Introduction to Mendelian Randomization

Using genes to tell us about environmental exposures to inform causality

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(Some slides adapted from Prof David Evans)

Acknowledgement of **Country**

The University of Queensland (UQ) acknowledges the Traditional Owners and their custodianship of the lands on which we meet.

We pay our respects to their Ancestors and their descendants, who continue cultural and spiritual connections to Country.

We recognise their valuable contributions to Australian and global society.

Outline and Learning Objectives

By the end of the lecture, you should be able to:

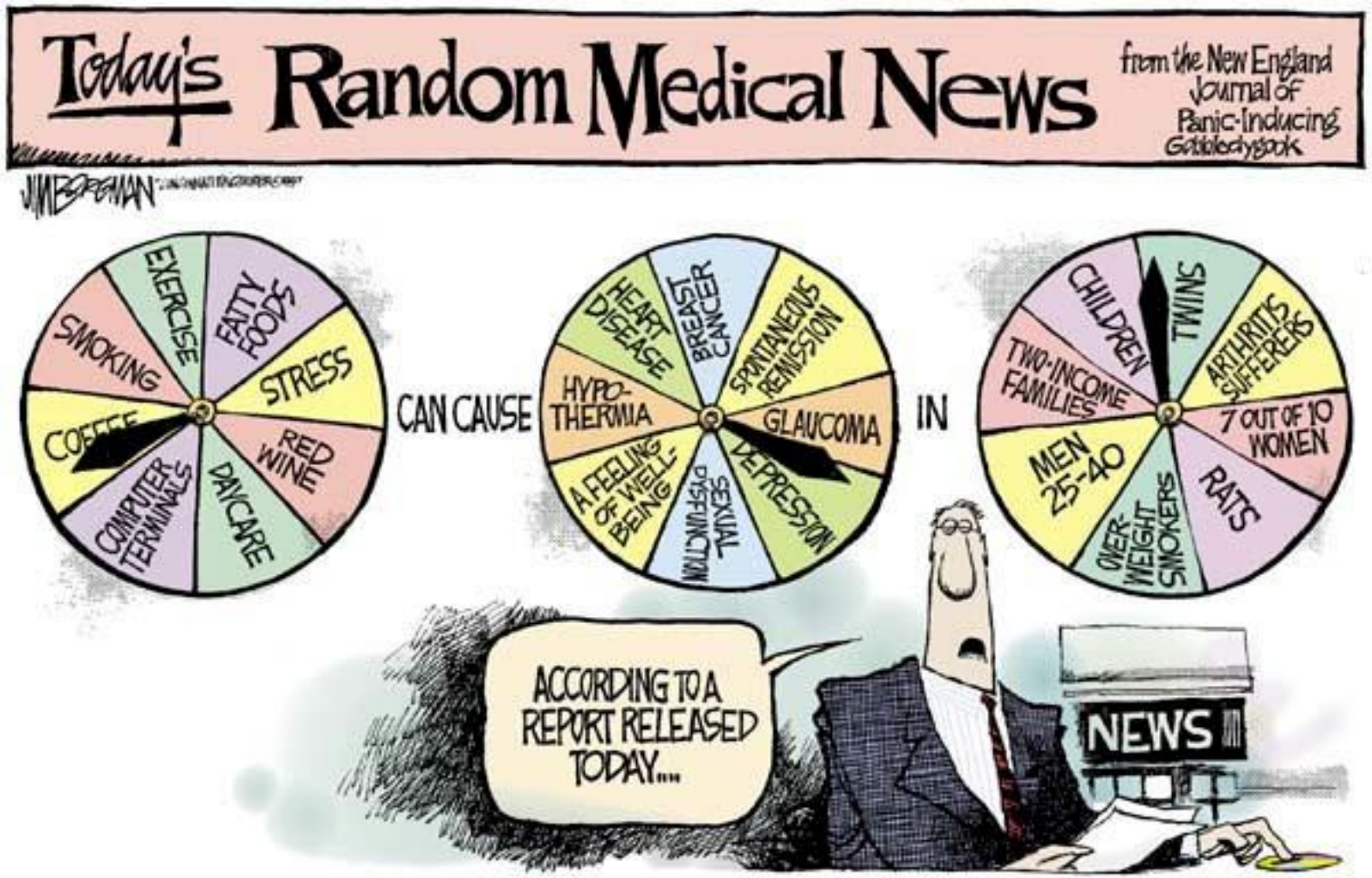
1. Explain why observational studies cannot reliably establish causality.
2. Describe how Mendelian randomization (MR) uses genetics to infer causality.
4. Understand how Directed Acyclic Graphs (DAGs) represent causal relationships.

