A structural approach to bias:
Causal diagrams provide an internally coherent and transparent approach for observational studies

OR

What you never wanted but needed to know about confounding and didn't even know to ask

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Background

- Why Observational? Limited RCTs with respect to PICO
- Results/Interpretation = Data + Assumptions

"It's a rather interesting phenomenon. Every time I press this lever, the graduate student breathes a sigh of relief"

Background

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- Results/Interpretation = Data + Assumptions
- Randomized Trial: Does treatment Z reduce mortality?

$$
\begin{tikzcd}
& & & \text{Causes of Adherence} \arrow[dl] \arrow[dr] & \\
\text{Randomization} \arrow[r] & \text{Assigned Rx} \arrow[r] & \text{Rx Received} \arrow[rr] & & \text{Outcome}
\end{tikzcd}
$$

- Some participants do not adhere to their Rx assignment

"The perfect study exists only in the minds of those who do no research." (Tim Noakes)

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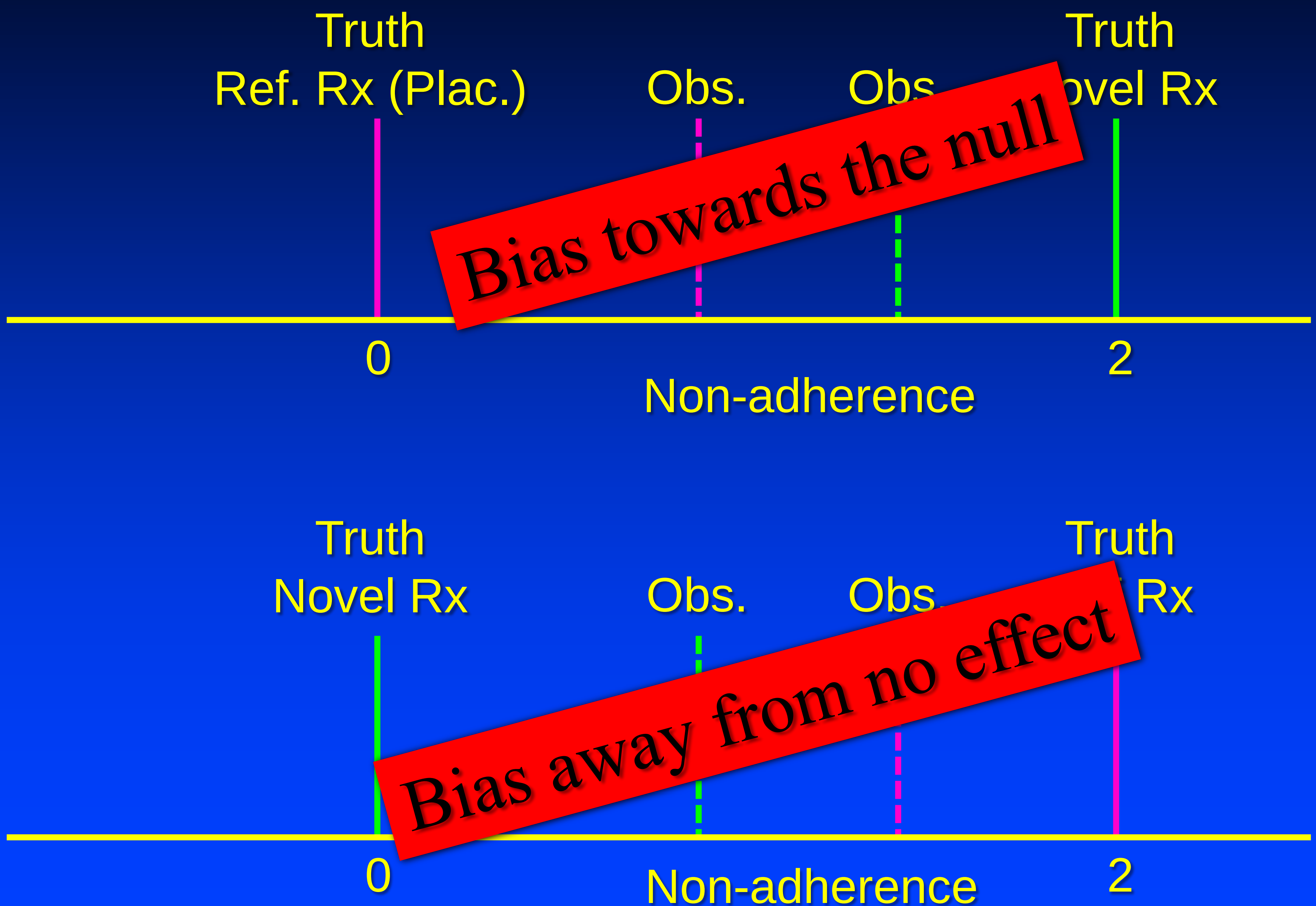
Causes of Adherence

Randomization → Assigned Rx → Rx Received → Outcome

- Intention to Treat (ITT): treatment assignment
  - ⇒ Regulatory Agency: avoids overestimation of effect (vs. placebo…)

ITT Biased Towards No Effect?



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Randomization → Assigned Rx → Rx Received → Outcome

- Intention to Treat (ITT): treatment assignment
  - ⇒ Regulatory Agency: avoids overestimation of effect (vs. placebo…)
  - ⇒ Health Policy: requires % adherence (& reasons) = target population
- Patient wants measure of treatment effectiveness

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Causes of Adherence

Randomization → Assigned Rx → Rx Received → Outcome

- ITT measures effect of treatment assignment
  - ⇒ Regulatory Agency: avoids overestimation of effect (vs. placebo…)
  - ⇒ Health Policy: requires % adherence (& reasons) = target population

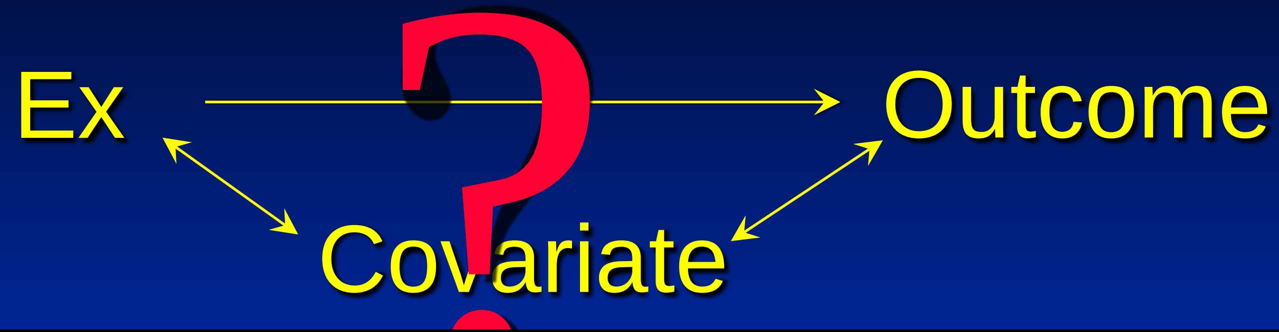
- Patient wants measure of treatment effectiveness
  - ⇒ Analyses based on adherence-data have important assumptions
  - ⇒ Analyses based on observational data have important assumptions

OVERVIEW

- Causal diagrams and Individual Studies
  - ⇒ Confounding has *always* been focused on causes, not associations
  - ⇒ Similar to logic models, with more explicit assumptions

