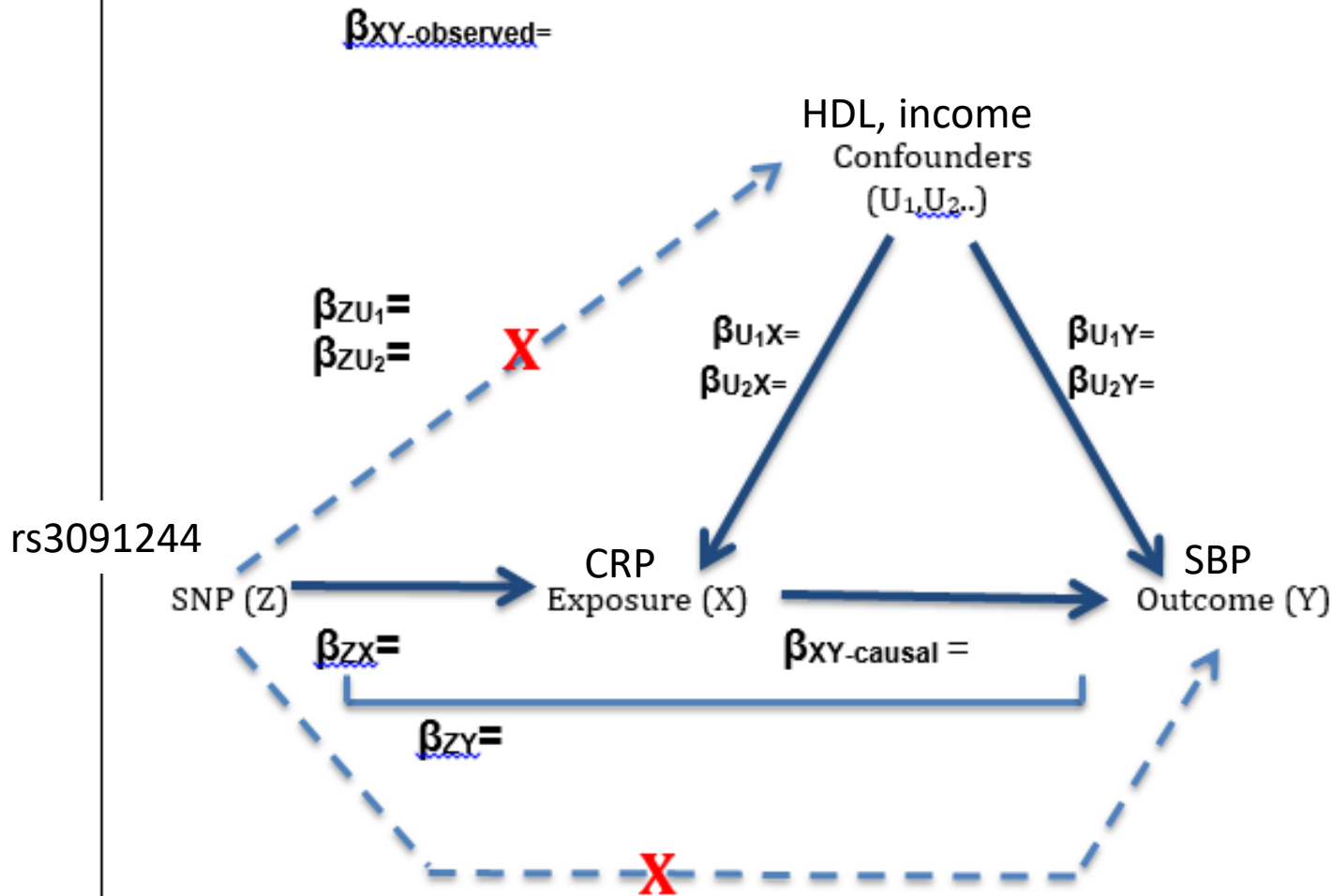# Mendelian Randomization:
Practical

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)

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

Graphical representation of a Mendelian Randomization IV analysis

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

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

rs3091244

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

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

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

CRP
Exposure (X)

SBP
Outcome (Y)

SNP (Z)

$\beta_{ZX}=$

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

$\beta_{ZY}=$

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

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

```
mkdir MR_PRACTICAL
cd MR_PRACTICAL
cp /faculty/davide/BOULDER2019/MR_PRACTICAL/* .

In R:
setwd("~/MR_PRACTICAL/")
data<-read.table(file= "data.txt", header = TRUE)
head(data)
attach(data)
```

1.   Observational analyses (simple linear regressions in R)
a. CRP-SBP OLS association
```
# Run observational OLS regression for BP & CRP
summary(lm(SBP~CRP))

# Plot the observational association between BP and CRP
plot(CRP,SBP)
abline(lm(SBP~CRP),col="red")
```

Applied research question: Does having higher proinflammatory CRP causally increase your blood pressure?
*Why: **to get a grip on the data, look at the MR assumptions***

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

b. SNP rs3091244 – CRP association

```
# Observational OLS regression of CRP on CRP SNP
summary(lm(CRP~rs3091244))


#Is rs3091244 a strong instrument?


# Plot the relationship between CRP and rs3091244
plot(rs3091244, CRP)
abline(lm(CRP~rs3091244),col="red")
```

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

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

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

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

```
# Confounders
summary(lm(SBP~INCOME))
summary(lm(CRP~INCOME))
summary(lm(INCOME~rs3091244))


summary(lm(SBP~HDL))
summary(lm(CRP~HDL))
summary(lm(HDL~rs3091244))
```

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

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

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

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

Run a covariate-adjusted model for the association between CRP & BP

summary(lm(SBP~CRP))

summary(lm(SBP~CRP+INCOME+HDL))

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

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

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

Why: 1st MR/IV method to test causality

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

Run the necessary OLS regressions to compute a Wald estimator

OLS regression of CRP on CRP SNP

summary(lm(CRP~rs3091244))

OLS regression of BP on CRP SNP

summary(lm(SBP~rs3091244))

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

From the above output, compute the causal effect using the Wald estimator, as well as it's SE and 95% CI. What do the results show and what do they mean?

Formulas for Wald Estimator

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

Wald estimator causal Beta =

SE =

95% CI =

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

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

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

Rerun the observational OLS of CRP and SBP and compare with the results from the Wald estimator. What do you notice about the Beta and SEs?

\# Observational OLS regression

summary(lm(SBP~CRP))

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

From the above output, compute the causal effect using the Wald estimator, as well as it's SE and 95% CI. What do the results show and what do they mean?

Wald estimator causal Beta = -0.1014 / 0.041937 = -2.417913
SE = 0.1396 / 0.041937 = 3.328803
95% CI = -2.417913 ± 6.524454

Rerun the observational OLS of CRP and SBP and compare with the results from the Wald estimator. What do you notice about the Beta and SEs?
# Observational OLS regression
summary(lm(SBP~CRP))

Conclusion

CRP observationally associated with SBP

No evidence that CRP causally affects SBP