 Mini-break

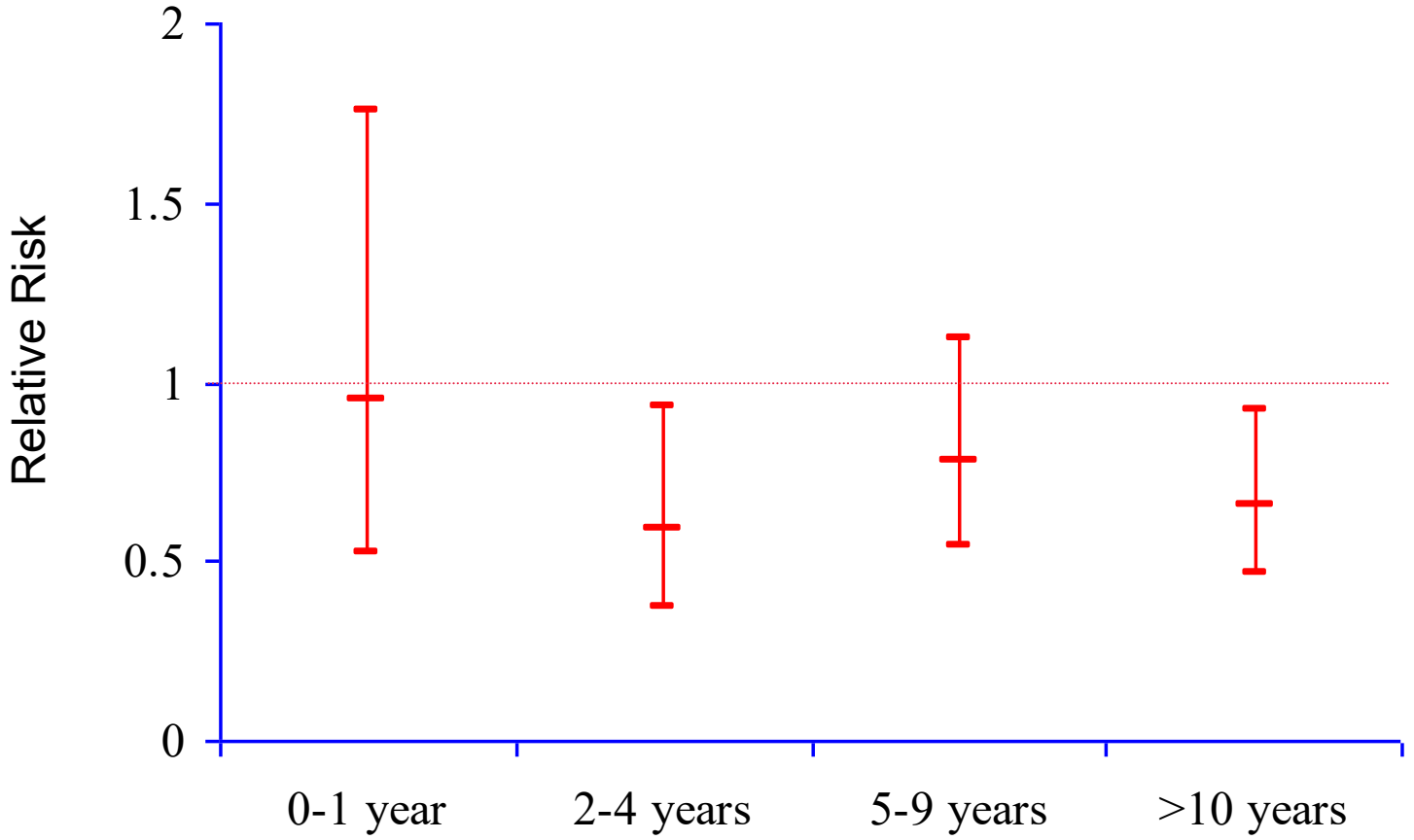
4. Understand the three core assumptions of MR.
5. Calculate causal effects using one-sample and two-sample MR.
6. Recognize the major limitations of MR

