

Mendelian Randomization

An introduction to (standard) methods
and applications.

Jodie Lord
Methods Meeting 2020

To Cover:

1

The overarching premise of Mendelian Randomization.

1

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2

Overview of core MR statistical framework and assumptions.

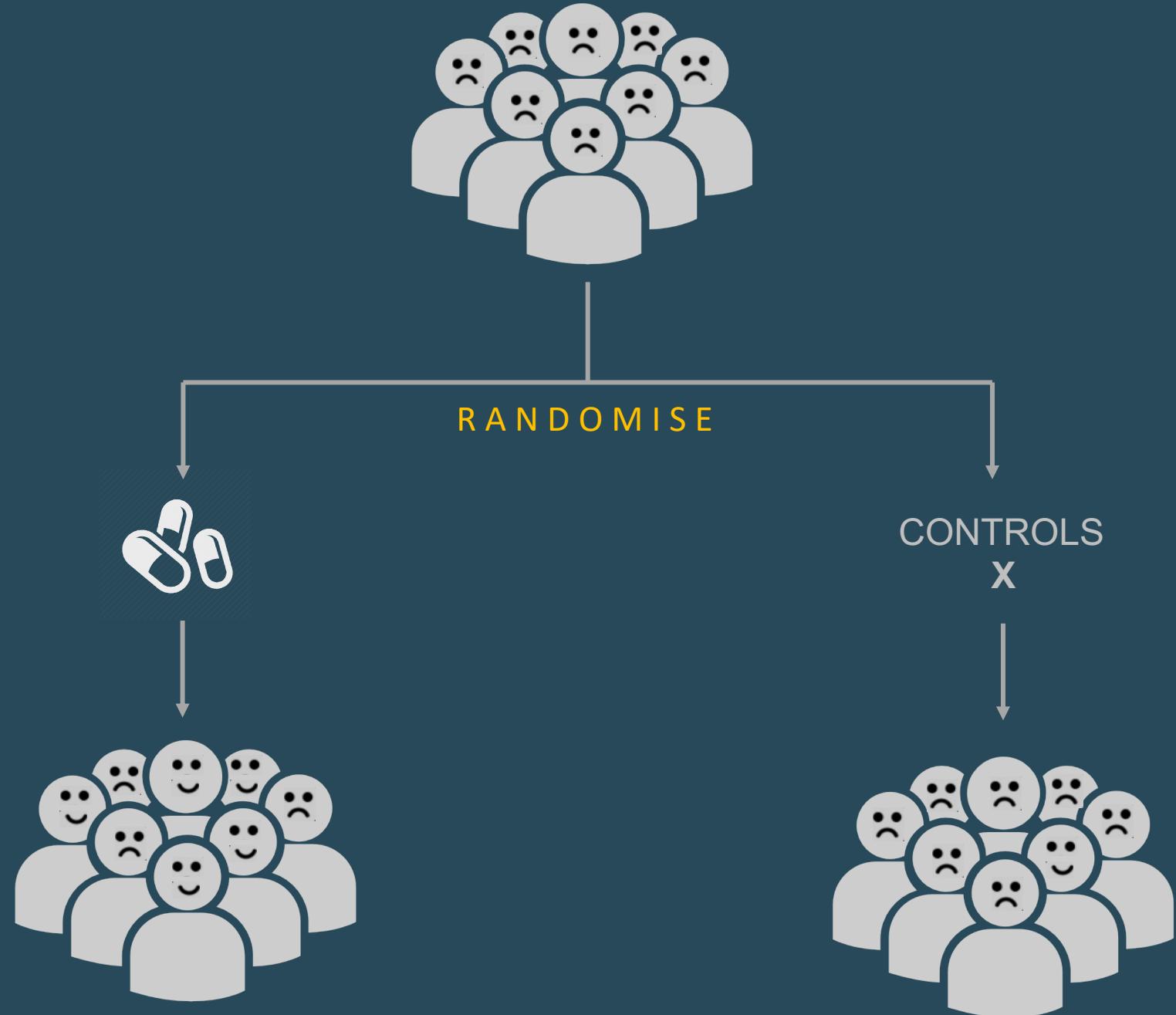
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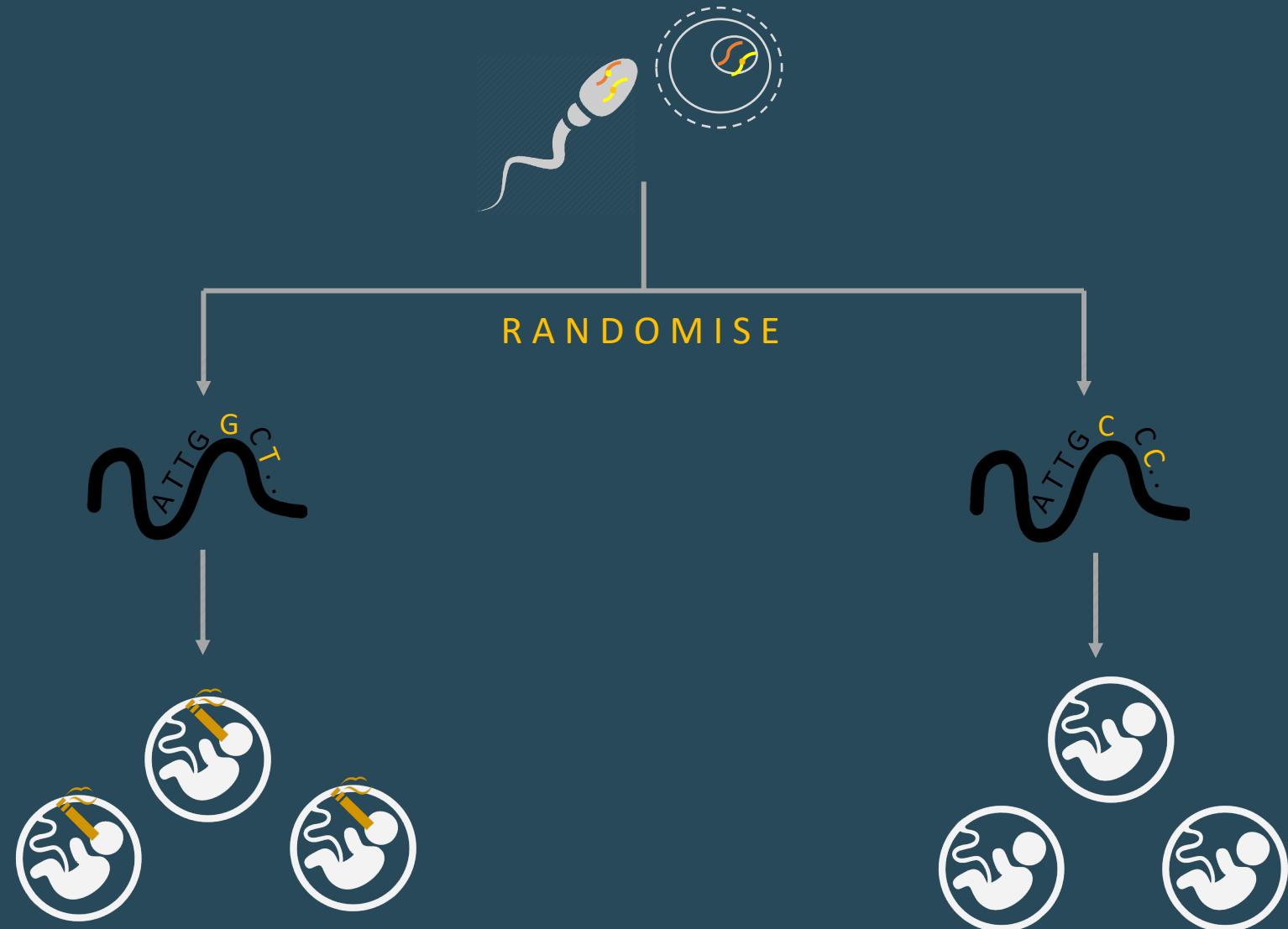
Randomized Control Trials...



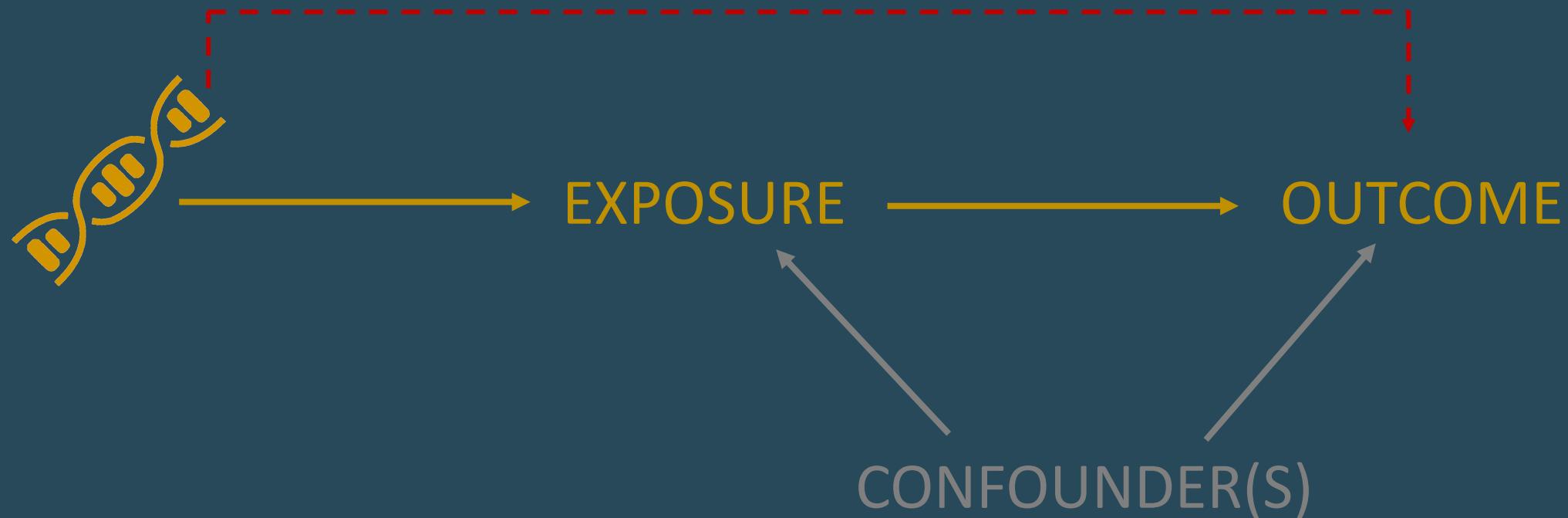
Our Genetics = Natures Randomizer...

