------------------------------------------------------------------
```

Example: Baron and Kenny stage 1 with *X*

```
. regress y z x

      Source |       SS           df       MS      Number of obs   =     2,000
-------------+----------------------------------   F(2, 1997)      =  26046.03
       Model |  6528.95699         2   3264.4785   Prob > F        =    0.0000
    Residual |  250.293909     1,997  .125334957   R-squared       =    0.9631
-------------+----------------------------------   Adj R-squared   =    0.9630
       Total |   6779.2509     1,999  3.39132111   Root MSE        =    .35403

------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           z |   2.972461   .0158354   187.71   0.000     2.941405    3.003516
           x |   1.013537   .0078207   129.60   0.000     .9981994    1.028874
       _cons |    .517581   .0113033    45.79   0.000     .4954135    .5397485
------------------------------------------------------------------------------
```

Example: Baron and Kenny stage 2

```
. regress m z

      Source |       SS           df       MS      Number of obs   =     2,000
-------------+----------------------------------   F(1, 1998)      =   6093.09
       Model |  2005.94485         1  2005.94485   Prob > F        =    0.0000
    Residual |   657.77453     1,998  .329216481   R-squared       =    0.7531
-------------+----------------------------------   Adj R-squared   =    0.7529
       Total |  2663.71938     1,999  1.33252595   Root MSE        =    .57377

------------------------------------------------------------------------------
           m |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           z |   2.003332   .0256646    78.06   0.000        1.953    2.053664
       _cons |    .243557   .0183192    13.30   0.000     .2076303    .2794837
------------------------------------------------------------------------------
```

Example: Baron and Kenny stage 2 with *X*

```
. regress m z x

      Source |       SS           df       MS      Number of obs   =     2,000
-------------+----------------------------------   F(2, 1997)      =  20466.07
       Model |  2539.80709         2  1269.90355   Prob > F        =    0.0000
    Residual |  123.912288     1,997  .062049218   R-squared       =    0.9535
-------------+----------------------------------   Adj R-squared   =    0.9534
       Total |  2663.71938     1,999  1.33252595   Root MSE        =     .2491

------------------------------------------------------------------------------
           m |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           z |   2.002023    .011142   179.68   0.000     1.980172    2.023874
           x |   .5104128   .0055027    92.76   0.000     .4996211    .5212044
       _cons |   .2466425   .0079531    31.01   0.000     .2310453    .2622398
------------------------------------------------------------------------------
```

Example: Baron and Kenny stage 3

```
. regress y m z

      Source |       SS           df       MS      Number of obs   =     2,000
-------------+----------------------------------   F(2, 1997)      =  29029.82
       Model |  6553.82765         2  3276.91382   Prob > F        =    0.0000
    Residual |  225.423249     1,997  .112880946   R-squared       =    0.9667
-------------+----------------------------------   Adj R-squared   =    0.9667
       Total |   6779.2509     1,999  3.39132111   Root MSE        =    .33598

------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           m |    1.79947      .0131   137.36   0.000     1.773779    1.825161
           z |  -.6298759   .0302419   -20.83   0.000    -.6891849   -.5705669
       _cons |   .0731805   .0111914     6.54   0.000     .0512324    .0951285
------------------------------------------------------------------------------
```

Example: Baron and Kenny stage 3 with *X*

```
. regress y m z x

      Source |       SS           df       MS      Number of obs   =     2,000
-------------+----------------------------------   F(3, 1996)      =  34817.68
       Model |  6652.13483         3  2217.37828   Prob > F        =    0.0000
    Residual |  127.116066     1,996  .063685404   R-squared       =    0.9812
-------------+----------------------------------   Adj R-squared   =    0.9812
       Total |   6779.2509     1,999  3.39132111   Root MSE        =    .25236