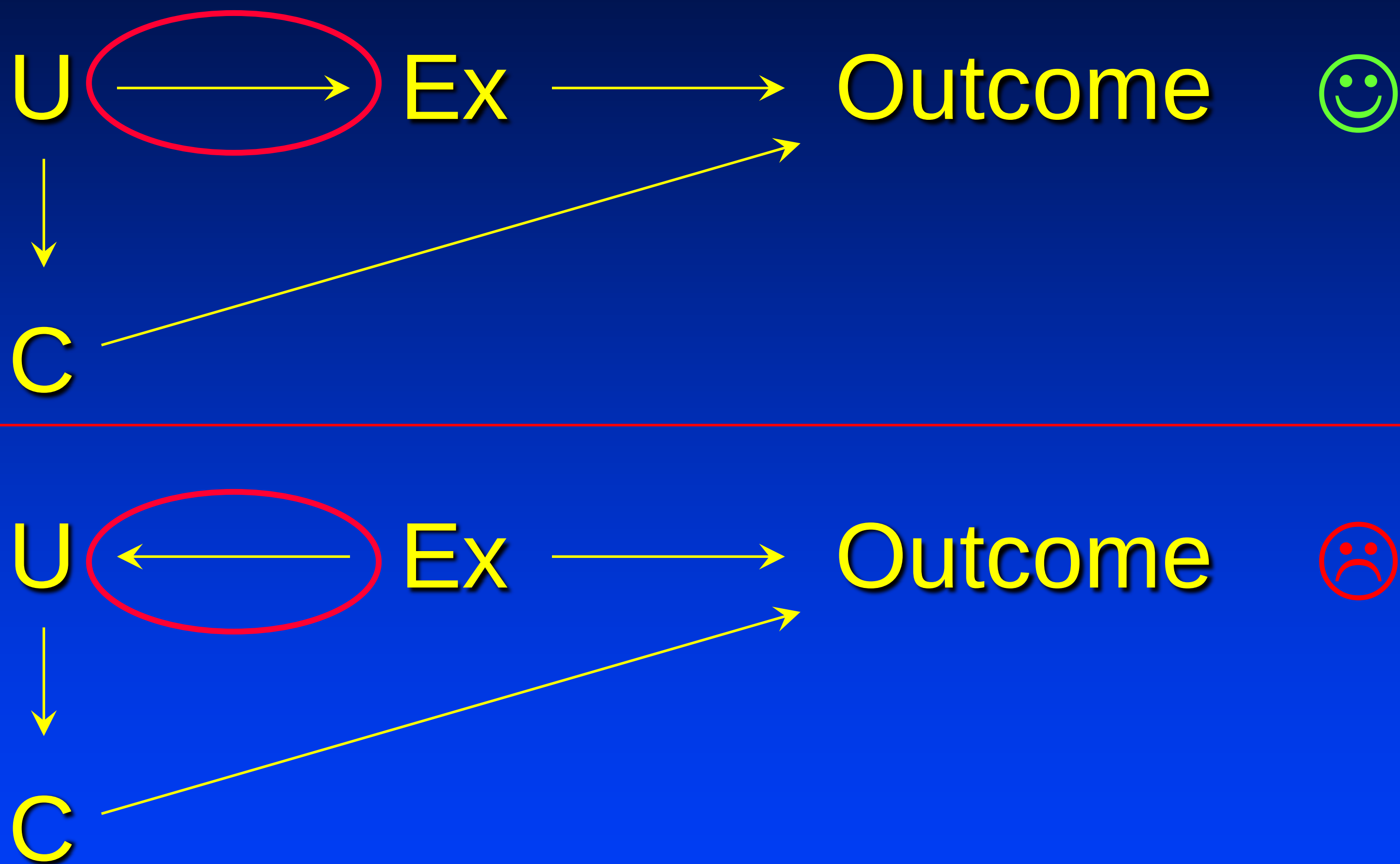
- Cochrane Risk of Bias Tool (observational studies)
  - ⇒ Combining studies that use different regression models
  - ⇒ Bias-amplifying covariates
  - ⇒ Possible modifications

“STANDARD” CONFOUNDER



⇒ Must cause the exposure, or be a marker for a cause of the exposure

POTENTIAL CONFOUNDER?



(Hernán Am J Epid 2002)

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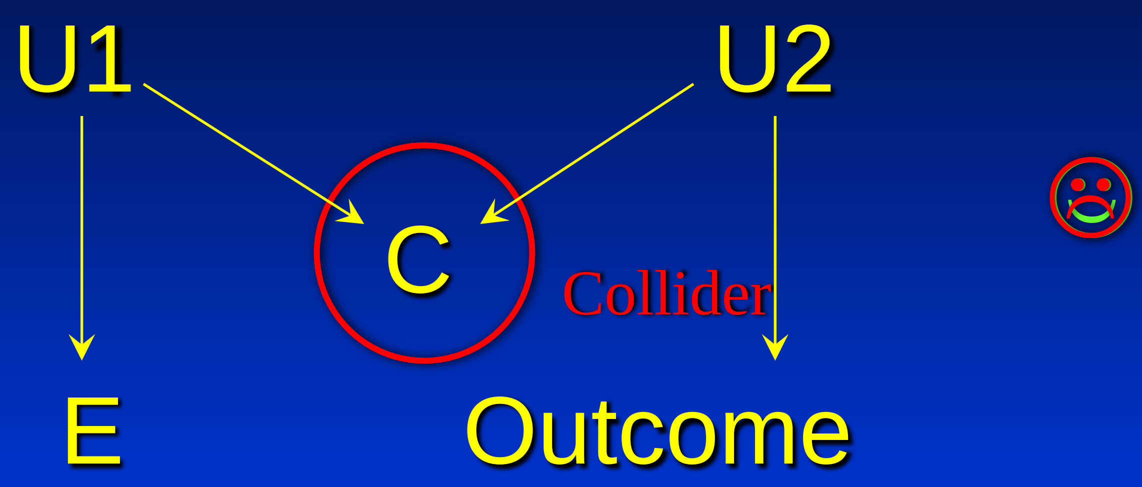
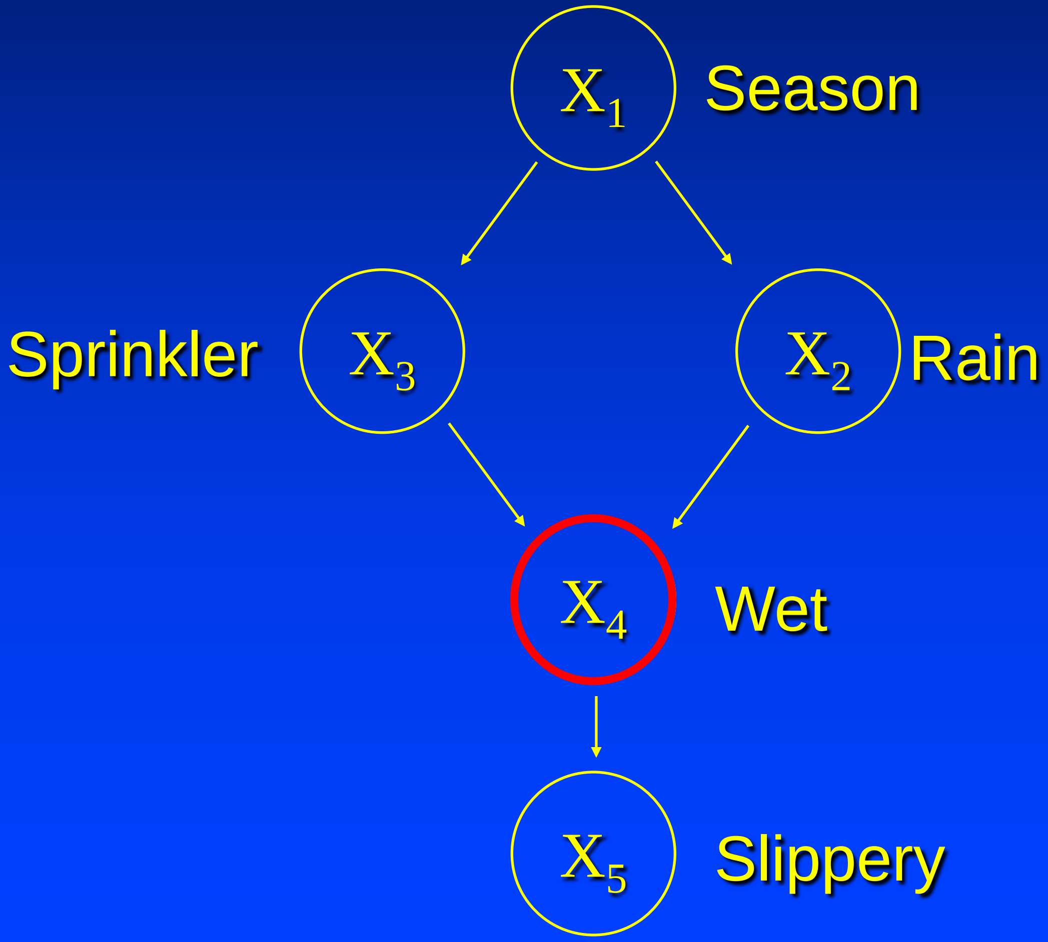


Must cause the outcome, or be a marker for a cause of the outcome
Must cause the exposure, or be a marker for a cause of the exposure

(Hernán Am J Epid 2002)