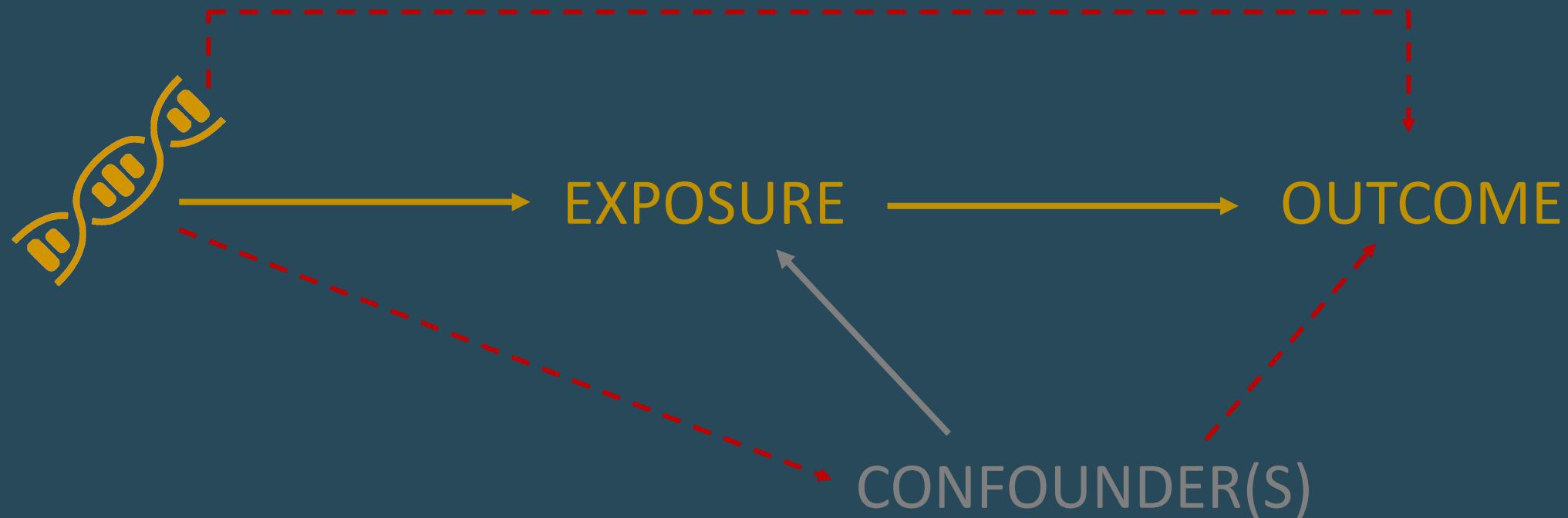






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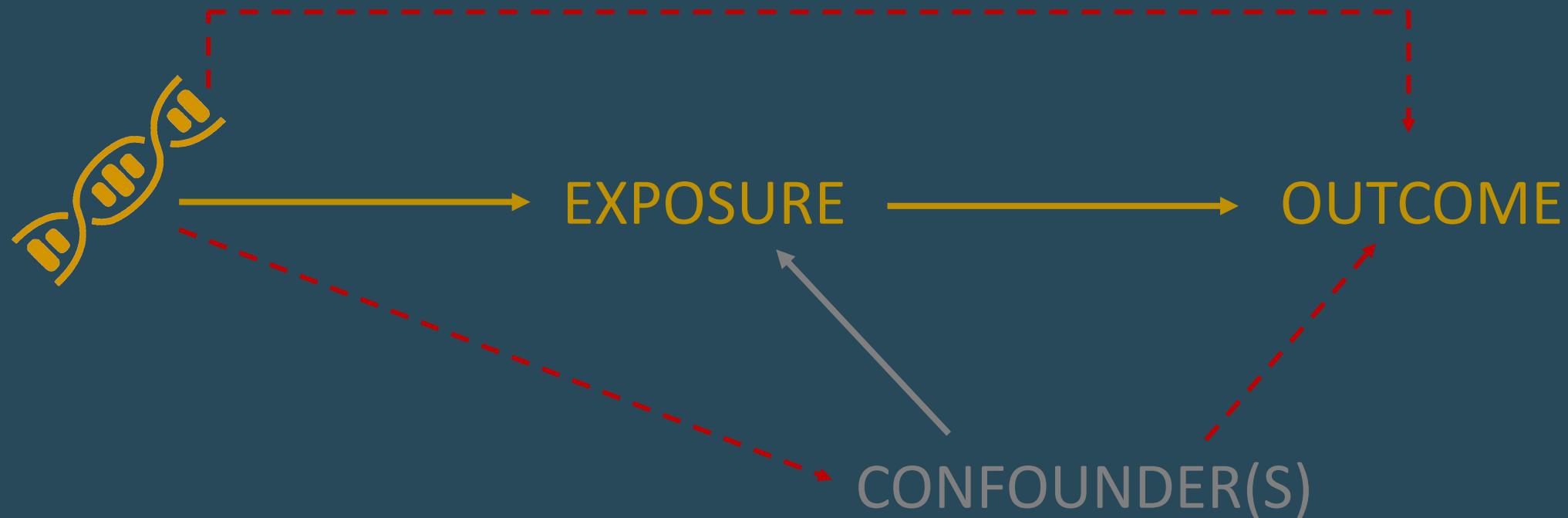
Introduction to univariable methodology.

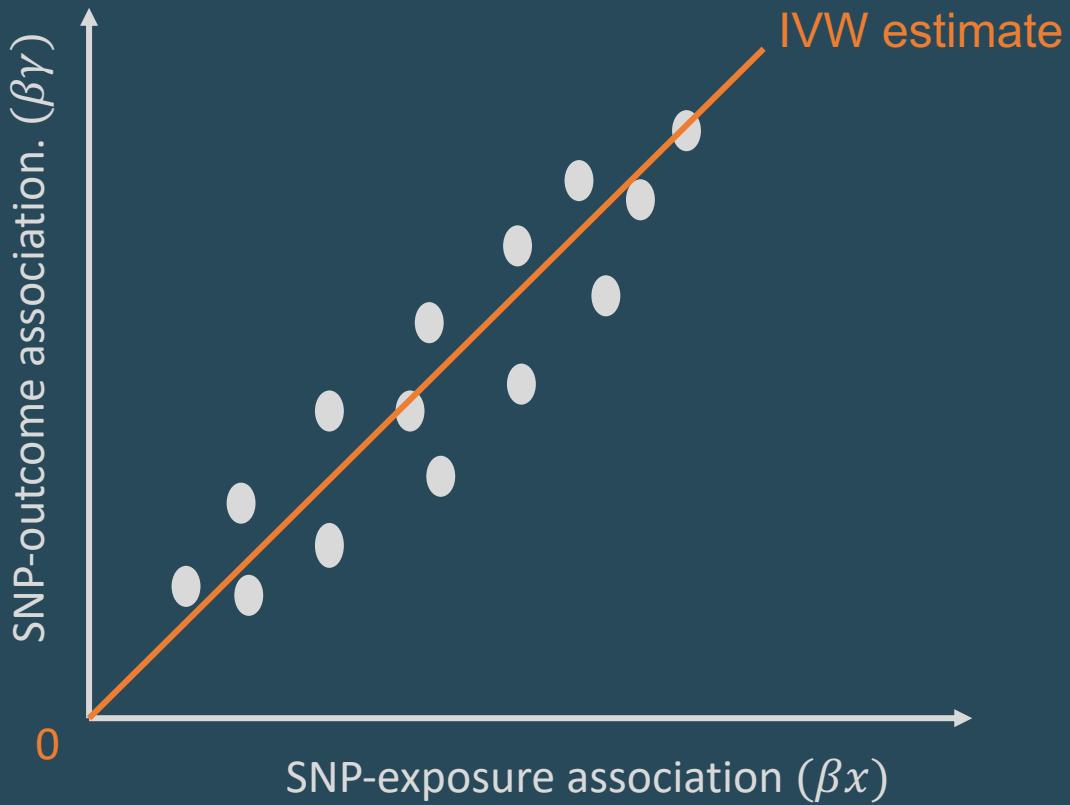
(USING SUMMARY STATISTICS)