------------------------------------------------------------------------------
           y |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
           m |    .997032   .0226706    43.98   0.000     .9525715    1.041493
           z |   .9763796   .0467696    20.88   0.000     .8846572    1.068102
           x |   .5046391   .0128442    39.29   0.000     .4794496    .5298286
       _cons |   .2716705   .0098074    27.70   0.000     .2524367    .2909043
------------------------------------------------------------------------------
```

Estimator for the indirect effect

- The traditional regression approach estimates it by:
  - fitting separate regression models for *M* and *Y*
  - using these to estimate regression coefficients α and β
  - and generating the product of these estimates to estimate $\alpha\beta$
  - This is also known as the **product of coefficients** method
- An alternative way of estimating it is given by:
  - fitting a regression of *Y* on *Z* only
  - use this to provides an estimate of the total effect ITT = $\alpha\beta + \gamma$
  - then adding *M* as a further explanatory variable in the model for *Y*
  - using the latter regression to estimate the direct effect γ
  - and generating the difference of these estimates to estimate $\alpha\beta$
  - This is known as the **difference in coefficient** method

Target effect

- The difference in coefficient method is popular in epidemiology as it only involved fitting models for the clinical outcome *Y*.
  - (Epidemiologists are used to looking at change in regression coefficients after including covariates in the model.)
- However, in trials we actually want to see the treatment effect on the intermediate variable *M* (α) in addition to the indirect effect
  - So here we focus on the product of coefficient approach.
- We refer to α as the **target effect**
- In any approach, it is essential to show that the treatment has shifted the mediator for mediation through this variable to occur.

Inferences for indirect and direct effects

- Sobel (1982) derived a formula for the estimating the asymptotic standard error (SE) of the product of coefficients estimator.
  - The formula only requires estimates and SEs provided after fitting the individual regression equations for *M* and *Y*.
- Symmetric confidence intervals derived using this SE rely on asymptotic normality.
- As the distribution of the product estimator is likely to be skewed for finite samples alternative inferences derived by bootstrapping are to be preferred.

Proportion mediated

- Proportion of the effect that is mediated, or the indirect effect divided by the total effect.
- Such a measure, though theoretically informative, is very unstable and should not be computed if ***total effect*** is small.
- Note that this measure can be greater than one or even negative when there is inconsistent mediation
  - Direct and indirect effects in opposite signs
  - Direct effect larger than total effect
- Kenny advises only computing this measure if standardized ***total effect*** is at least ±0.2.
- Can include confidence intervals for this.

B&K: what have we assumed?

- Our path diagram (the causal model) is the correct one!
- In the present context (an RCT), we have assumed that treatment allocation is random.
- We have assumed that there is no (or negligible) measurement error in the mediator.
- We have assumed the absence of confounding (as if the level of the mediator is also allocated randomly – usually after controlling for observed confounders).
- We have assumed that there is no interaction between mediator and treatment on outcome.