Pearl's Rules - Explanation

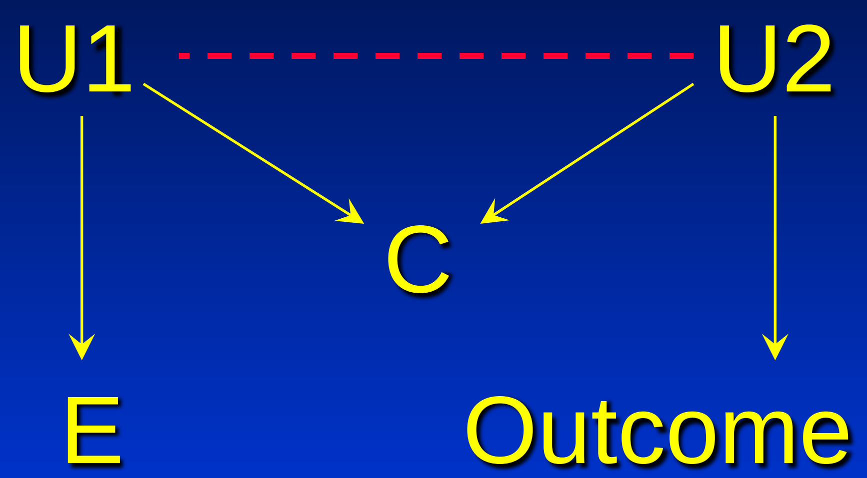


If one knows the value of the "collider", the parents are associated.

If wet: the sprinkler is more likely to be on if there was no rain.

(Shrier & Platt, 2008)

Potential Confounder vs. Collider?



Must cause the outcome, or be a marker for a cause of the outcome
Must cause the exposure, or be a marker for a cause of the exposure

(Cole & Hernán Int J Epid 2002)

COMMON COLLIDER BIASES

Case-control selection bias

Condition on common effect

Estrogen → Fracture → Emerg → Hospitalization

Myo. Infar. → Emerg

Complex Attrition bias

Condition on common effect

Treatment → Side effects → Drop Out

Disease → Side effects

Disease → Death

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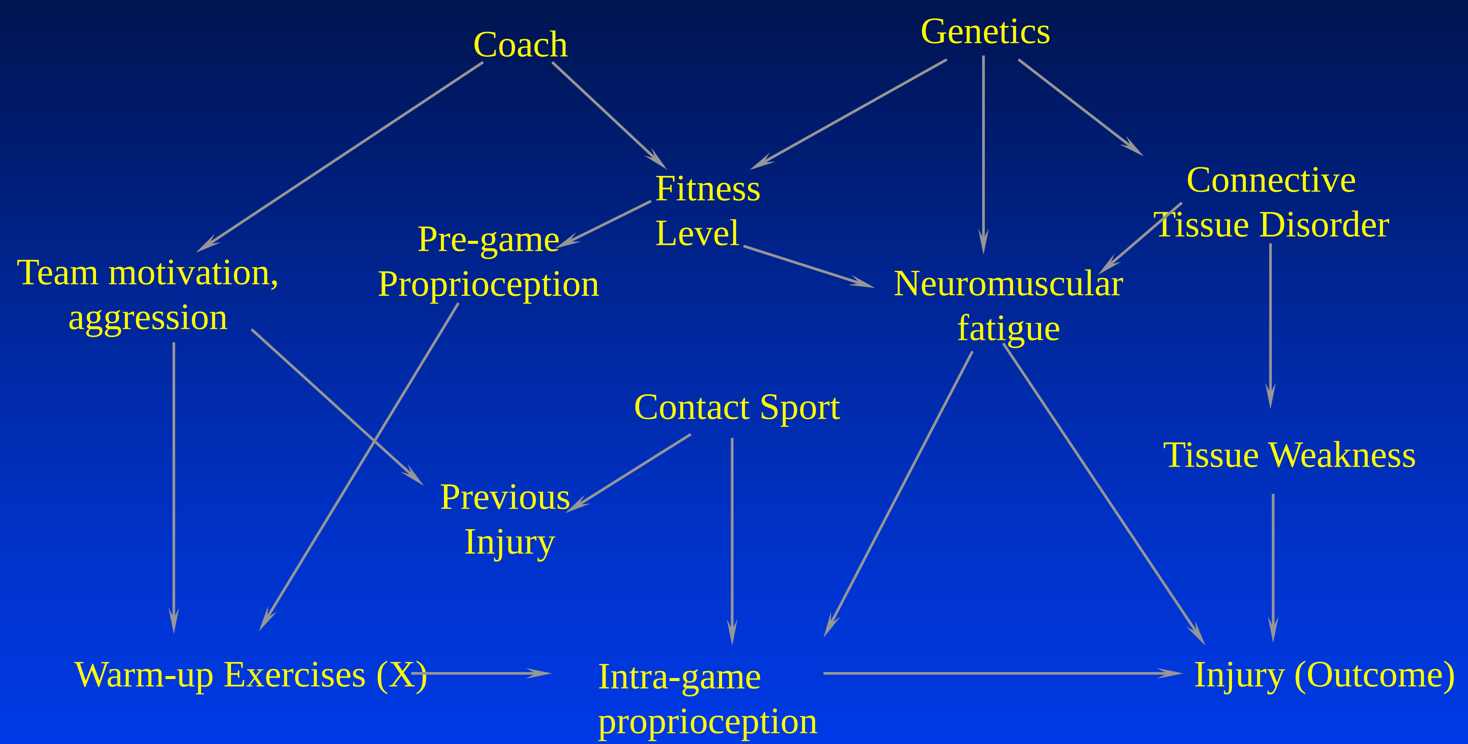
  - ⇒ Combining studies that use different regression models
  - ⇒ Allocation Concealment, Placebo Effect

Complex Causal DAGs



Which measurements should be included in the model if we are interested in the relation between X and Outcome?

(Pearl. Causality Book)

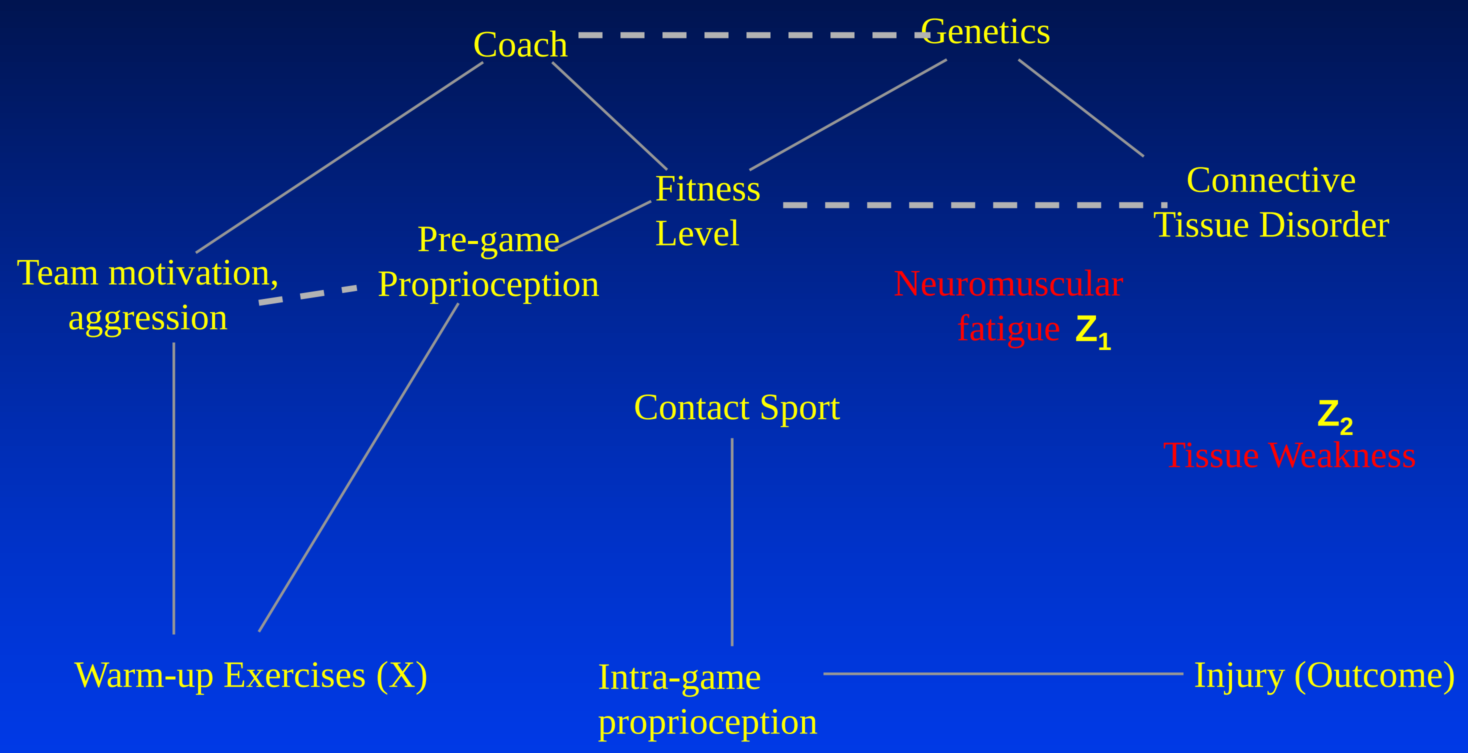
Complex Causal DAGs

Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

Pearl's Rules: 6-Step Simple Algorithm

(Pearl. Causality Book)

6th Step of Pearl's Algorithm



Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1 and Z_2 remove confounding?