Inverse Variance Weighted MR



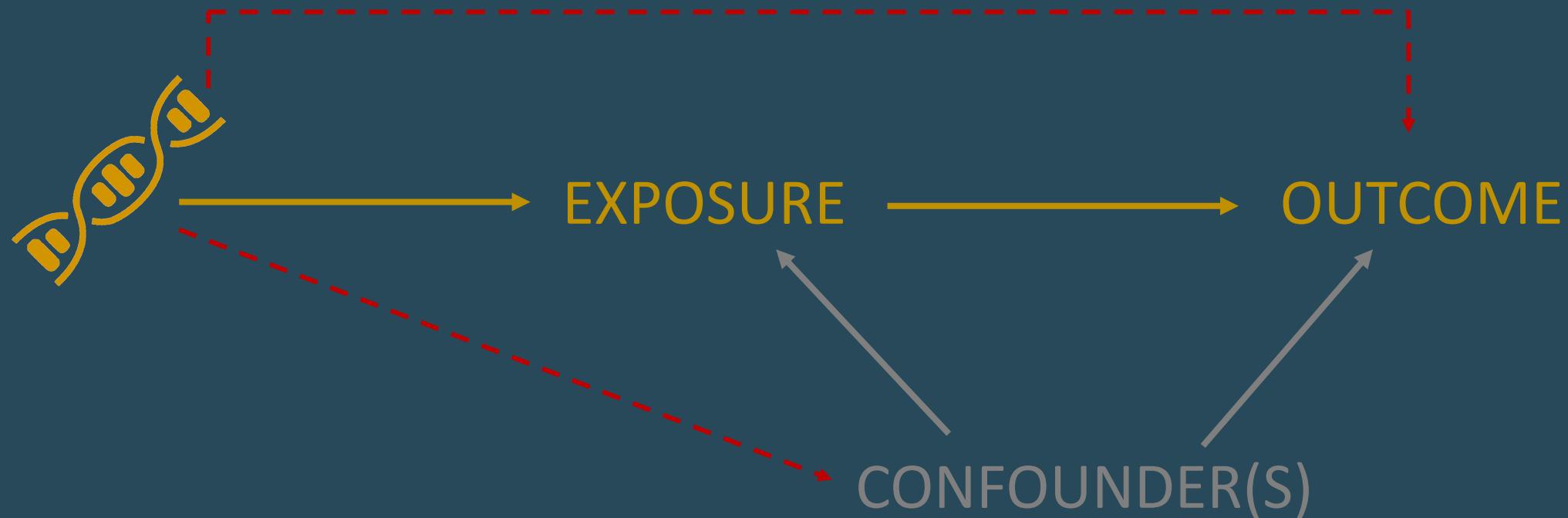
EXPOSURE

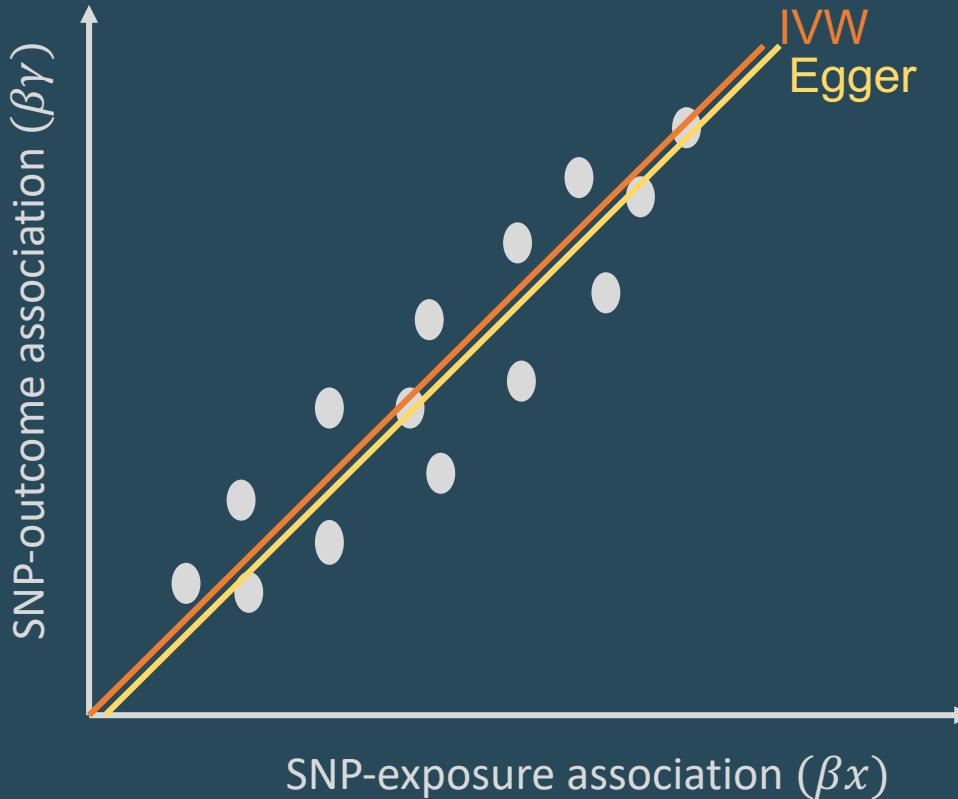


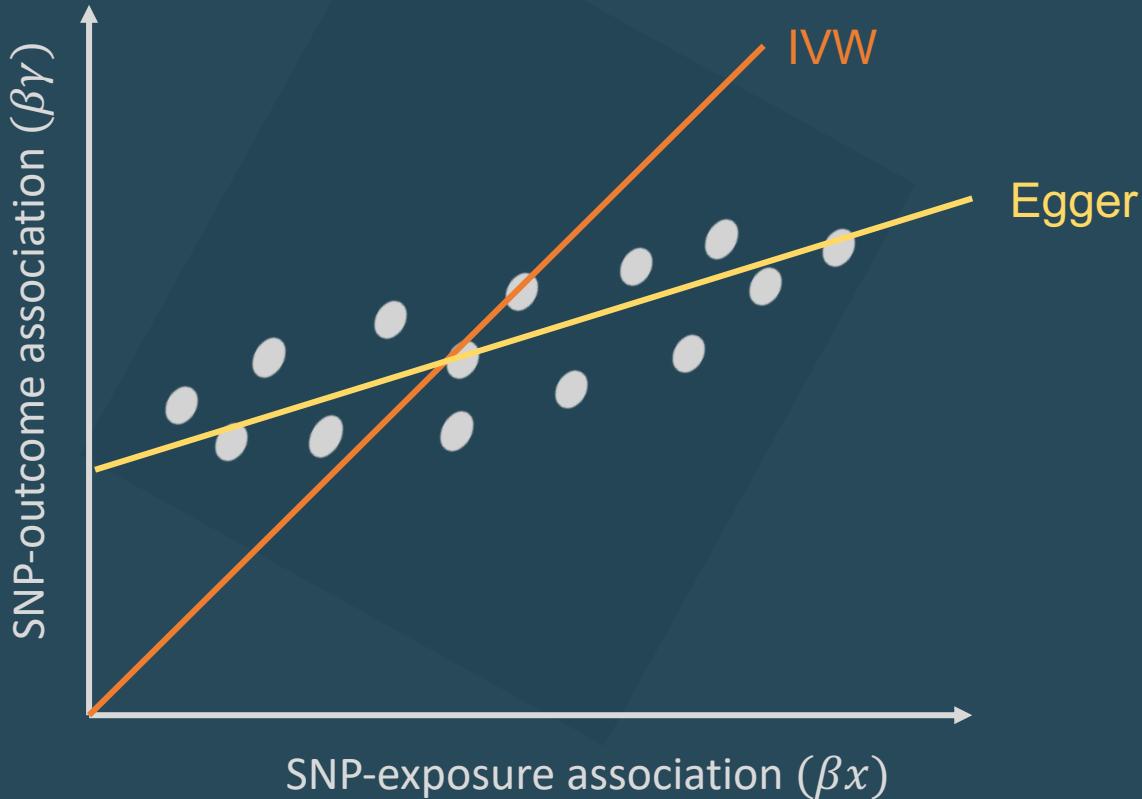


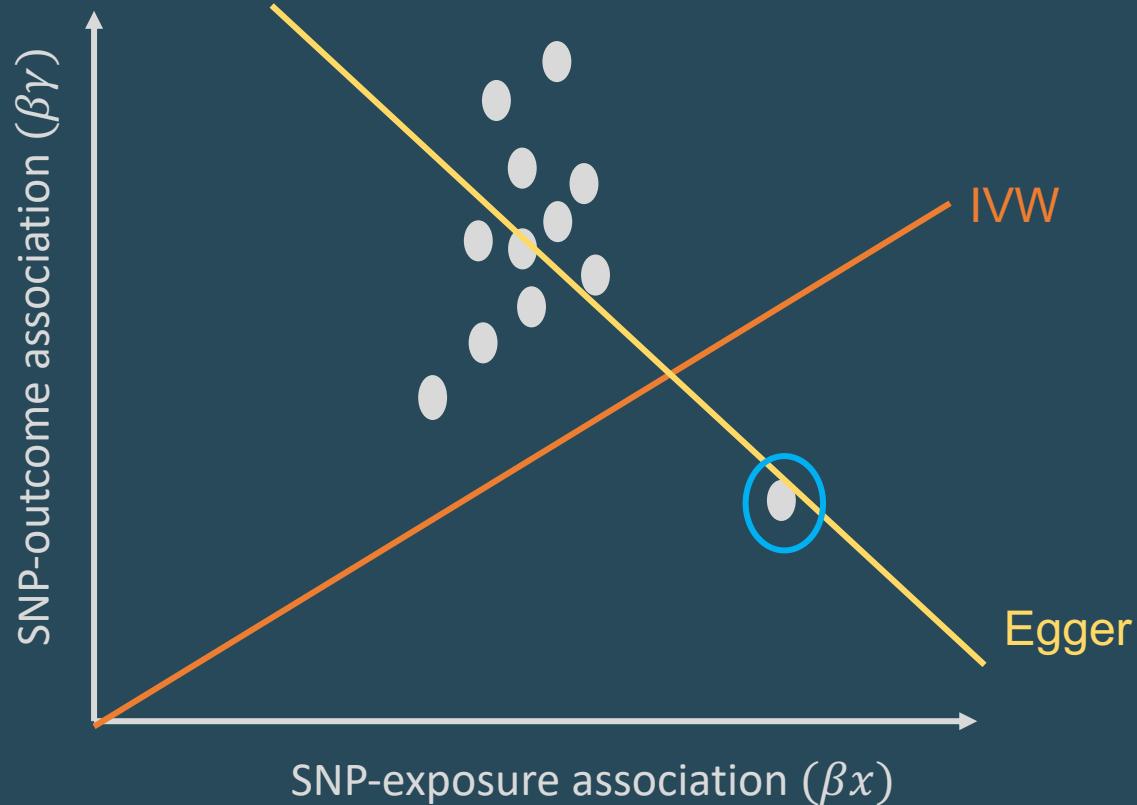
Robust Methods: MR Egger

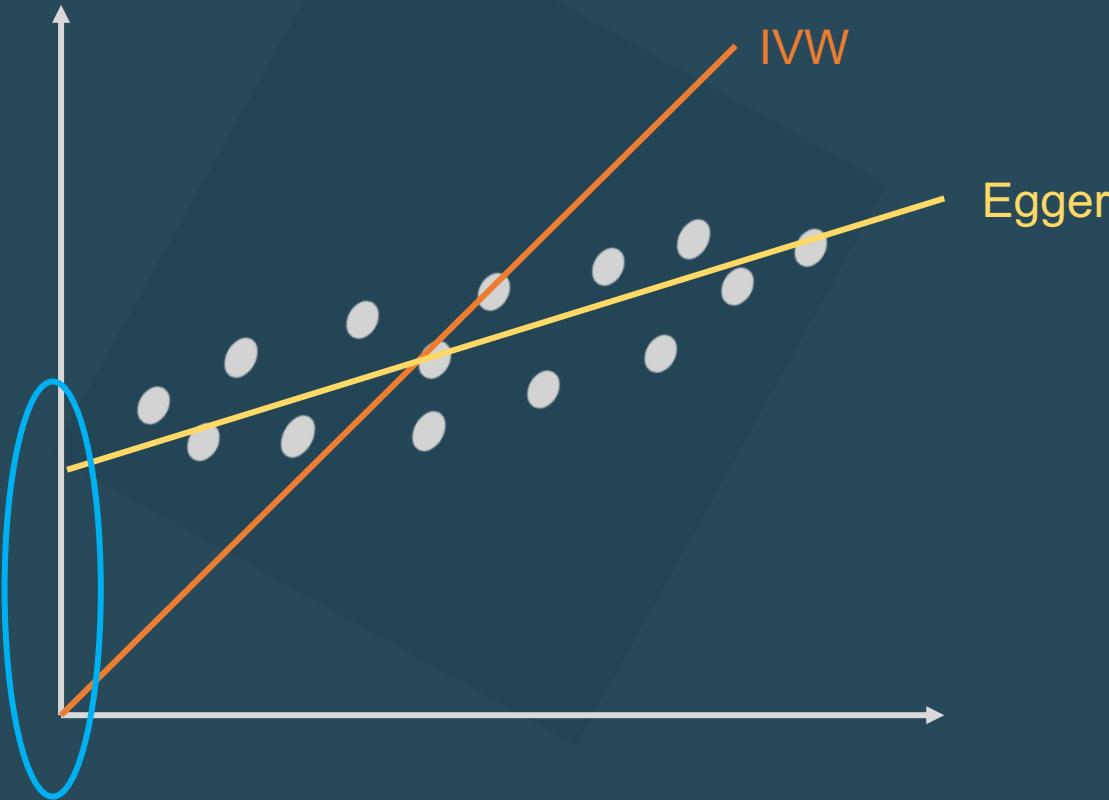
- Same as inverse variance weighted MR, but no intercept constraint.



