Mendelian Randomization:
Practicum
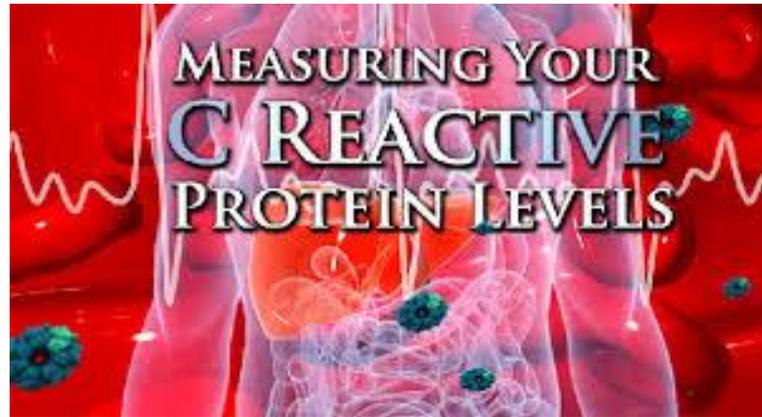
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Applied research question:
Does having higher proinflammatory CRP causally increase your blood pressure?

1. Observational analyses (simple linear regressions in R)

2. MR/IV Analyses: Wald Estimator (simple linear regression)

3. MR/IV Analyses: TSLS (AER-package)

4. Manual TSLS (simple linear regression)

5. Weak instrument bias

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Graphical representation of a Mendelian Randomization IV analysis
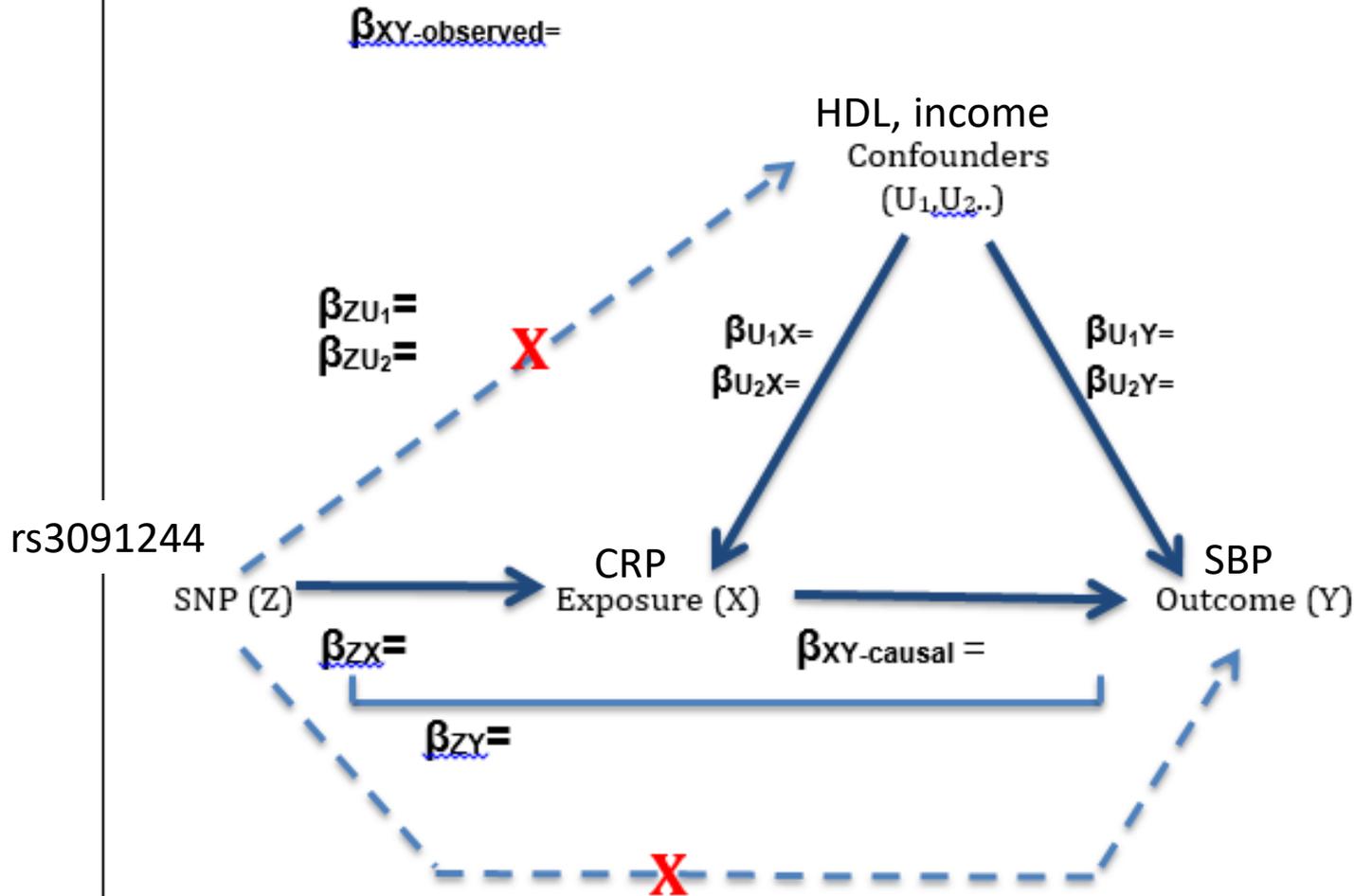
$\beta_{XY\text{-observed}}=$