If X is disconnected from Outcome (d-separation), there is no confounding

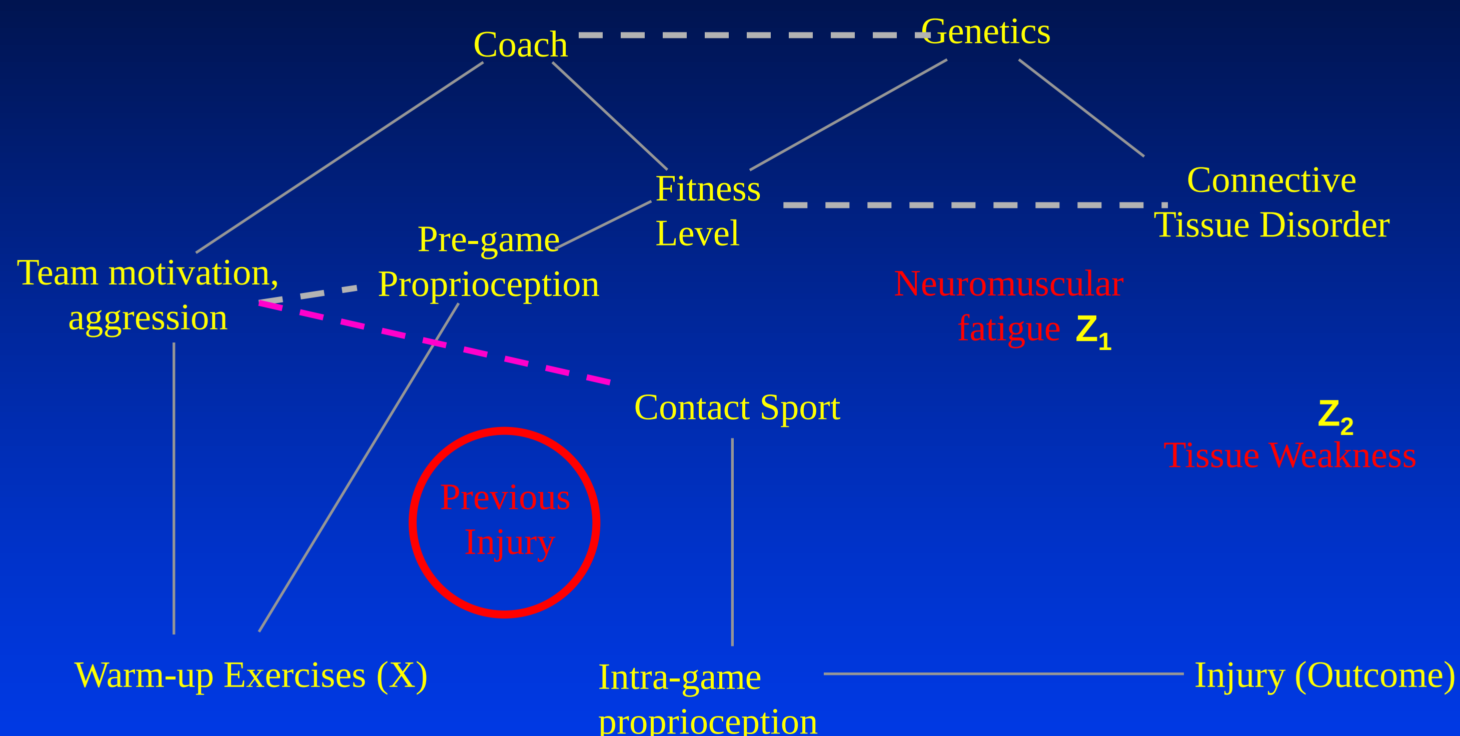
(Pearl. Causality Book)

Confounders vs. Confounding

Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1, Z_2 and Z_3 remove confounding?

(Shrier & Platt, 2008)

Confounders vs. Confounding



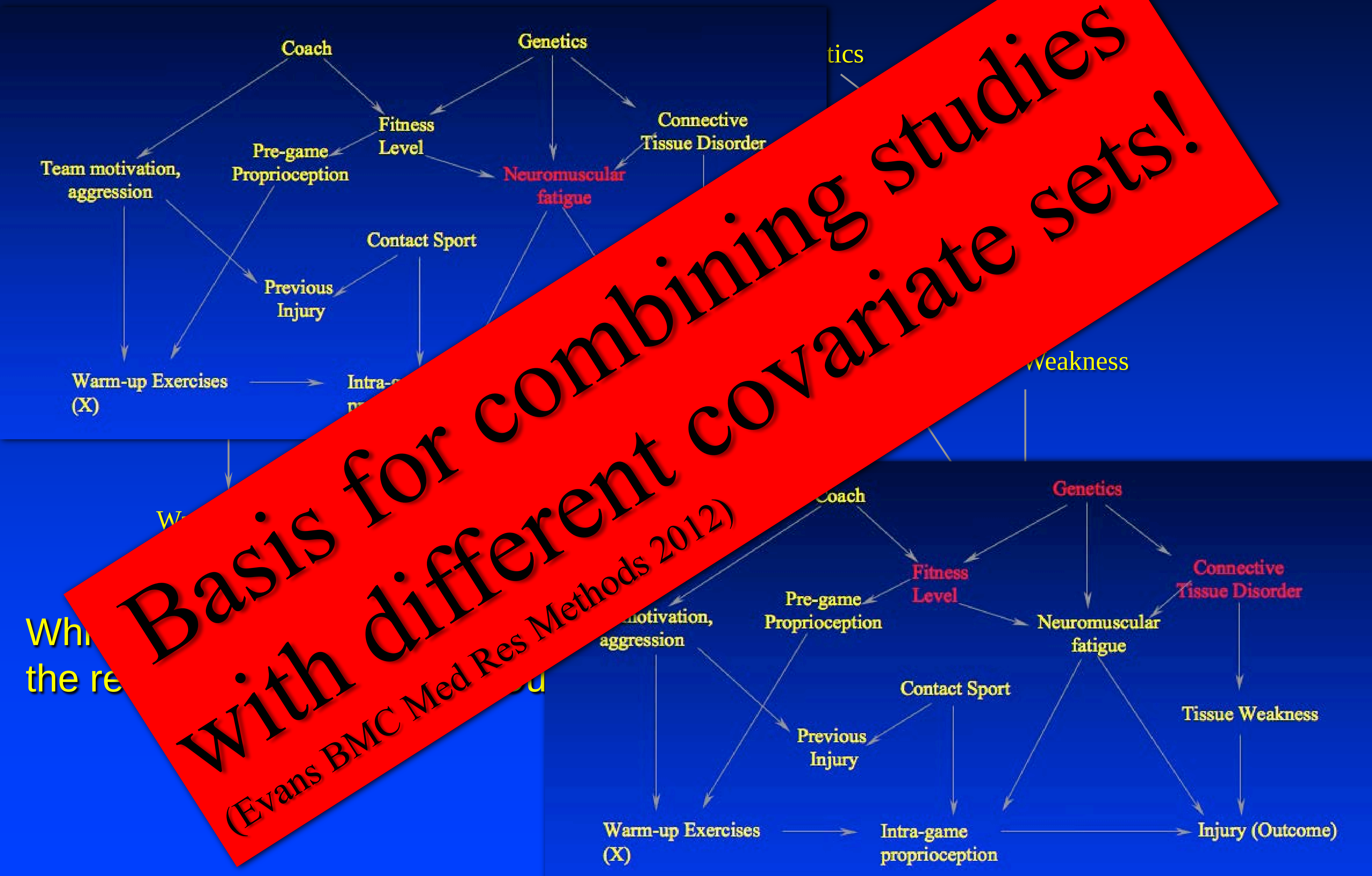
Which measurements should be included in the model if we are interested in the relation between X and Outcome? Do Z_1, Z_2 and Z_3 remove confounding?