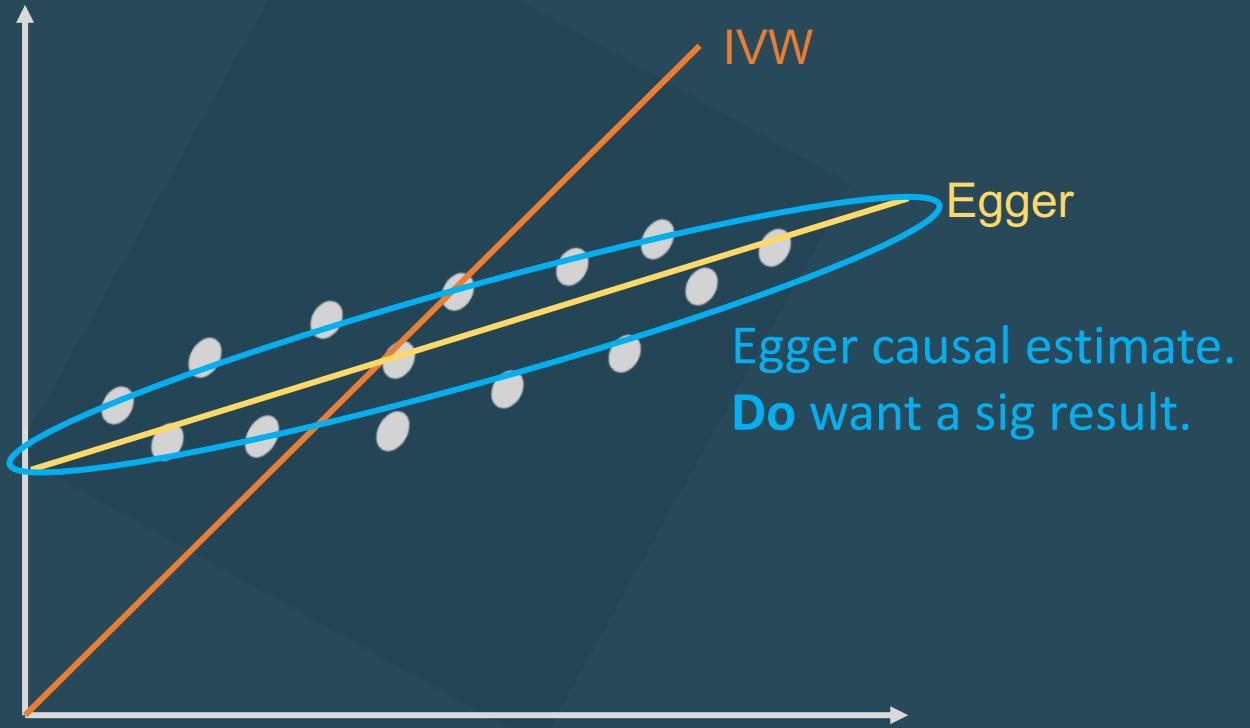


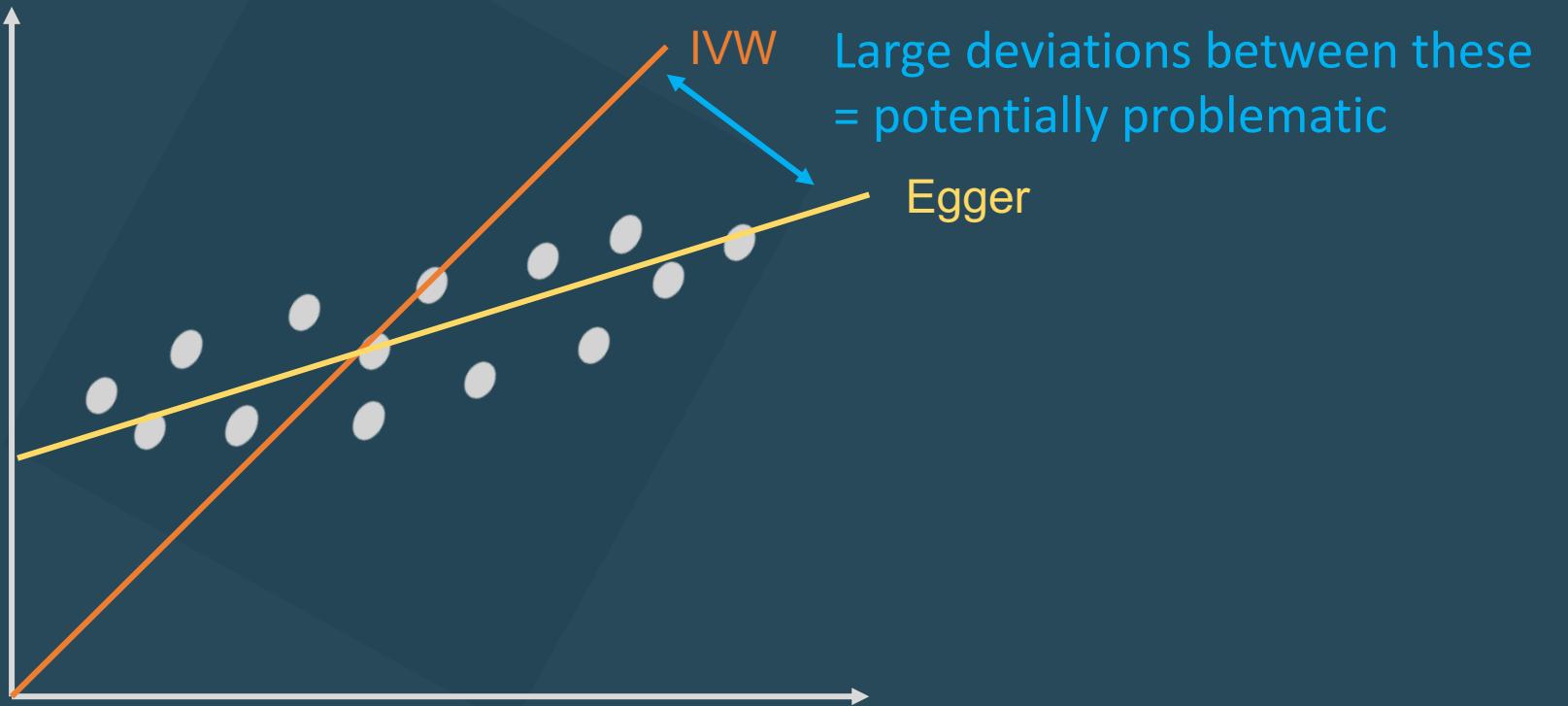






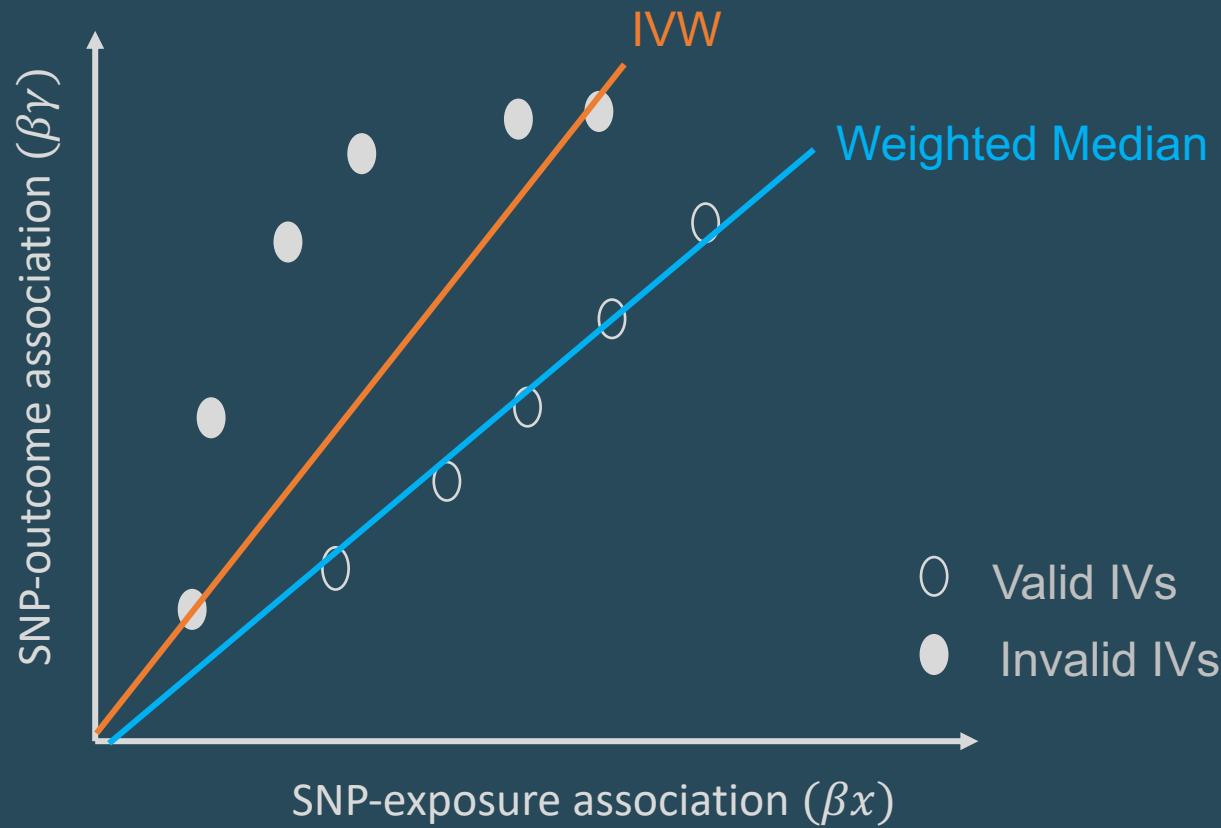
Intercept test.
Don't want a sig result





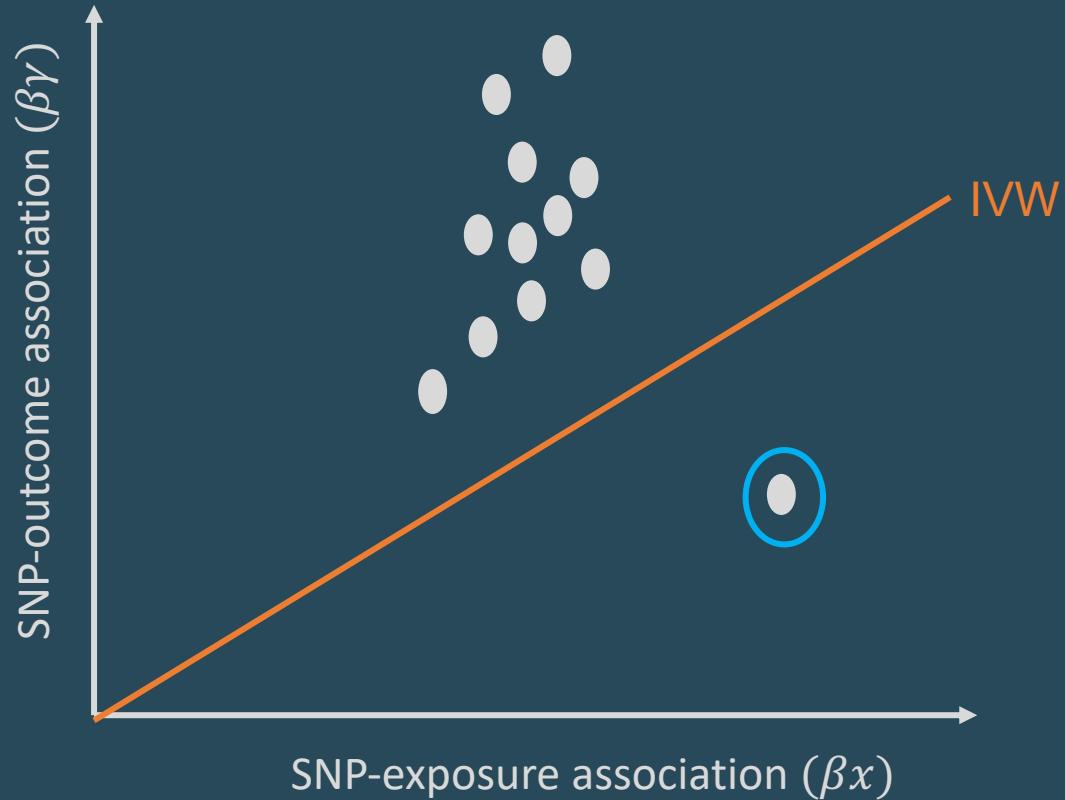
Robust Methods: Weighted Median

- Takes the median of the weighted estimates as the true causal effect.
- Median estimate is less influenced by outliers than standard IVW estimates.
- Key assumption: >50% variants are valid instruments.



(Image stolen / adapted from Burgess.S, 2018)