35

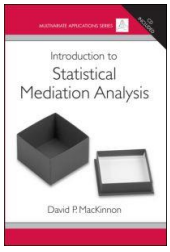
Confounder adjustment

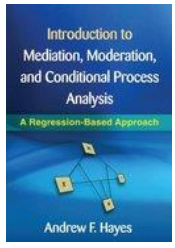
- In a conventional ITT analysis it is common to include baseline prognostic variables as covariates in an ANCOVA model. Although to some extent this is to allow for possible baseline imbalances, the main purpose of this is to increase precision of the treatment effect estimate.
- Frequently the covariates include baseline (pre-randomisation) measurements of the relevant outcome.
- The same prognostic variables are likely to be important sources of confounding in the estimation of the joint effects of treatment and mediator on outcome.
- Of particular importance here are the baseline measurements of both the mediator and the outcome. They are likely to be important prognostic markers and, if the mediation model is valid, likely to be correlated with each other.

36

Statistical mediation analysis

- Statistical mediation analysis
  - Builds on Judd & Kenny (1981) and Baron & Kenny (1986)
  - Structural Equation Models
  - Monograph by David MacKinnon (2008).
  - Work by Kris Preacher and Andrew Hayes.





Effects of cognitive behaviour therapy for worry on persecutory delusions in patients with psychosis (WIT): a parallel, single-blind, randomised controlled trial with a mediation analysis

Daniel Freeman, Graham Dunn, Helen Startup, Katherine Pugh, Jacinta Cordwell, Helen Mander, Emma Černis, Gail Wingham, Katherine Shirvell, David Kingdon

Lancet Psychiatry 2015;
2: 305–13

WORRY INTERVENTION TRIAL
OXFORD SOUTHAMPTON

- Efficacy and Mechanism Evaluation programme

MRC Medical Research Council

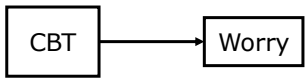
NHS National Institute for Health Research

Hypothesis

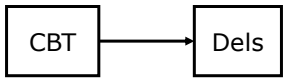
1. A brief psychological worry intervention will reduce worry in patients with persecutory delusions.
2. A brief psychological worry intervention will reduce persecutory delusions.
3. The improvements will be maintained at follow-up.
4. Worry will be the main mediator of change in persecutory delusions.

WiT hypotheses

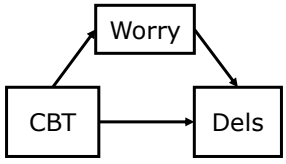
- Hypothesis 1:



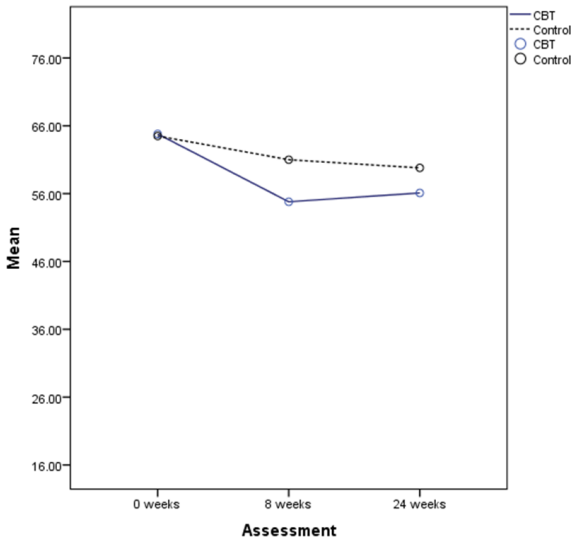
- Hypothesis 2:



- Hypothesis 4:

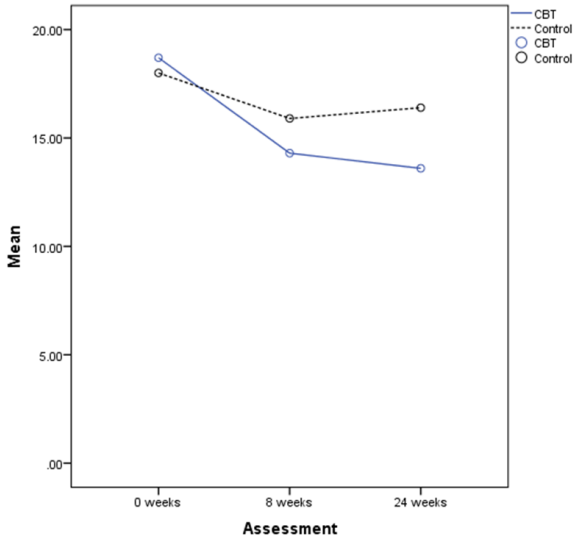


Effect on mediator: Worry (PSWQ)



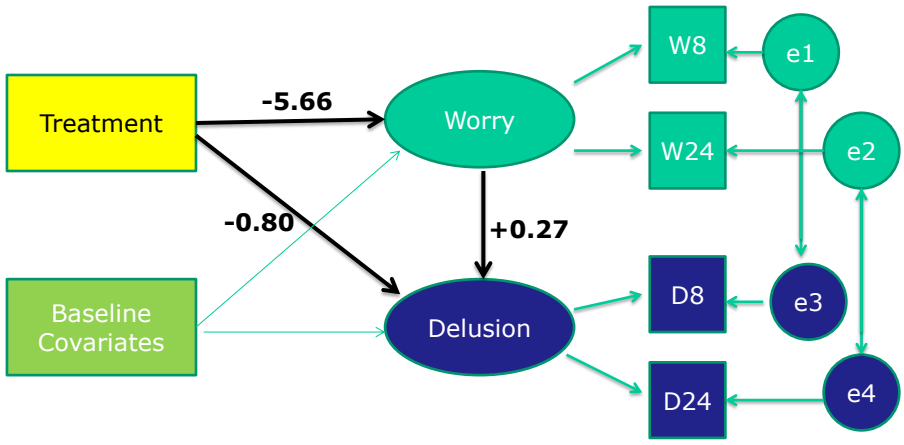
Reduction due to CBT in PSWQ of 5.2 points (95% CI 2.5 to 7.8), p<.001, d=0.5.

Effect on outcome: Delusions (PSYRATS)



Reduction due to CBT in PSYRATS of 2.5 points (95% CI 1.2 to 3.8), p<.001, d=0.5.

WiT: mediation model



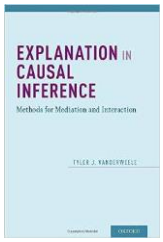
Total effect = -0.80 - 5.66*0.27 = -2.33
Mediated effect = -5.66*0.27 = -1.53 (66%)

Summary: Statistical mediation analysis

- The Baron and Kenny (1986) procedure and subsequent estimation of the indirect effect can be appropriate, provided:
  - Continuous outcome and continuous mediator
  - All relevant confounders are included in all the models and there are no unmeasured confounders (e.g. excluding covariates)
  - Correct functional form (e.g. linearity)
  - There are no interactions between treatment and mediator on outcome.
- Using the bootstrap option is probably recommended for estimating the standard error of the indirect effect.
- This applies for the use of structural equation modelling more generally too.

Causal mediation analysis

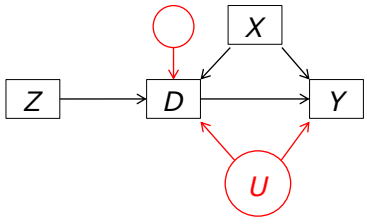
- Statistical mediation (B&K) has four main problems:
  1. Unmeasured confounding between mediator and outcome
  2. No interactions between exposure and mediator on outcome