X is NOT disconnected from Outcome

Including Previous Injury" Introduces Bias!

(Shrier & Platt, 2008)

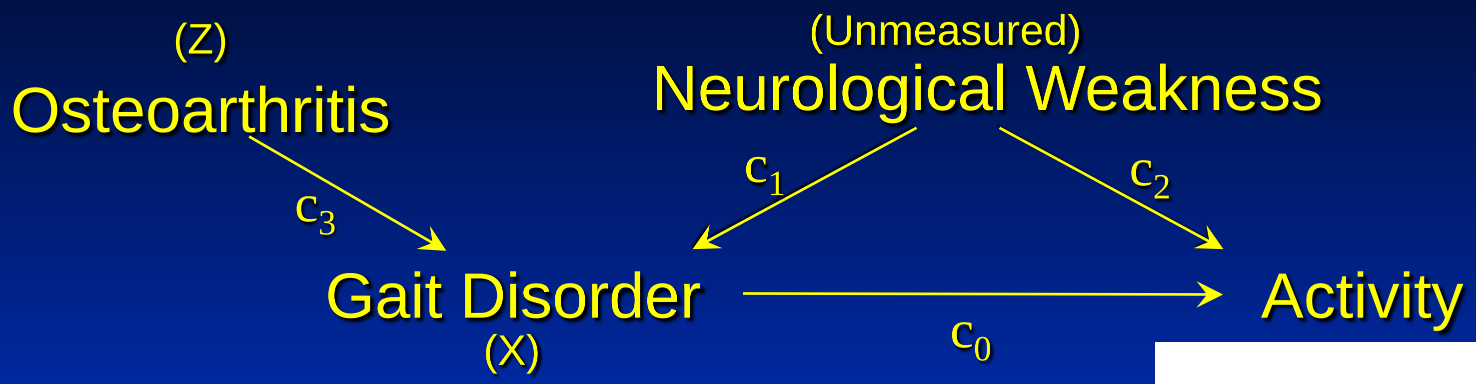
Unbiased Covariate Sets?



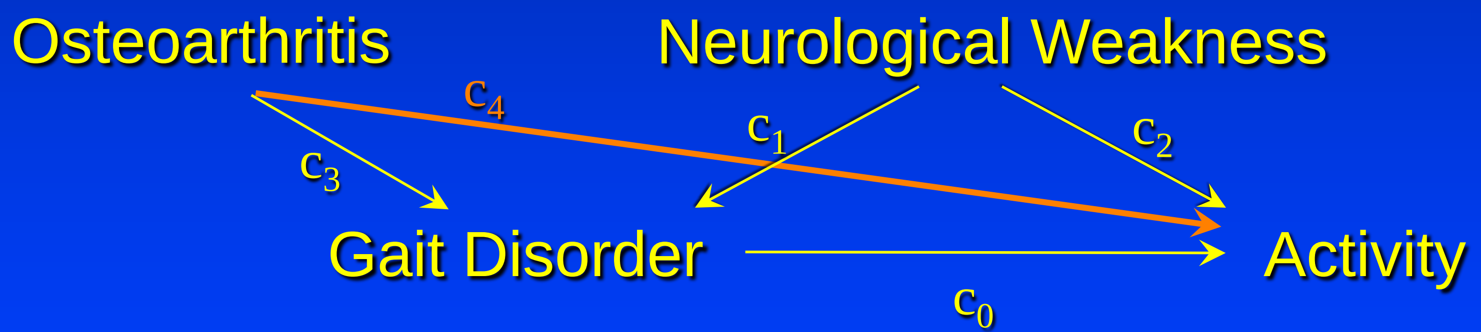
Basis for combining studies with different covariate sets!

(Evans BMC Med Res Methods 2012)

BIAS-AMPLIFYING COVARIATES



$$Bias_{Gait|Z} = \frac{Bias_{Gait}}{1 - c_3^2}$$



To decrease bias: $$\frac{c_4}{c_3} \geq \frac{c_2 c_1}{1 - c_3^2}$$

??? Propensity Scores ???

i.e. best predictor of Exp is most likely to increase bias

http://ftp.cs.ucla.edu/pub/stat_ser/r356.pdf

RISK OF BIAS TOOL

Allocation generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Was the allocation sequence adequately generated? **For obs. studies, was the allocation based on the indications for treatment, or presence of outcome (introduces bias)?**

No changes for:

1. Allocation Concealment
2. Blinding (investigator, participant, assessor)
3. Incomplete Outcome Data
4. Selective Outcome Reporting

(Shrier. Res Synth Methods 2012)

RISK OF BIAS TOOL

Other sources of bias.	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Was the study apparently free of other problems that could put it at a high risk of bias? **In particular, were there any other "co-interventions" by design or association through clustering that could explain the results?**
Analytical Procedures	**Describe the statistical methods used to minimize bias.**	**Were appropriate statistical analyses used to minimize bias? A causal diagram outlining the theoretical causal relationships between variables of interest would be beneficial**

(Shrier. Res Synth Methods 2012)

SUMMARY

- Observational studies address treatment effectiveness: patient-oriented analysis
- Epidemiology has always focused on causes
- Causal diagrams greatly enhance transparency when combining studies that use different adjustment sets
- Risk of Bias tool may lead to double-counting of bias, and inappropriate inferences
- “Placebo effect” assumes treatment allocation does not affect outcome
- Current Risk of Bias tool appropriate for observational studies with slight modifications

But still not as good as 2014 version!

OBJECTIVES

REFERENCES

- Causal Diagrams

⇒ Hernan et al. A structural approach to bias. Epidemiology 2004;15:615-625

⇒ Shrier & Platt. Reducing bias through directed acyclic graphs. BMC Med Res Methodol 2008;8:70.

⇒ Evans et al. Combining directed acyclic graphs and the change-in-estimate procedure as a novel approach to adjustment-variable selection in epidemiology. BMC Med Res Methodol 2012;12:156

⇒ Textor et al. DAGitty: A graphical tool for analyzing causal diagrams. Epidemiology 11;22:745.

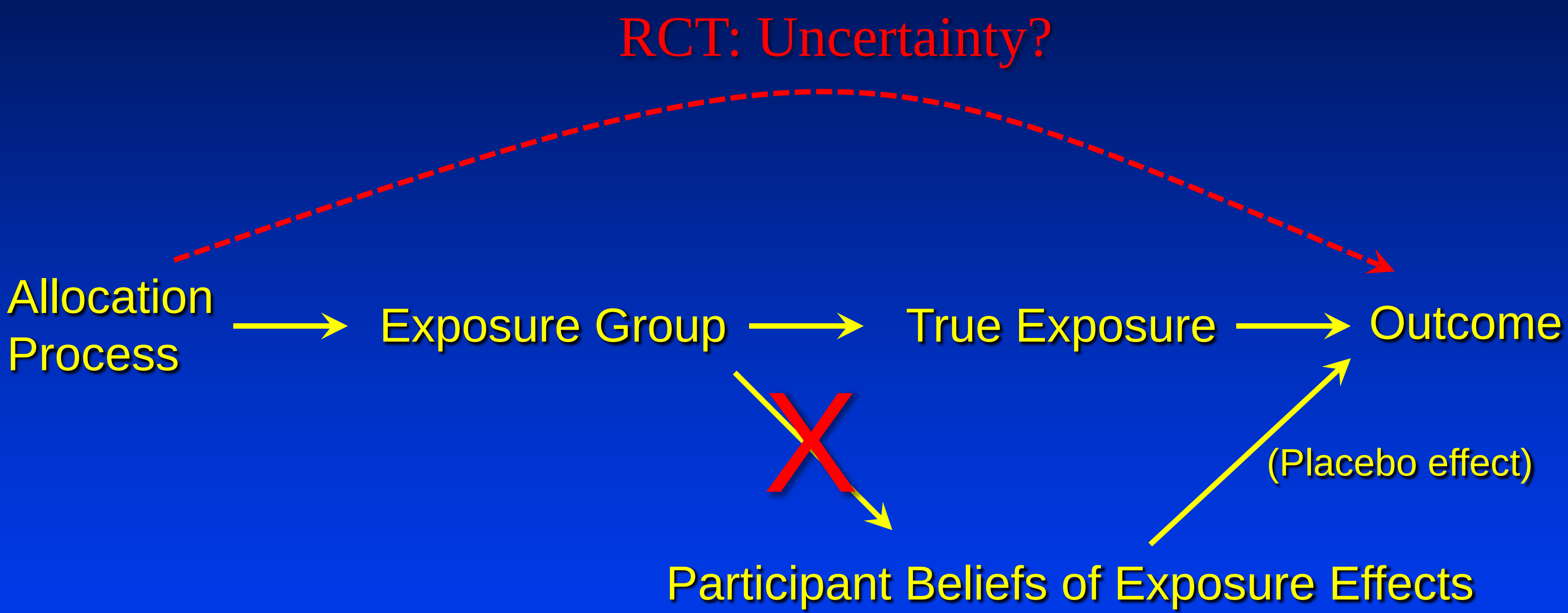
⇒ Pearl. Some thoughts concerning transfer learning, with applications to meta-analysis and data-sharing estimation. http://bayes.cs.ucla.edu/csl_papers.html (R-387)