 Morning tea

Inferring causality in observational studies

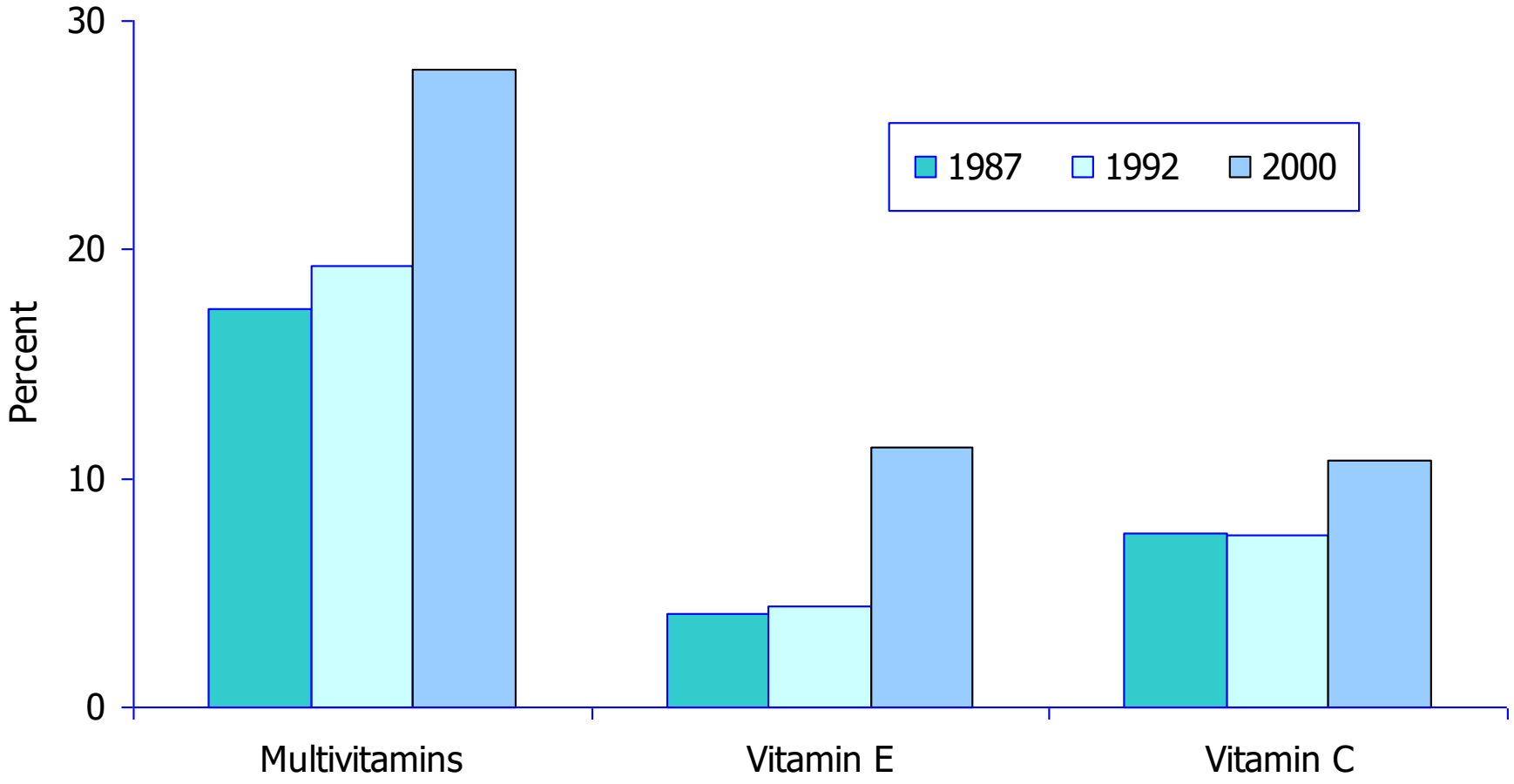


Coronary Heart Disease risk according to duration of current Vitamin E supplement use compared to no use