  3. Doesn't easily extend to non-linear models
  4. Assumes correctly specified models



- Causal mediation analysis has arisen from the causal inference literature, and addressed these problems.
- We will look at these methods:
  - Instrumental variables (rest of this lecture)
  - Regression models and IPW (next lecture)
- Formally defines the causal mediation parameters (next lecture)

Instrumental Variables (IVs)

- An instrumental variable (IV) is:
  - a variable that does not appear in the outcome model
  - is uncorrelated with the error term
  - is correlated with the endogenous explanatory variable



Z is instrument for *D* in model for *Y*

Two stage least squares procedure

- The first stage involves:
  - Regress *D* on *Z* and *X* using OLS then save the predicted values of *D*.
  - $D = \alpha_0 + \alpha_1 Z + \alpha_2 X + \omega$
- Then at the second stage:
  - Regress *Y* on the predicted value of *D,* and *X* using OLS.
  - $Y = \beta_0 + \beta_1 \widehat{D} + \beta_2 X + \varepsilon$
- A correction needs to be made to the standard errors if performing this manually – standard software does this
  - e.g. **`ivregress`** in Stata.
- Note that covariates are included in both stages.
- Under normality 2SLS and LIML are asymptotically equivalent.

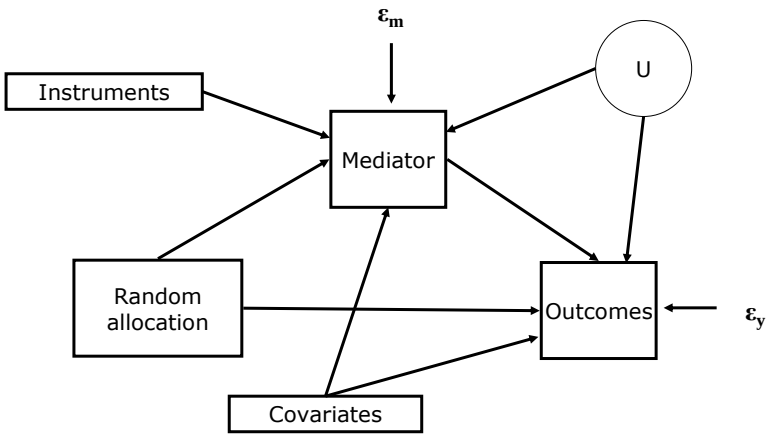
IV vs regression estimators

- For "large" samples we would expect IV estimates to correct bias in ordinary least squares (OLS) estimates due to residual confounding.
- However, even if IV properties hold and sample size large enough this comes at price of variance inflation.
- In addition, for weak IVs (variables that predict very little of the non-accounted variance in the endogenous variable *M*) IV estimators can be more biased than OLS estimates – this is known as weak instrument bias.
  - This bias can be a major problems when instruments are selected post hoc and tend not to be very predictive of *M*.
  - New work on Stein-like estimators which combine the two (Ginestet, Emsley, Landau, 2016).

Instruments in mediation

- When we are trying to estimate the direct effect of randomisation we need alternative instruments.
  - Randomisation (*Z*) very useful in other contexts.
  - But can't provide an IV here.
- Likewise, if we have more than one endogenous variable (multiple mediators), then we need multiple instruments.
- For IV model identification, we always need to have as many instruments as we have endogenous variables

Instruments in mediation analysis



Finding instruments

- We need variables that are strong predictors of the process measures but do not themselves influence outcome.
- One possibility is the **selection** of baseline variables which interact with randomized group to predict mediators.
- In Stata: `ivregress 2sls y z x(m=z*x)`

(Set of) endogenous variable(s)

(Set of) instrumental variable(s)

Response variable and exogenous covariates

Interaction between baseline covariates and randomisation

- We often use randomisation by baseline interactions as instruments:
  - Gennetian LA, Morris PA, Bos JM, Bloom HS (2005). "Constructing instrumental variables from experimental data to explore how treatments produce effects."
  - Since then used in Dunn and Bentall (2007), Ten Have *et al.* (2007), Albert (2008), Emsley *et al.* (2010), Small (2012).
- Key idea:
  - Randomisation ensures that there is no unmeasured confounding for the interaction instrument and the outcome.
  - We assume that the interaction effect operates solely by changing the mediator; hence the moderation is fully mediated.