- Bias Modelling

⇒ Turner et al. Bias modelling in evidence synthesis. J Roy Stat Soc A 2009;172:21-47. (Thompson et al. A proposed method of bias adjustment for meta-analyses of published observational studies. Int J Epidemiol 2011;40:765-777)

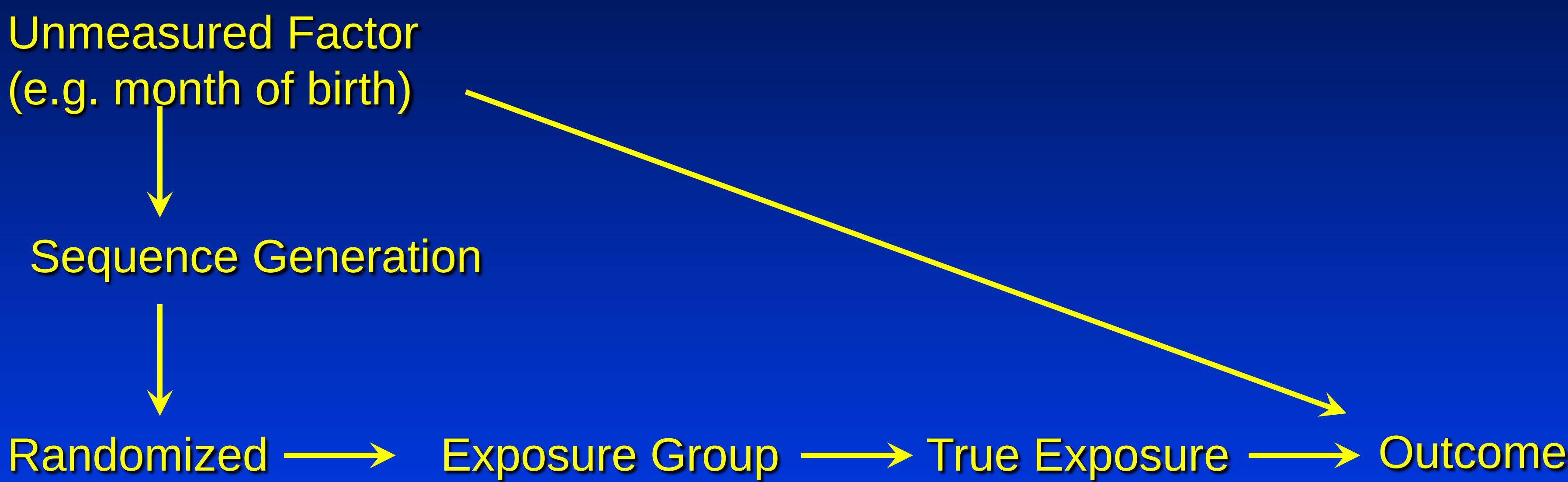
⇒ Shrier. Structural approach to bias in meta-analyses. Res Synth Meth 2012;2:223-237

Blinding: Placebo Effect

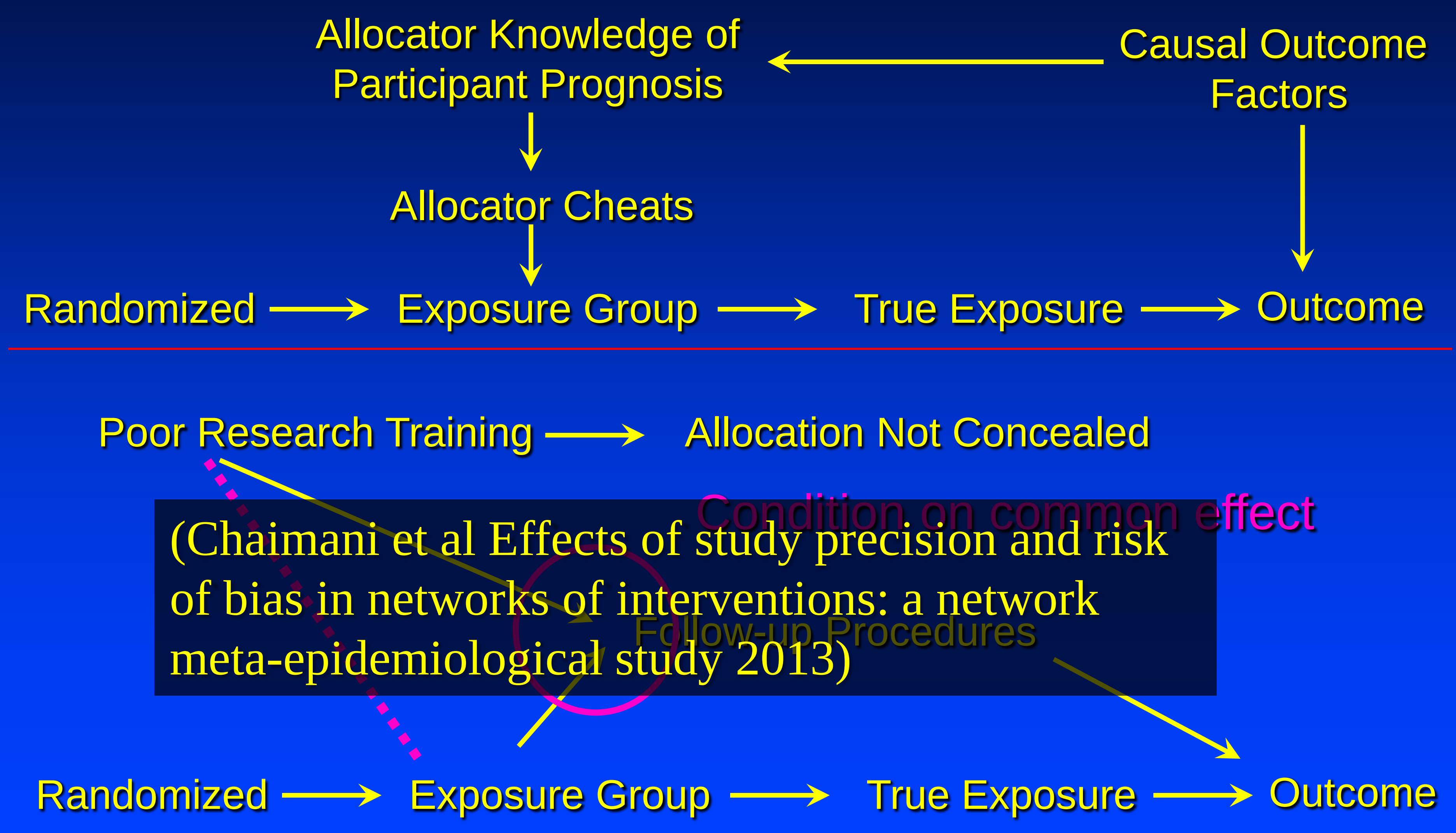


(Shrier, Epidemiology 2013)