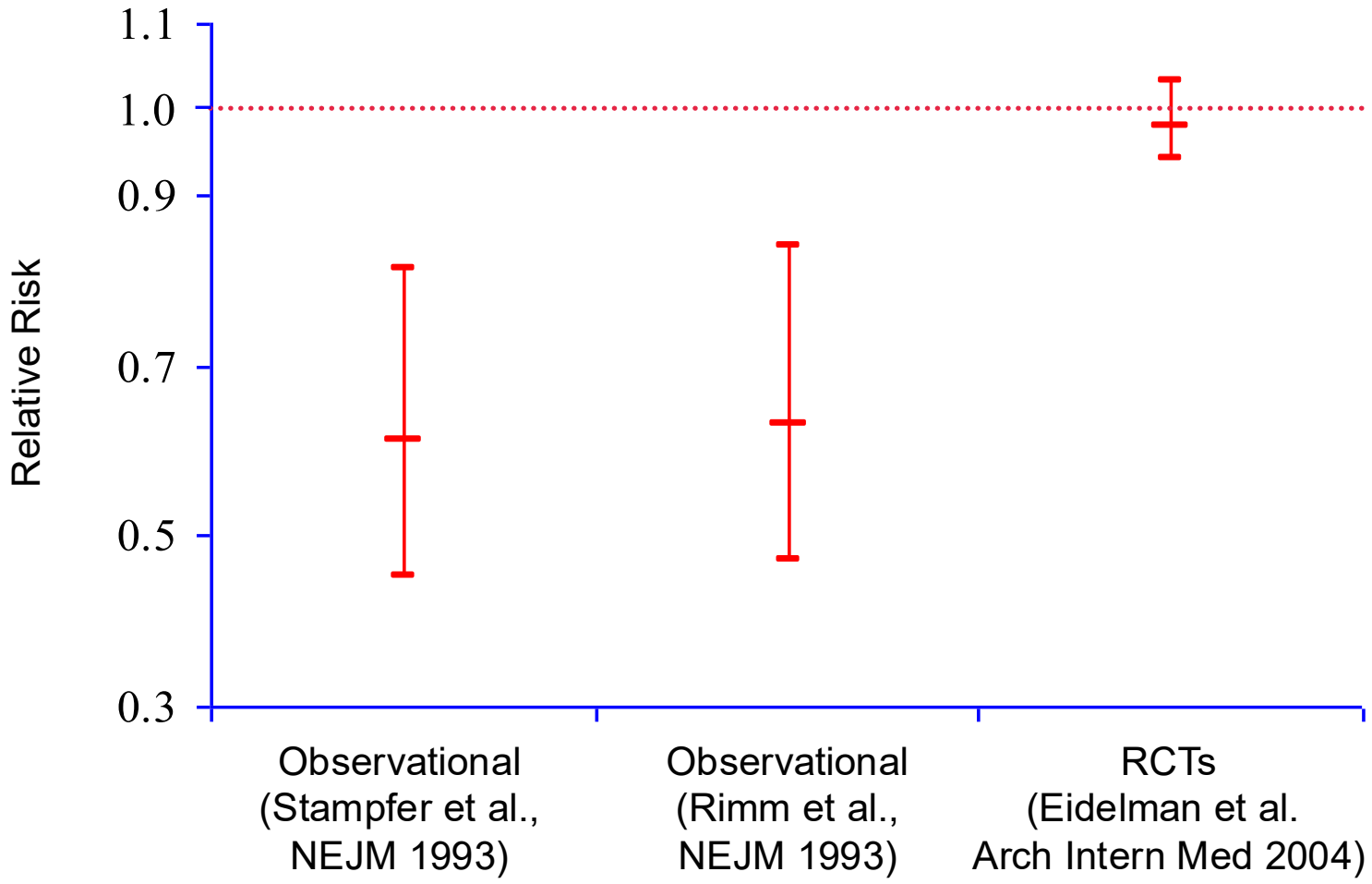
Rimm et al. NEJM 1993; 328: 1450-6

Use of vitamin supplements by US adults



Millen AE, Journal of American Dietetic Assoc 2004;104:942-950

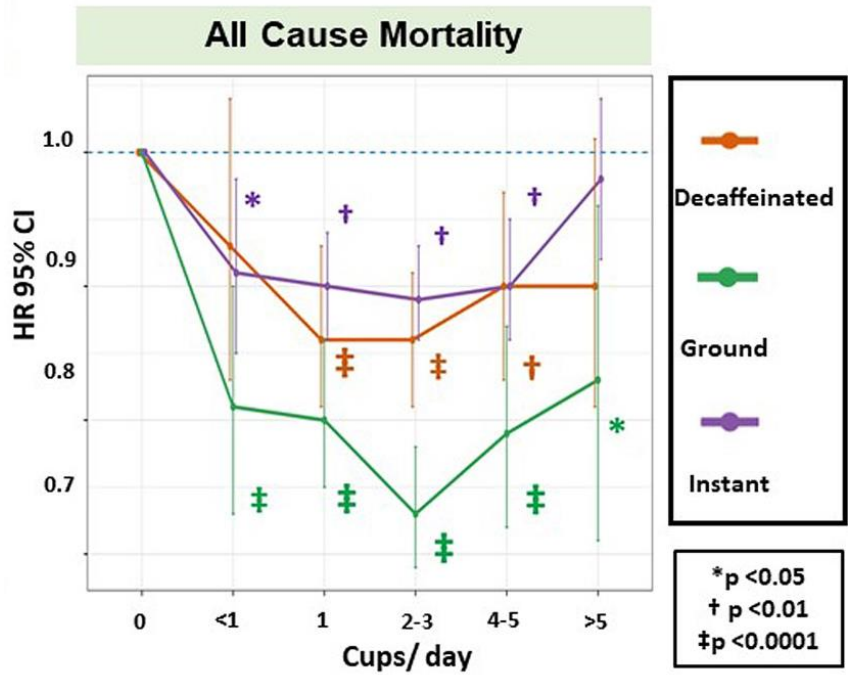
Vitamin E supplement use and risk of Coronary Heart Disease



Many other examples that media draw causal inference from observational studies

› Eur J Prev Cardiol. 2022 Dec 7;29(17):2240-2249. doi: 10.1093/eurjpc/zwac189.

The impact of coffee subtypes on incident cardiovascular disease, arrhythmias, and mortality: long-term outcomes from the UK Biobank



"*It turns out that drinking a few cups of coffee each day may actually do more than just give you a jolt at work — **it might even help you live longer***." – CBS News.

"*You've probably heard of the many benefits of drinking coffee…But did you know that **coffee can also increase your lifespan**? That's what scientists behind a new research study announced recently*." – USA Today.

Evidence synthesis: Maternal and child health

OPEN ACCESS

Maternal caffeine consumption and pregnancy outcomes: a narrative review with implications for advice to mothers and mothers-to-be

Jack E. James

10.1136/bmjebm-2020-111432

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjebm-2020-111432).