HDL, income
Confounders
$(U_1, U_2..)$

$\beta_{ZU_1}=$
$\beta_{ZU_2}=$

$\beta_{U_1X}=$
$\beta_{U_2X}=$

$\beta_{U_1Y}=$
$\beta_{U_2Y}=$

rs3091244

CRP
Exposure (X)

SBP
Outcome (Y)

SNP (Z)

$\beta_{ZX}=$

$\beta_{XY\text{-causal}}=$

$\beta_{ZY}=$

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*Why: **to get a grip on the data, look at the MR assumptions***

1. **Observational analyses** (simple linear regressions in R)

    a. CRP-SBP OLS association

    b. SNP rs3091244 – CRP association

    c. confounders' (*HDL, Income*) effect on CRP & SBP

    d. comparison unadjusted and covariate-adjusted OLS observational CRP-SBP regressions

    e. conclude

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Why: 1st MR/IV method to test causality

2. MR/IV Analyses: **Wald Estimator** (simple linear regressions)

Formulas for Wald Estimator

Where Z=SNP instrument, X=Exposure, Y=Outcome

$$\text{Causal } \beta_{IV} = \frac{\beta_{ZY}}{\beta_{ZX}}$$

$$SE_{IV} = \frac{SE_{ZY}}{\beta_{ZX}}$$

$$95\% \text{ CI} = \beta_{IV} \pm 1.96^{*} SE_{IV}$$

a. compute the causal effect using the Wald estimator

b. compare Wald with the observational OLS of CRP-SBP

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Why: 2nd method to test causality

3. MR/IV Analyses: **TSLS** (AER R-package)

\# General format for TSLS command:

\# summary(ivreg(Outcome~Exposure | Instrument))

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Why: 2nd method to test causality - TSLS how does it work?

4. **Manual TSLS** (two stage least squares)

a. Stage1: regress CRP on SNP

b. Stage2: use predicted CRP

`(predicted_CRP <- predict(Stage1))` to predict SBP

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5. **Weak instrument bias**: an issue ?

Assessing instrument strength with the F-stat (looking for ≥ 10).
For Single SNP MR, the F-statistic is calculated as:

$$F_{stat} = \frac{R^2 * (N-1)}{(1-R^2)}$$

where R^2 is the variance explained in exposure by the SNP, and N is number of individuals in the study. This statistic is available in the output for OLS and TSLS

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Steps:

1. Copy the data, the scripts and the ppt

```
mkdir MRpractical
cp -r /faculty/camelia/2017/friday/* MRpractical
```

2. Run the analyses as described in the ppt & the R-script (easy/difficult)

3. Go to **mr.surge.sh** to provide your answers (10 MC questions)

4. As you're running the commands, fill in the graphical representation of the IV analysis with the appropriate variables and beta-coefficient

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