  - Baseline values of mediator or clinical outcome (severity) are good candidates.
- Practical problem: Identifying such baseline variables *post hoc* often leaves us with weak instruments.

Finding instruments

- Possibilities for IVs:
  1. Measure baseline variables which moderate treatment effect via the mediators (mediated moderation).
     - *Possibilities in stratified medicine trials (Dunn et al. 2013)*
  2. Use of a multi-centre trial.
     - *Approach used in Emsley et al. (2010)*
  3. Joint analysis of several similar trials.
  4. Use of gene as an instrument (Mendelian randomisation).
  5. Randomisation to multiple treatments.

Moderators - predictive markers

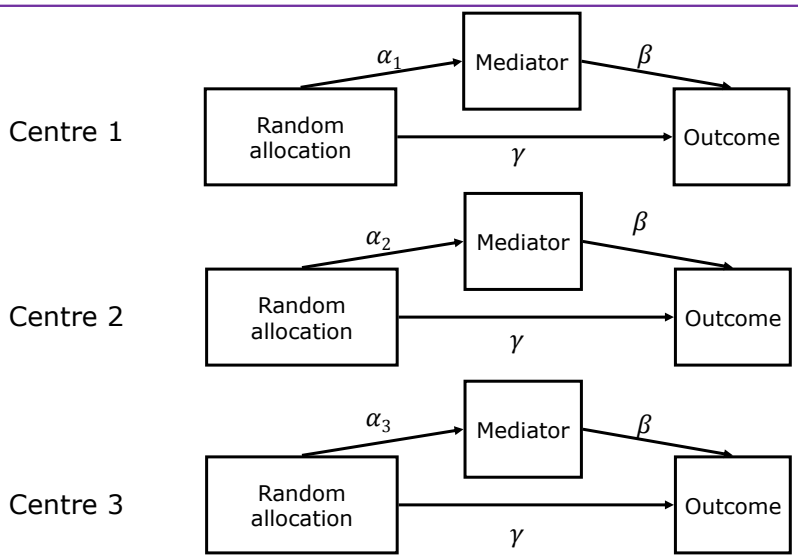
- Moderators are baseline (*pre-randomisation*) characteristics that influence the effect of treatment.
- They are baseline treatment effect-modifiers.
- Possible to get moderated mediation or mediated moderation.
- Possible examples: sex, age, genetic markers, previous history of illness, treatment centre, therapist, etc.
- **If** the whole of the effect of moderation is through the effect of treatment on the mediator (mediated moderation) then the moderator by treatment interaction can be treated as an **instrumental variable** (IV).

54

Multi-centre trials

- We might expect a centre*Z interaction on Y in a multi-centre trial.
- If we are happy assume that this interaction operates only via the putative mediator (M) then centre*Z provides an IV for M.
- This will give k-1 IVs for k centres.

Designs for IVs - multi-centre trials



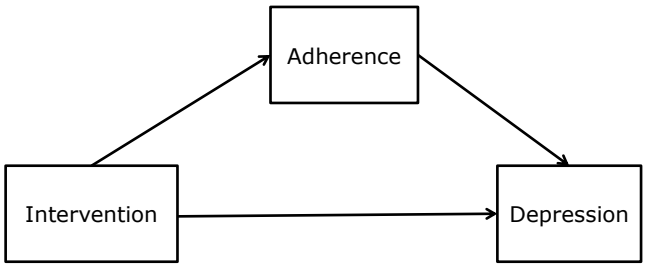
Example: PROSPECT

- **PROSPECT** (Prevention of Suicide in Primary Care Elderly: Collaborative Trial) was a prospective, randomised trial designed to evaluate the impact of a primary care-based intervention on the reduction of major risk factors (including depression) for suicide in later life.
- The trial was aimed at evaluation of an intervention based on treatment guidelines tailored for the elderly with care management compared with treatment as usual.
- Data from this trial have also been analysed in detail in a series of papers developing and illustrating the estimation of direct and indirect treatment effects in randomised controlled trials in the presence of possible hidden confounding between the intermediate and the final outcome (Dunn et al. (2015) contains a summary).

57

Example: PROSPECT analysis

- **Use of concomitant medication**
  Does psychotherapy improve compliance with anti-depressant medication which, in turn, leads to better outcome? What is the direct effect of psychotherapy?



PROSPECT: results

Hamilton depression scores: mean (s.d.)
At 4 months, *hamda*

Site	Control	Treated
1	13.42 (8.12)	11.98 (7.75)
2	14.10 (8.55)	12.12 (7.29)
3	12.98 (8.53)	9.97 (6.92)

Total participants: 297 (152 controls; 145 treated) with complete outcome data (Hamilton score at 4 months).

59

PROSPECT: results

Postrandomisation adherence to antedepressant medication: number (%)

Site	Control	Treated
1	20 (37.7)	44 (83.0)
2	19 (33.3)	45 (83.3)
2	30 (71.4)	34 (89.5)

60

PROSPECT: summary of data

- There appears to be a beneficial effect of the intervention on the 4-month HDRS score, but there is also a clear effect of intervention on adherence to antidepressant medication – could this be explaining the observed ITT effect on outcome?
- Test this using B&K and IV with interactions
- In our analyses reported below, like those of previous authors, we make no attempt to allow for the clustering of the data within primary care practices.

61

PROSPECT analysis: ITT effect