Sequence Generation

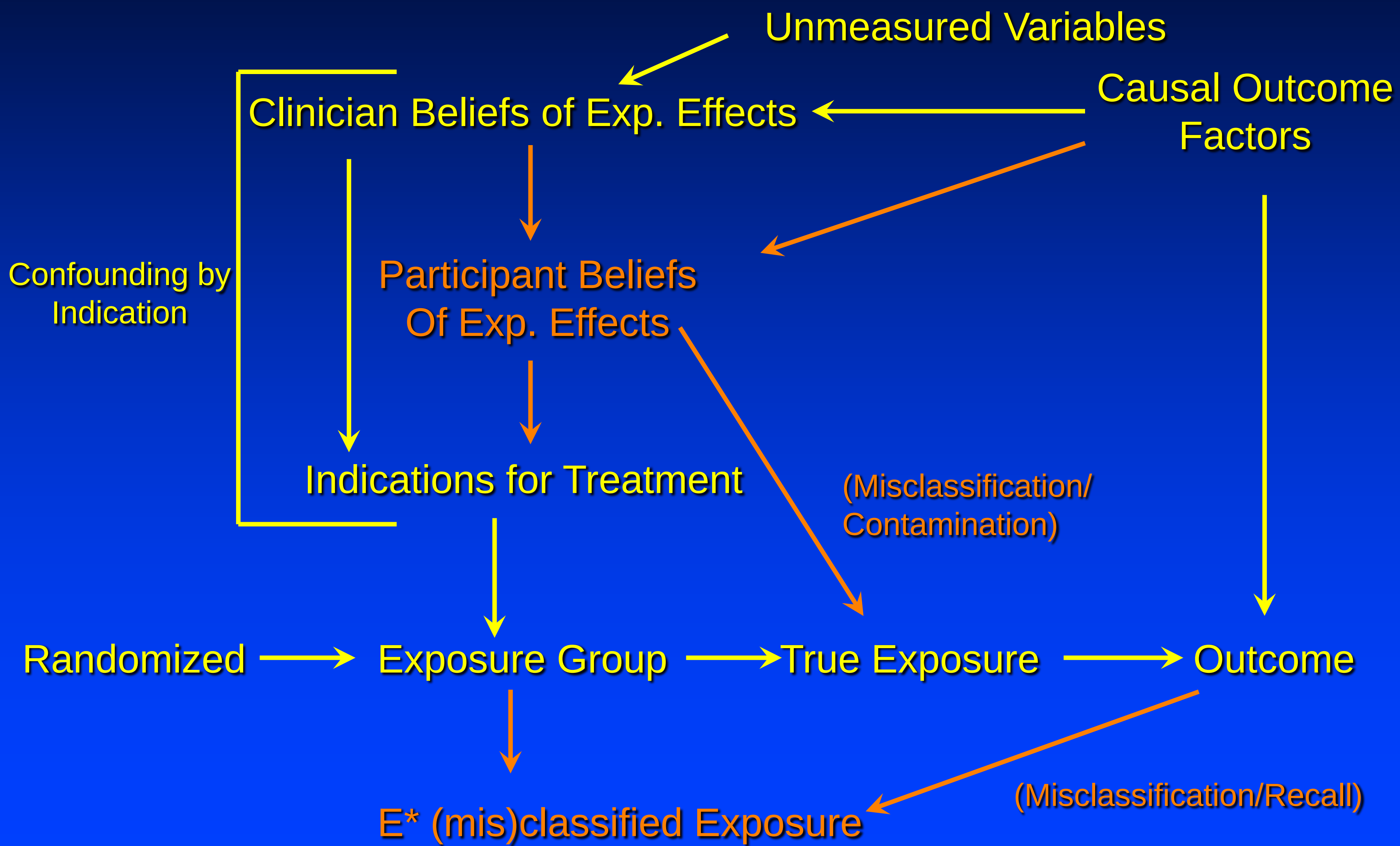


Allocation Concealment

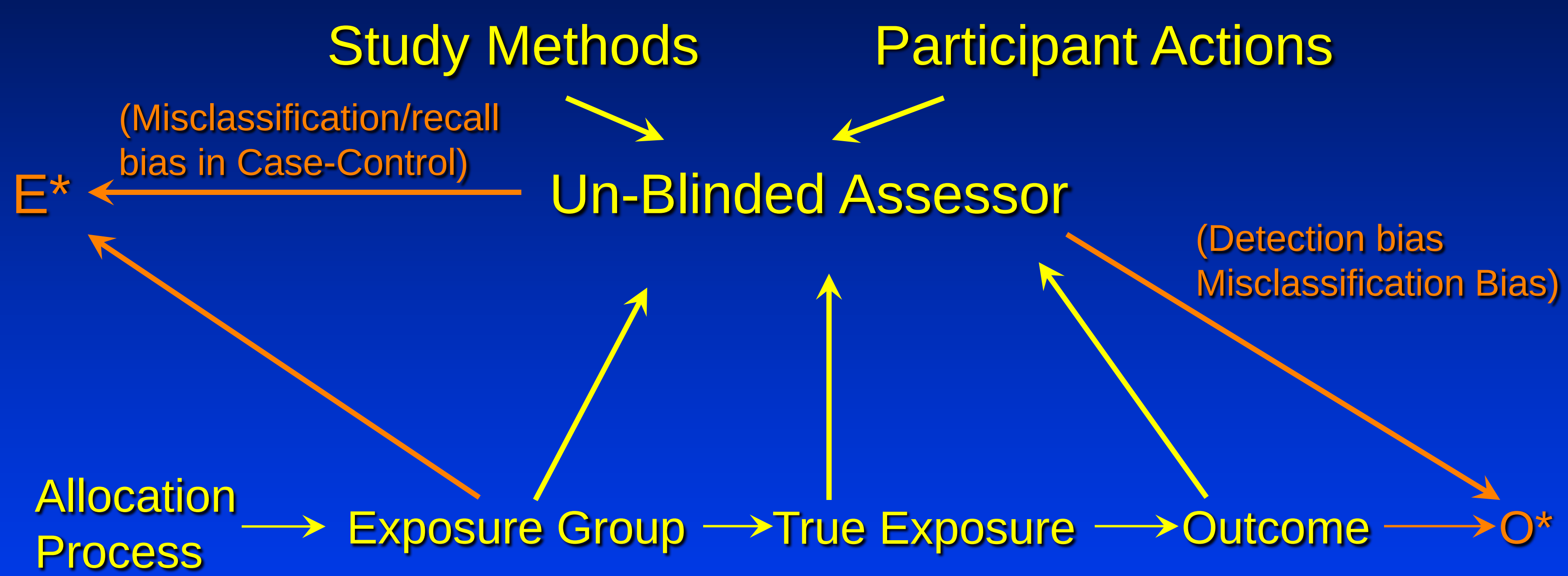


(Chaimani et al Effects of study precision and risk of bias in networks of interventions: a network meta-epidemiological study 2013)

Blinding: Investigator / Particip.