Other sensitivity analyses: Leave-one-out



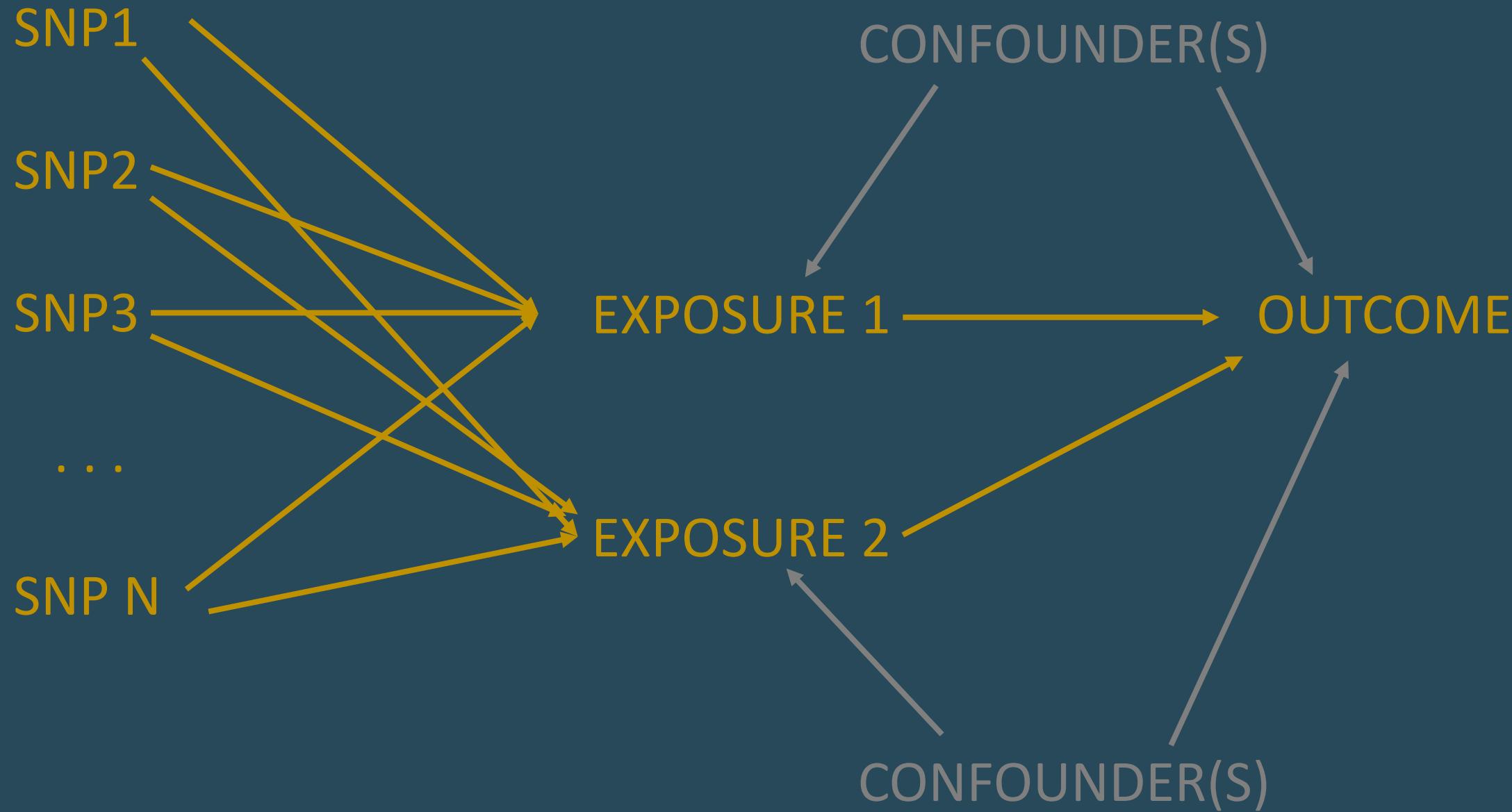


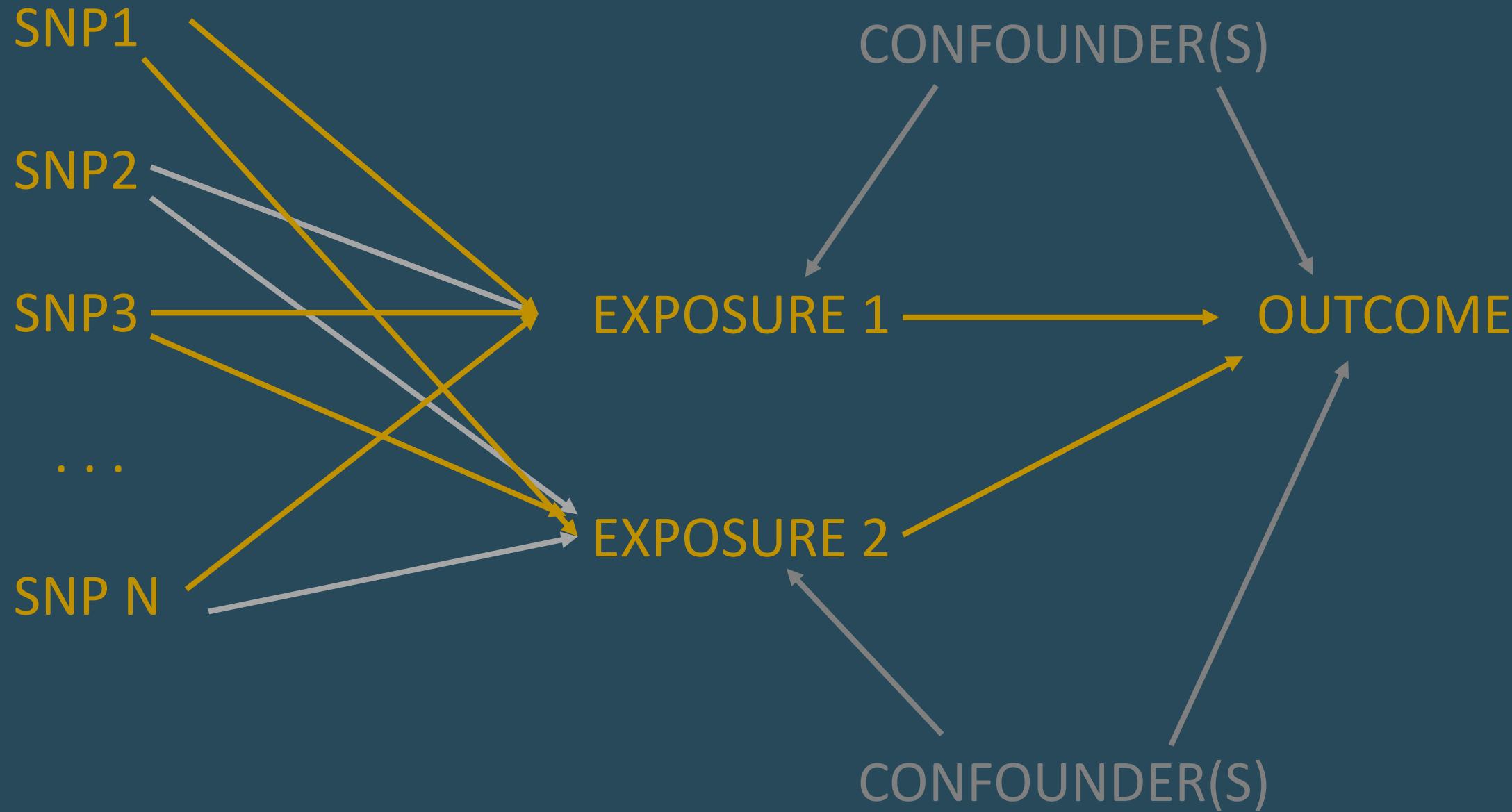
Other checks / analyses you can perform...

- Check heterogeneity using **Cochran's Q**
- Inspect balanced pleiotropy using **funnel plots**
- Conduct further robust methods such as **weighted mode**
- Further outlier checks and removals using **MR-PRESSO**

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Standard Multivariable Framework





MV-MR for Mediation Analyses

MV-MR for Dimension Analyses

BUT FIRST...

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Confounders:

EXPOSURE

OUTCOME

CAUSES

CAUSES

CONFOUNDER





CAUSES



CAUSES

SPURIOUS ASSOCIATION INDUCED WHEN NOT CONTROLLED FOR

Colliders:

EXPOSURE

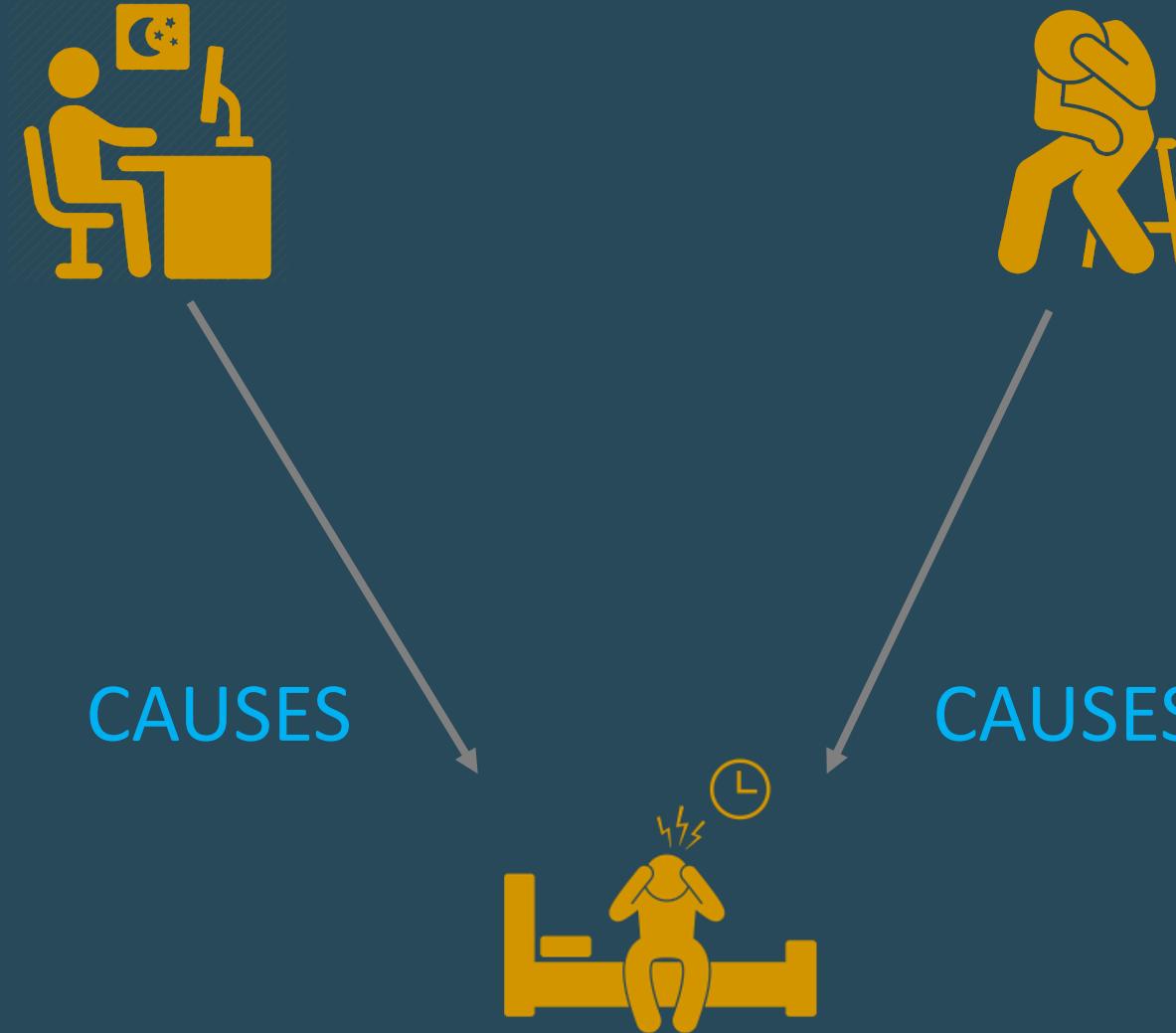
CAUSES

OUTCOME

CAUSES

COLLIDER



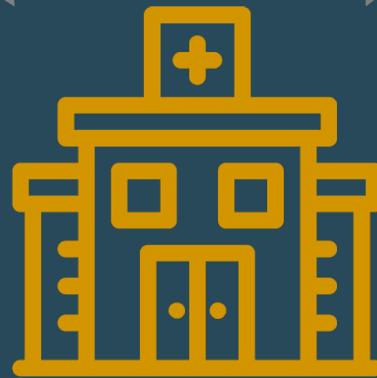


SPURIOUS ASSOCIATION INDUCED WHEN CONTROLLED FOR



CAUSES

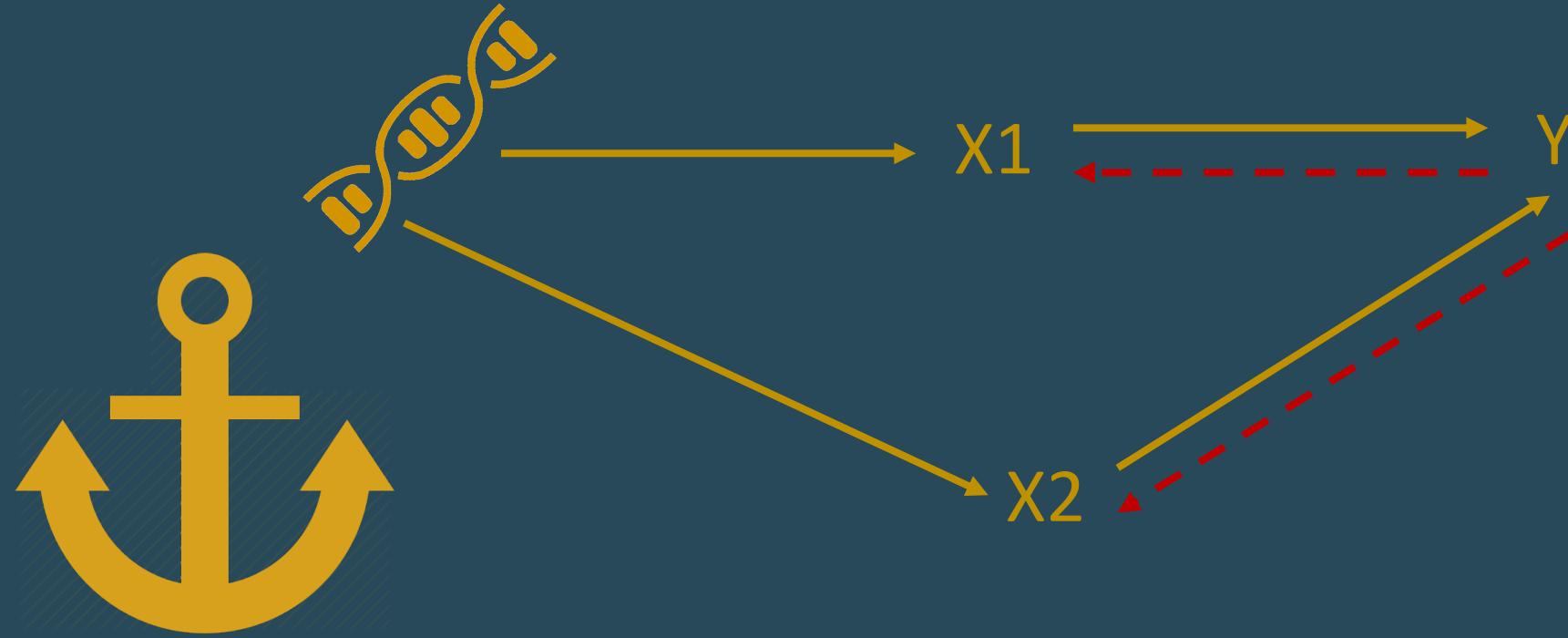
COVID19



CAUSES

ALSO INDUCED THROUGH ASCERTAINMENT BIAS

- MV-MR overcomes collider bias...



DIRECTION ANCHORED

Mediators:

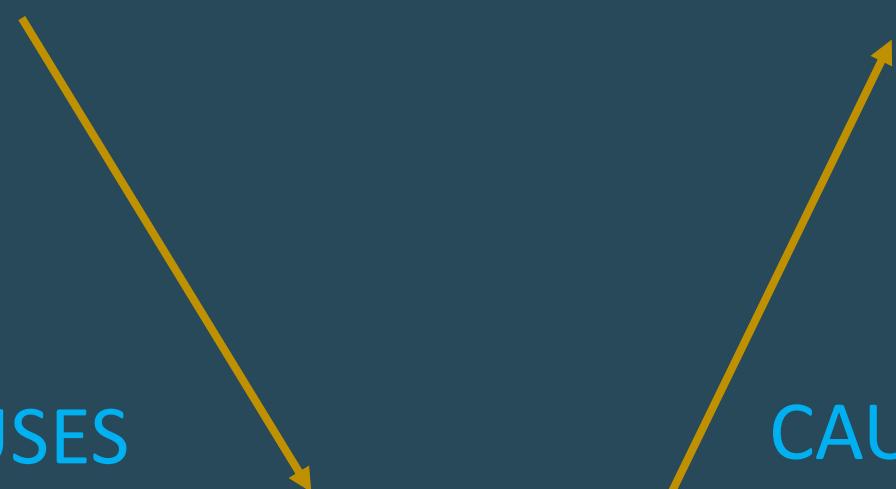
EXPOSURE

CAUSES

OUTCOME

CAUSES

MEDIATOR





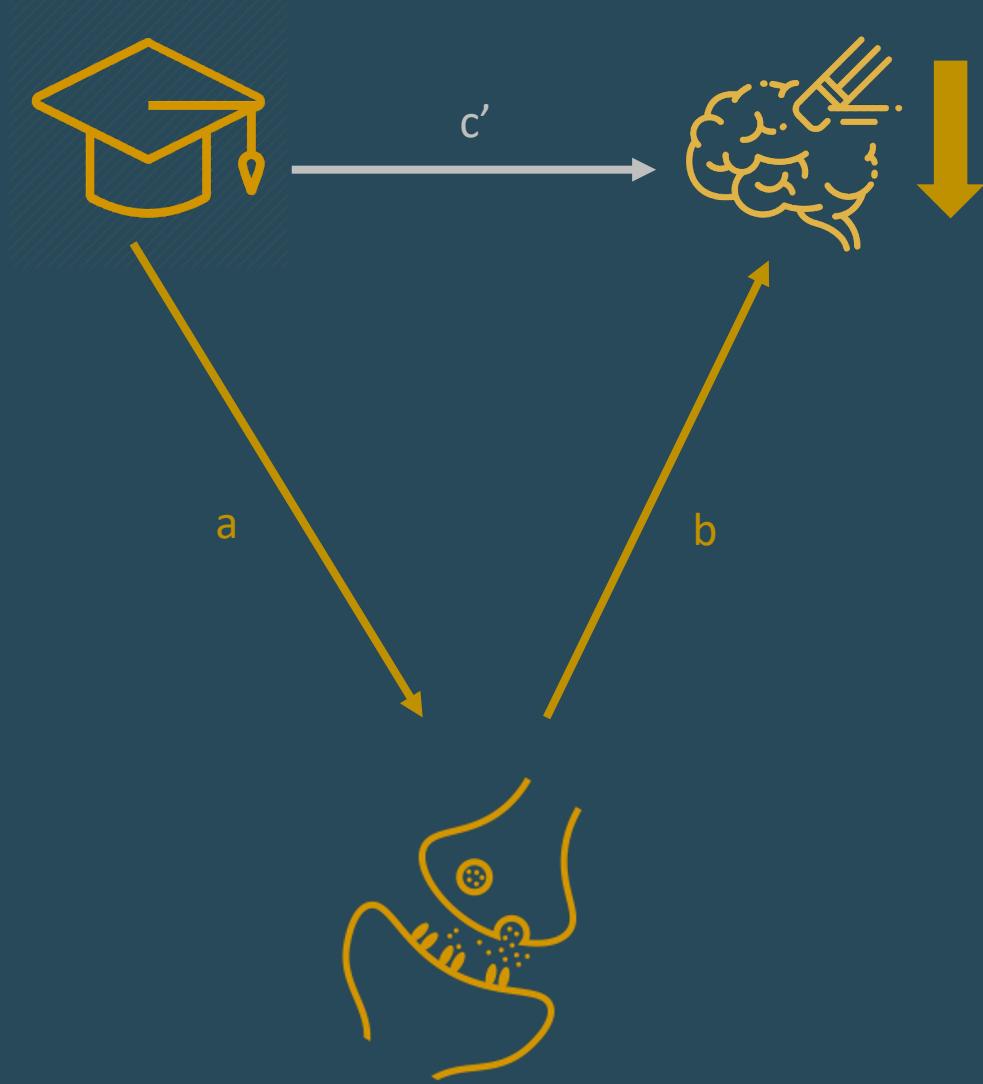
CAUSES



CAUSES



TOTAL EFFECT

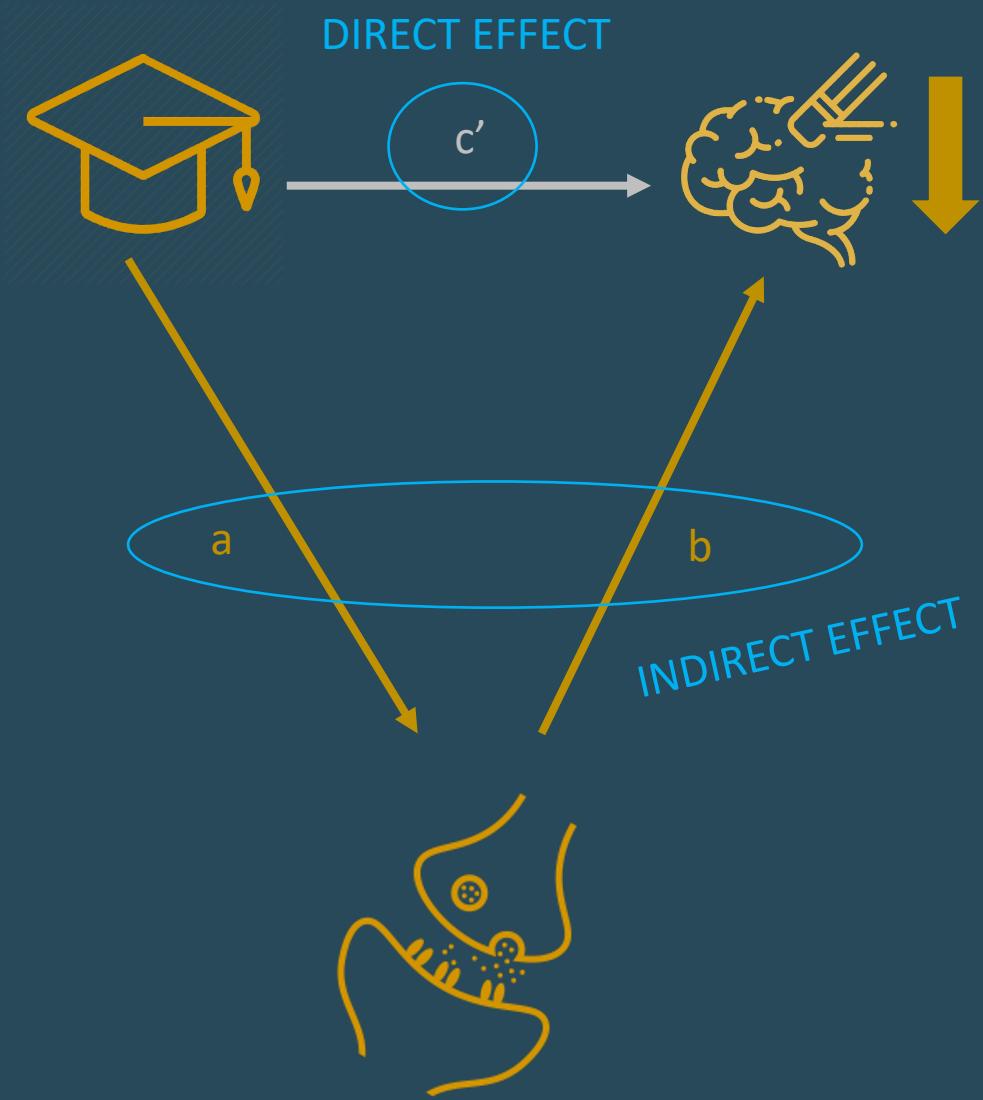


MEDIATED EFFECT

TOTAL EFFECT

$$c = (a * b) + c'$$

MEDIATED EFFECT



TOTAL EFFECT

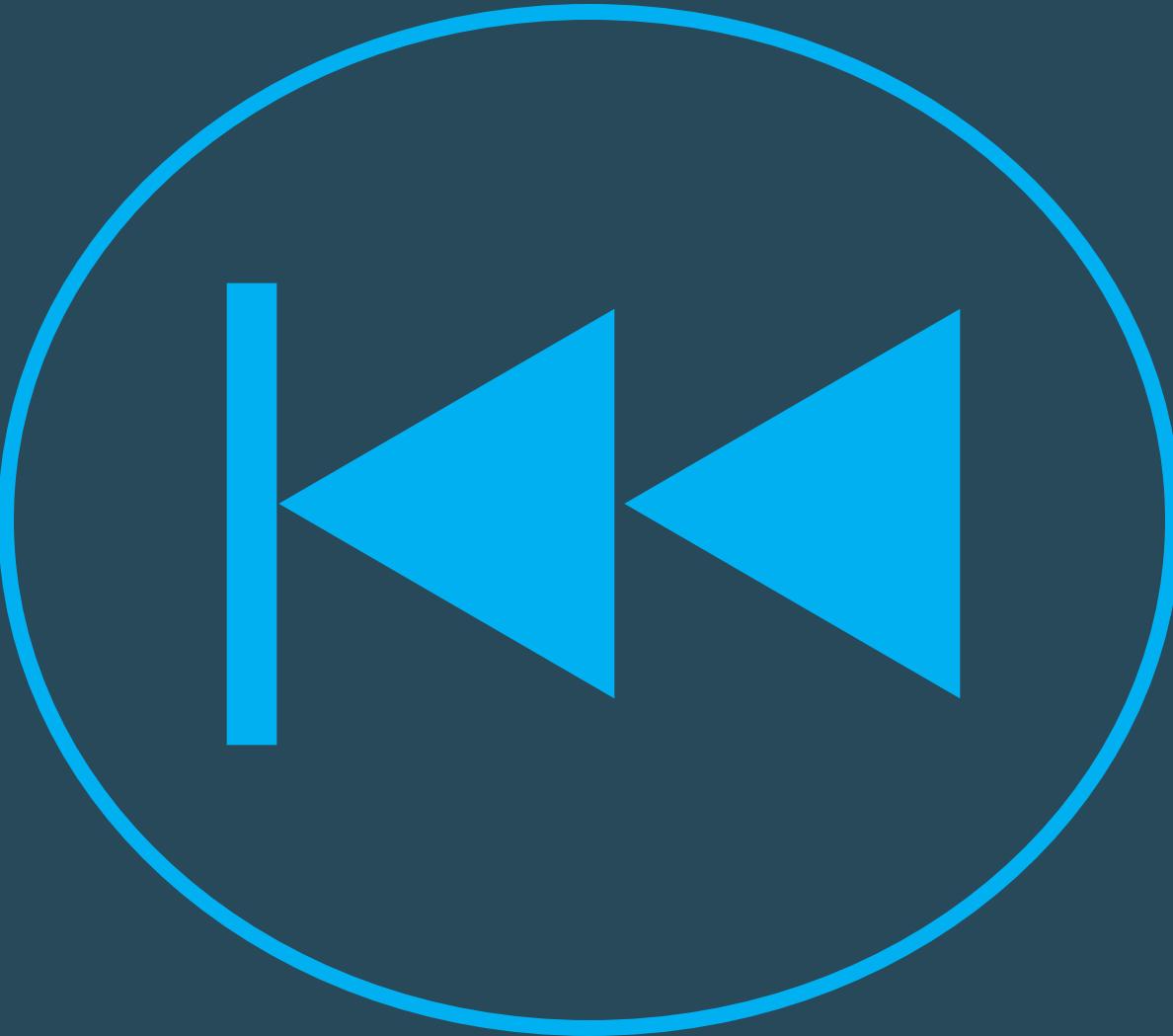
$$c = (a * b) + c'$$

$$M = a * b$$

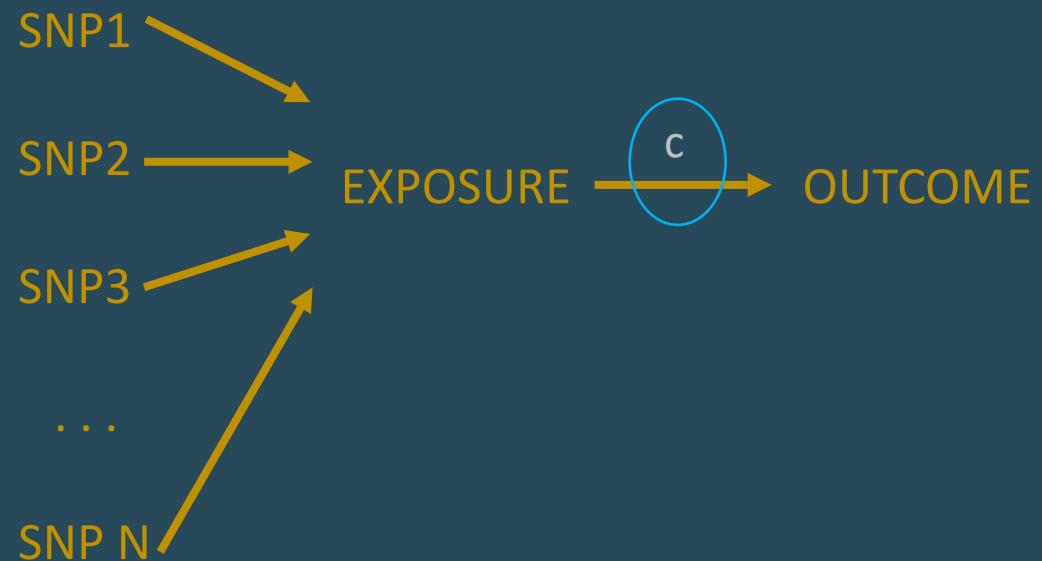
OR

$$M = c - c'$$

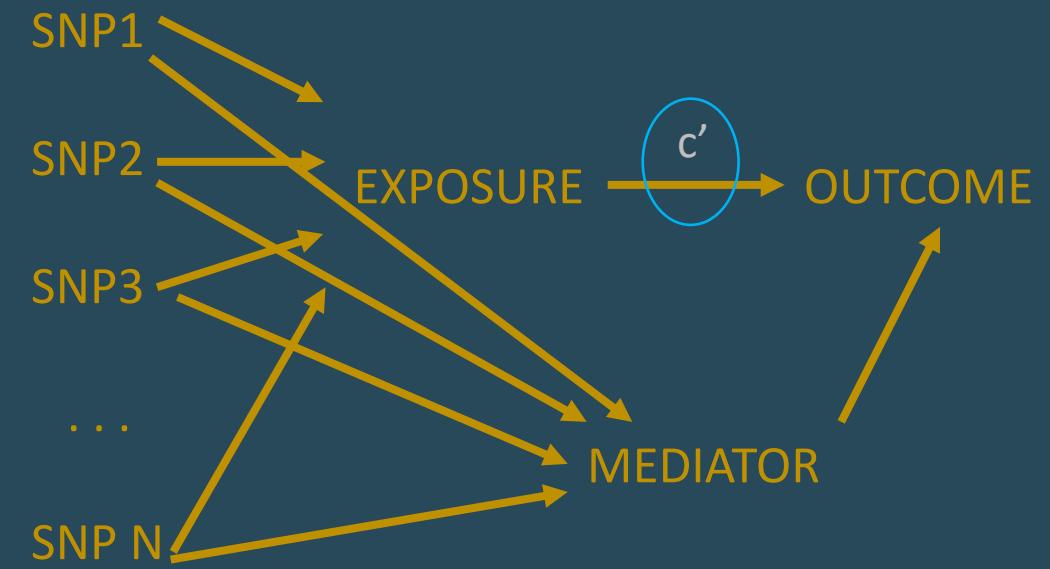
MEDIATED EFFECT



MV-MR for Mediation Analyses



UNIVARIABLE MR: TOTAL EFFECT



MULTIVARIABLE MR: DIRECT EFFECT

- Difference between total and direct estimates indicate presence of mediation.

**Some other things you may want to know...
But not enough time to cover today.**

Other Robust Methods / Sensitivity

Weighted mode.

[<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5837715/>]

MR-PRESSO

[<https://www.nature.com/articles/s41588-018-0099-7>]

More on robust methods from Bristol Uni.

[<https://www.bristol.ac.uk/integrative-epidemiology/mr-methods/introduction-to-mr/robust-methods-for-mr/>]

Other MR methods / approaches

Bayesian model averaging (*for high throughput data*).

[<https://www.nature.com/articles/s41467-019-13870-3>]

MR-RAPS (*dealing with pleiotropy using robust adjusted profile score*).

[<https://arxiv.org/abs/1801.09652>]

MR-TRYX (*exploiting outliers to detect novel candidate traits associated with outlier*)

[<https://www.biorxiv.org/content/10.1101/476085v1.abstract>]

More useful bits

MR Base (platform for performing MR).

[<http://www.mrbase.org/>]

Good paper on MV-MR mediation.

[<https://www.genetics.org/content/207/2/481>]

MR with binary exposures

[<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6153517/>]

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Thank You!

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