```
. regress hdrs4 interven cad1 hdrs0 ssix01 SCR01 i.site

      Source |       SS       df       MS              Number of obs =     296
-------------+------------------------------           F(  7,   288) =   14.15
       Model |    4782.332     7  683.190285            Prob > F      =  0.0000
    Residual |  13900.7342   288  48.2664381            R-squared     =  0.2560
-------------+------------------------------           Adj R-squared =  0.2379
       Total |  18683.0662   295  63.3324277            Root MSE      =  6.9474

------------------------------------------------------------------------------
       hdrs4 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    interven |  -3.146868   .8202073    -3.84   0.000    -4.761228   -1.532507
        cad1 |  -.2670142   .3355599    -0.80   0.427     -.927475    .3934467
       hdrs0 |   .6170188   .0709926     8.69   0.000     .4772886    .7567489
      ssix01 |   1.260566   .9543007     1.32   0.188    -.6177219    3.138854
       SCR01 |   1.302386   1.017657     1.28   0.202    -.7006019    3.305374
             |
        site |
           2 |  -.4021913   .9523825    -0.42   0.673    -2.276704    1.472321
           3 |  -2.281121   1.050199    -2.17   0.031     -4.34816   -.2140821
             |
       _cons |   2.992302    1.40711     2.13   0.034     .2227792    5.761825
------------------------------------------------------------------------------
```

PROSPECT analysis: B&K step 3 with covariates

```
      Source |       SS       df       MS              Number of obs =     296
-------------+------------------------------           F(  8,   287) =   12.56
       Model |  4844.86609     8  605.608261            Prob > F      =  0.0000
    Residual |  13838.2001   287   48.216725            R-squared     =  0.2593
-------------+------------------------------           Adj R-squared =  0.2387
       Total |  18683.0662   295  63.3324277            Root MSE      =  6.9438