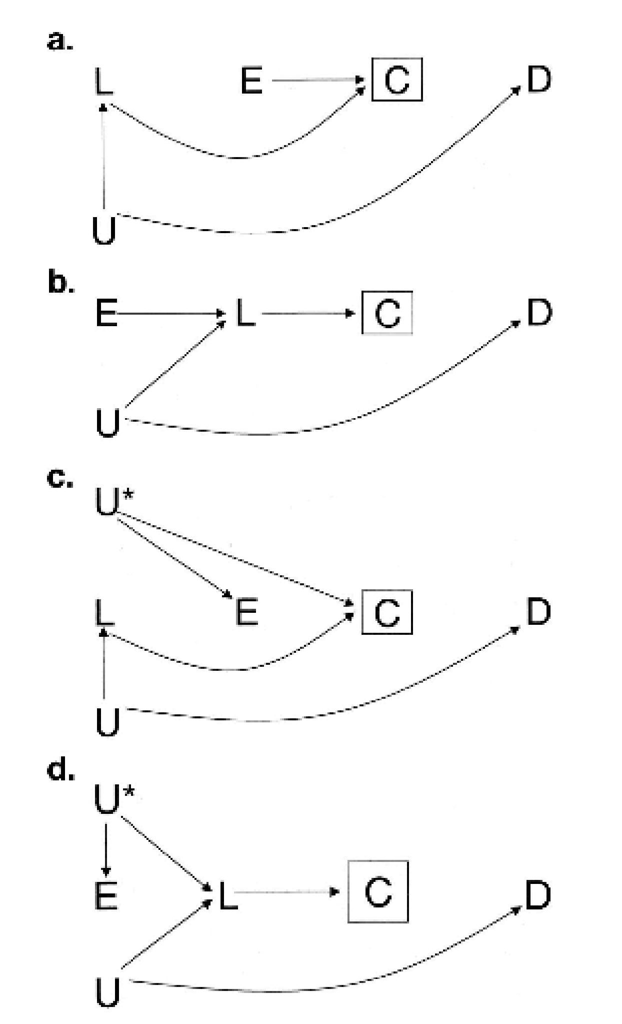
Blinding: Assessor



Incomplete Outcome Data

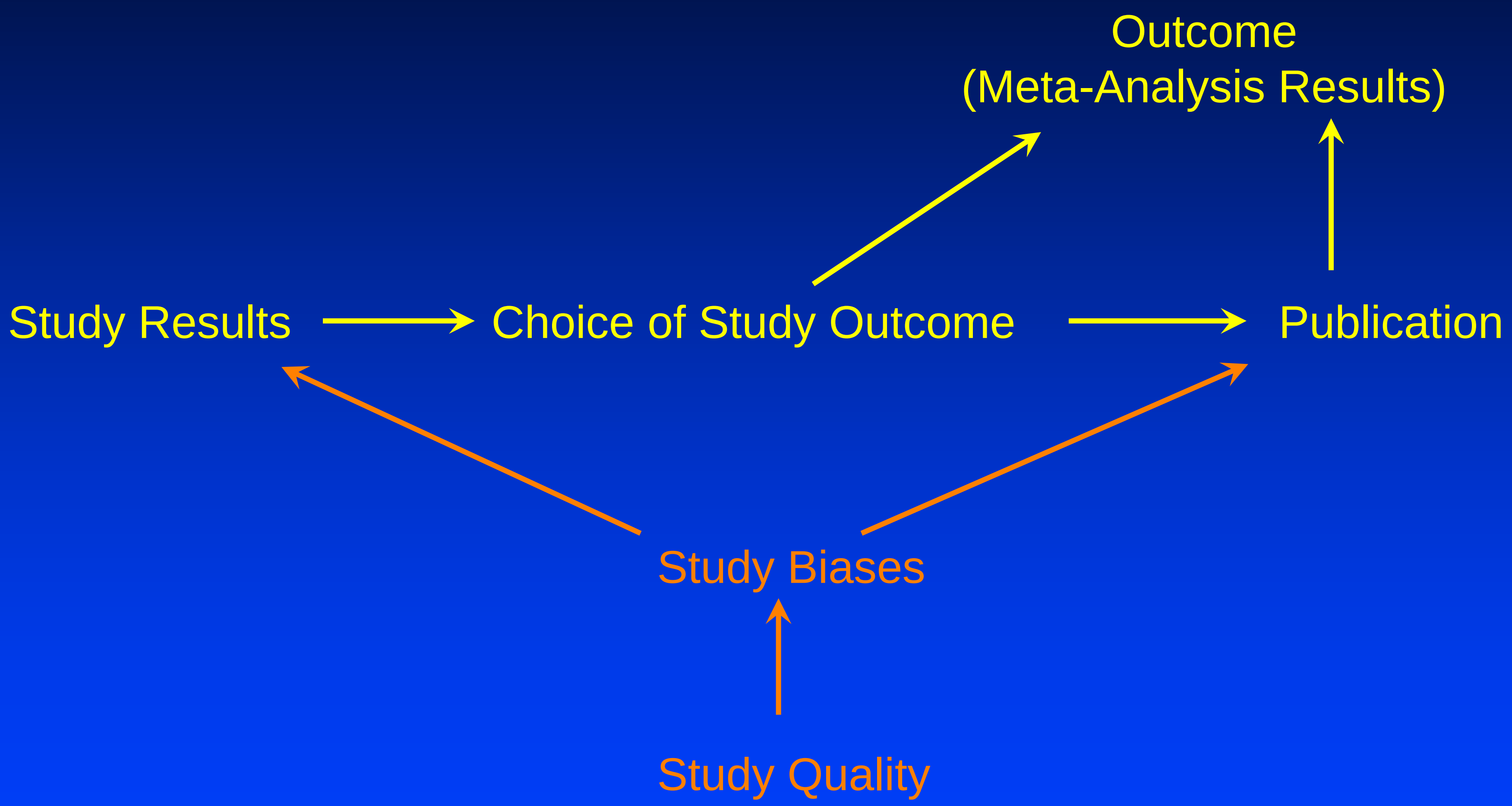
Allocation Process → Exposure Group → True Exposure → Outcome

True Exposure → Side Effects Causing Loss to Follow-Up



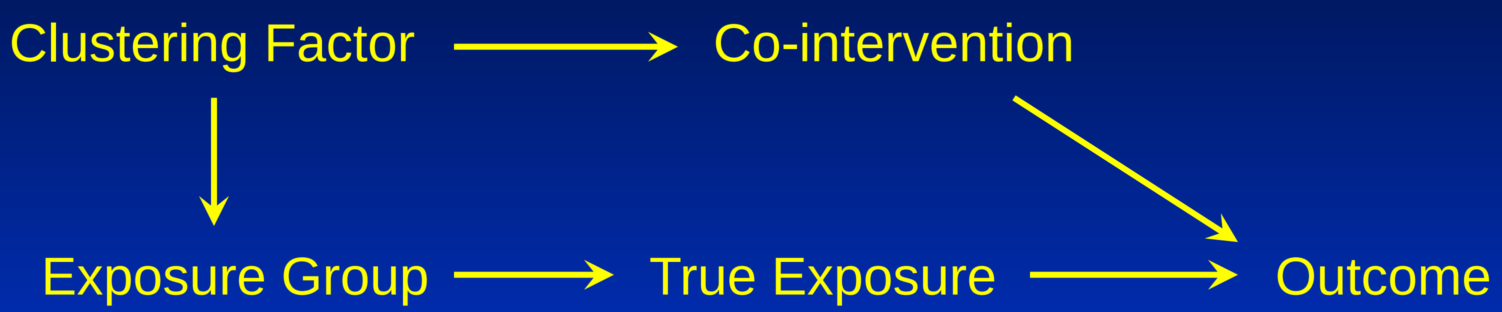
(Hernán Am J Epid 2002)

Selective Outcome Reporting

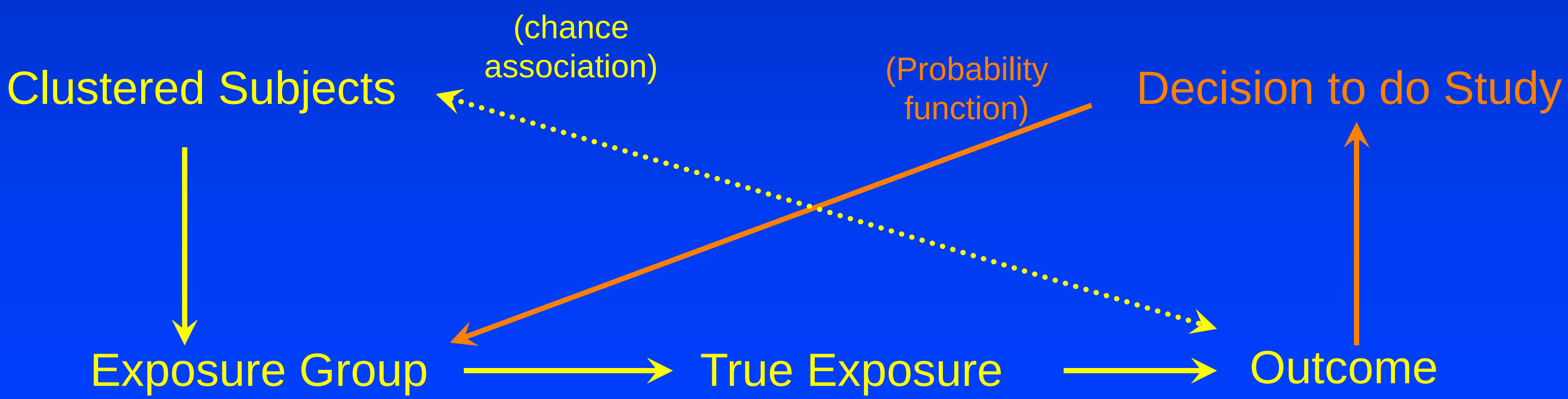


Other Biases: Cluster Effects

Cluster by Time (pre-post), Location



Regression to the Mean



"STANDARD" CONFOUNDER?

- A variable may (i.e. potential confounder) affect the magnitude or direction of the estimated effect if it is associated with exposure and outcome:
  - ⇒ Associated with Exposure:
    - ⇒ is not caused by exposure (e.g. lie along the causal path)
    - ⇒ is not a marker for a variable caused by exposure
  - ⇒ Associated with Outcome:
    - ⇒ is not caused by the outcome
    - ⇒ Is not a marker for a variable caused by the outcome