------------------------------------------------------------------------------
       hdrs4 |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    interven |   -2.65566    .926331    -2.87   0.004    -4.478924   -.8323957
       amedx |  -1.243843   1.092209    -1.14   0.256    -3.393599    .9059137
        cad1 |  -.1386153   .3538307    -0.39   0.696    -.8350476    .5578169
       hdrs0 |   .6205773   .0710248     8.74   0.000     .4807817    .7603729
      ssix01 |   1.254604   .9538235     1.32   0.189    -.6227728     3.13198
       SCR01 |   1.482406   1.029343     1.44   0.151    -.5436123    3.508424
       site2 |  -.4626671    .953372    -0.49   0.628    -2.339155    1.413821
       site3 |  -2.131408   1.057859    -2.01   0.045    -4.213552   -.0492626
       _cons |    3.21632   1.420075     2.26   0.024     .4212372    6.011402
------------------------------------------------------------------------------
```

PROSPECT trial: IV approach with all interactions

```
ivregress 2sls hdrs4 interven cad1 hdrs0 ssix01 SCR01 site2 site3 (amedx =
inter_ssix01 inter_hdrs0 inter_cad1 inter_SCR01 inter_site2 inter_site3), first

First-stage regressions
-----------------------
------------------------------------------------------------------------------
       amedx |      Coef.   Std. Err.      t    P>|t|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
    interven |   .7825965   .1398924     5.59   0.000     .5072307    1.057962
        cad1 |    .166495   .0254223     6.55   0.000     .1164533    .2165366
       hdrs0 |   .0065731   .0051473     1.28   0.203    -.0035588    .0167051
      ssix01 |  -.0475454   .0721387    -0.66   0.510    -.1895441    .0944533
       SCR01 |   .2530611   .0746616     3.39   0.001     .1060962    .4000259
       site2 |   -.018463   .0664307    -0.28   0.781     -.149226       .1123
       site3 |   .1969925   .0734302     2.68   0.008     .0524516    .3415334
inter_ssix01 |   .0504564   .0967541     0.52   0.602    -.1399956    .2409083
 inter_hdrs0 |   -.003633   .0071484    -0.51   0.612    -.0177041     .010438
  inter_cad1 |   -.118277   .0341169    -3.47   0.001    -.1854331   -.0511209
 inter_SCR01 |  -.2627584   .1029091    -2.55   0.011    -.4653259   -.0601909
 inter_site2 |  -.0099335    .095321    -0.10   0.917    -.1975645    .1776975
 inter_site3 |  -.1681695   .1054282    -1.60   0.112    -.3756956    .0393566
       _cons |  -.0465641   .0996531    -0.47   0.641    -.2427223    .1495942
------------------------------------------------------------------------------
```

PROSPECT trial: IV approach with all interactions

```
Instrumental variables (2SLS) regression              Number of obs =     296
                                                      Wald chi2(8)  =  102.68
                                                      Prob > chi2   =  0.0000
                                                      R-squared     =  0.2582
                                                      Root MSE      =  6.8425
------------------------------------------------------------------------------
       hdrs4 |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       amedx |   -1.95302   2.672201    -0.73   0.465    -7.190438    3.284397
    interven |  -2.375598   1.328982    -1.79   0.074    -4.980353    .2291584
        cad1 |  -.0654087   .4304821    -0.15   0.879    -.9091381    .7783208
       hdrs0 |   .6226062    .070337     8.85   0.000     .4847482    .7604642
      ssix01 |   1.251204   .9399736     1.33   0.183    -.5911102    3.093518
       SCR01 |   1.585044   1.074312     1.48   0.140    -.5205695    3.690658
       site2 |  -.4971475   .9469522    -0.52   0.600     -2.35314    1.358845
       site3 |  -2.046048    1.08319    -1.89   0.059    -4.169062    .0769655
       _cons |   3.344043   1.467043     2.28   0.023     .4686928    6.219394
------------------------------------------------------------------------------
Instrumented:  amedx
Instruments:   interven cad1 hdrs0 ssix01 SCR01 site2 site3 inter_ssix01
               inter_hdrs0 inter_cad1 inter_SCR01 inter_site2 inter_site3
```

PROSPECT: G-estimation and modified IV

- Ten Have et al. used a complex iterative G-estimation algorithm.
- Here we show that this is equivalent to a non-iterative 2SLS estimation procedure (much easier!) using the compliance score as the instrumental variable (IV).
- The compliance score is a function of the difference between the estimated proportion adhering to medication in the intervention group and that in the control group.

66

PROSPECT: modified IV

Step 1

//Run logistic regression in treatment group only and predict for everyone

```
logit amedx cad1 hamda1 ssix01 scr01 s1 s2 if interven==1
predict p1
```

//Run logistic regression in control group only and predict for everyone

```
logit amedx cad1 hamda1 ssix01 scr01 s1 s2 if interven==0
predict p0
```

67

PROSPECT: modified IV

Step 2

//Estimate proportions in control and treatment groups

```
tab interven
```

	Freq.	Percent	Cum.
0	152	51.35	51.35
1	144	48.65	100.00
Total	296	100.00	

68

PROSPECT: modified IV

Step 3

//Generate compliance score

```
generate cscore=(interven-0.4865)*(p1-p0)
```

//Fit compliance score as an instrumental variable

```
ivregress 2sls hamda cad1 hamda1 ssix01 scr01 s1
s2 interven (amedx=cscore)
```

69

PROSPECT: effect of mediator on outcome

Method of estimation	**Estimate**	**s.e.**
G-estimation (from paper)	-1.975	2.313
2SLS using function of compliance score as IV	-1.975	2.401
2SLS using interactions as IVs	-1.953	2.672
Regression as in B&K	-1.244	1.092

70

PROSPECT: estimates of the direct effect of the intervention on outcome

Method of estimation	Estimate	s.e.
G-estimation (from paper)	-2.367	1.274
2SLS using function of compliance score as IV	-2.367	1.316
2SLS using interactions as IVs	-2.376	1.329
Regression as in B&K	-2.656	0.926

71

PROSPECT: summary of mediation findings

- G-estimation and the modified IV method give identical estimates.
- The standard IV method also provides very similar estimates.
- The standard errors provided the three methods above are also very similar.
- B&K gives different (biased?) estimates but the precision of the estimates is a lot greater.
- Trade-off between bias and precision?
- Adherence to medication explains about 21% of the total effect of the intervention.

72

Equivalence with other causal methods

- Fischer-Lapp and Goetghebeur (1999) describe an algorithm for estimating the parameters of a structural mean model using g-estimation.
- Goetghebeur and Vansteelandt (2005) show how g-estimation consistently estimates treatment dose effects in the presence of hidden confounding and random errors in the mediators.
- In the context of treatment effect moderation by post-randomisation variables these methods have been shown to be equivalent to instrumental variables approaches (Dunn and Bentall (2007)).
- Ten Have, Joffe and colleagues (2007, 2012) propose a rank-preserving model for binary mediators estimated by g-estimation.
- This is also equivalent to an instrumental variables approach with interaction IVs for the mediator (Emsley and Dunn, 2012).

Instrumental variables & g-estimation

- SMMs have an implicit baseline covariate by randomisation interaction in the g-estimation algorithm, and when these interactions are included in the first stage of the 2SLS procedure as instruments, SMM and IV will give identical results (point estimates).

- Key assumption: the vital component of all our models is randomization which ensures that treatment-free outcome is independent of treatment allocation (i.e. $Z \perp Y(0)$) and therefore, given baseline covariates, X_i

$$E[Y_i(0)|Xi,Ri]=E[Y_i(0)|Xi]$$

Dunn & Bentall (2007); Emsley, Dunn and White (2010).

Added complexities in EME trials (not pursued here)

- Clustering
  (clustered RCTs, group therapies, therapist effects)
- Non-adherence to the interventions.
- Non-quantitative outcome variables (binary or survival data, for example).
- Longitudinal data structures.
  (growth curve and change-score models, for example)

75

Design tips for mediation in trials

- Measure all putative mechanisms in **both** treatment arms
- Collect measures at baseline, during the treatment phase and at endpoint
  - Allows you to test **when** the change in the mediator has occurred
  - **Baseline** measures have been shown to account for unmeasured confounding
- Think about and collect all possible **baseline and time-varying confounders**
- Use an appropriate analysis method.

Critical appraisal

- Is the investigator's model complete? What are the assumptions necessary for valid inference concerning causality (explicit or otherwise)? What's missing?
- If instrumental variable methods have been used, are the instruments really convincing?
- Have the authors acknowledged the potential sensitivity of their findings to the validity of their assumptions?

77

Key message

Yes, But What's the Mechanism?

(**Don't Expect an Easy Answer**)

Bullock, Green & Ha (2010).

78

Exercise

- Consider the design of an EME trial in your own area of application (or one of the examples).
- What might be the important **prognostic markers** (potential confounders)? How would you decide what to measure in your trial design?
- Similarly, thinking of the possible use of IV methods for the evaluation of the mediation, what might be the potential **predictive markers** (moderators)? How convinced might you be that they could be used to create valid instruments?

79

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80

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81