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Abstract

Objectives Caffeine is a habit-forming substance consumed daily by the majority of pregnant women. Accordingly, it is important that women receive sound evidence-based advice about potential caffeine-related harm. This narrative review examines evidence of association between maternal caffeine consumption and negative pregnancy outcomes, and assesses whether current health advice concerning maternal caffeine consumption is soundly based.

Methods Database searches using terms linking caffeine and caffeinated beverages to pregnancy outcomes identified 1261 English language peer-reviewed articles. Screening yielded a total of 48 original observational studies and meta-analyses of maternal caffeine consumption published in the past two decades. The articles reported results for one or more of six major categories of negative pregnancy outcomes: miscarriage, stillbirth, low birth weight and/or small for gestational age, preterm birth, childhood acute leukaemia, and childhood overweight and obesity.

Results Of 42 separate sets of findings reported in 37 observational studies, 32 indicated significantly increased caffeine-related risk and 10 suggested no or inconclusive associations. Caffeine-related increased risk was reported with moderate to high levels of consistency for all pregnancy outcomes except preterm birth. Of 11 studies reporting 17 meta-analyses, there was unanimity among 14 analyses in finding maternal caffeine consumption to be associated with increased risk for the four outcome categories of miscarriage, stillbirth, low birth weight and/or small for gestational age, and childhood acute leukaemia. The three remaining meta-analyses were also unanimous in reporting absence of a reliable association between maternal caffeine consumption and preterm birth. No meta-analyses were identified for childhood overweight and obesity, although four of five original observational studies reported significant associations linking maternal caffeine consumption to that outcome category.

Conclusions The substantial majority finding from observational studies and meta-analyses is that maternal caffeine consumption is reliably associated with major negative pregnancy outcomes. Reported findings were robust to threats from potential confounding and misclassification. Among both observational studies and meta-analyses, there were frequent reports of significant dose–response associations suggestive of causation, and frequent reports of no threshold of consumption below which associations were absent. Consequently, current evidence does not support health advice that assumes 'moderate'

Summary box

What is already known about this subject?

- Pharmacological actions of caffeine suggest potential threats to fetal development from maternal caffeine consumption.
- In recent decades, many observational studies of maternal caffeine consumption have reported potential increased risk for diverse negative pregnancy outcomes.
- However, current policy advice assumes that 'moderate' caffeine consumption during pregnancy is safe.

What are the new findings?

- Substantial majority findings from observational studies and meta-analyses indicate that maternal caffeine consumption is reliably associated with miscarriage, stillbirth, low birth weight and/or small for gestational age, childhood acute leukaemia and childhood overweight and obesity, but not preterm birth.
- Overall findings are robust to threats from potential confounding and misclassification.
- Findings frequently include significant dose–response associations suggestive of causation, and studies frequently report no threshold of consumption below which associations are absent.

How might it impact on clinical practice in the foreseeable future?

- Current evidence does not support assumptions about safe levels of maternal caffeine consumption.
- The cumulative scientific evidence supports advice to pregnant women and women contemplating pregnancy to avoid caffeine.

To cite: James JE. *BMJ Evidence-Based Medicine* 2021;**26**:114–115.

The New York Times

How Much Coffee Should You Drink During Pregnancy? Maybe None at All

A new review of studies suggests that avoiding caffeine altogether may be the safest bet during pregnancy.

12 People Who Should Never Drink Coffee, Say Dietitians

Shutterstock

COFFEE IS WIDELY KNOWN FOR MAGICALLY INCREASING FOCUS AND ENERGY, BUT THAT'S NOT THE CASE FOR ALL.

NUTRITION

Pregnant ladies, cut out the coffee

By **AGENCY**
Friday, 04 Sep 2020 | 1:00 PM MYT

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Japan sees record multiple pregnancies after fertility insurance...

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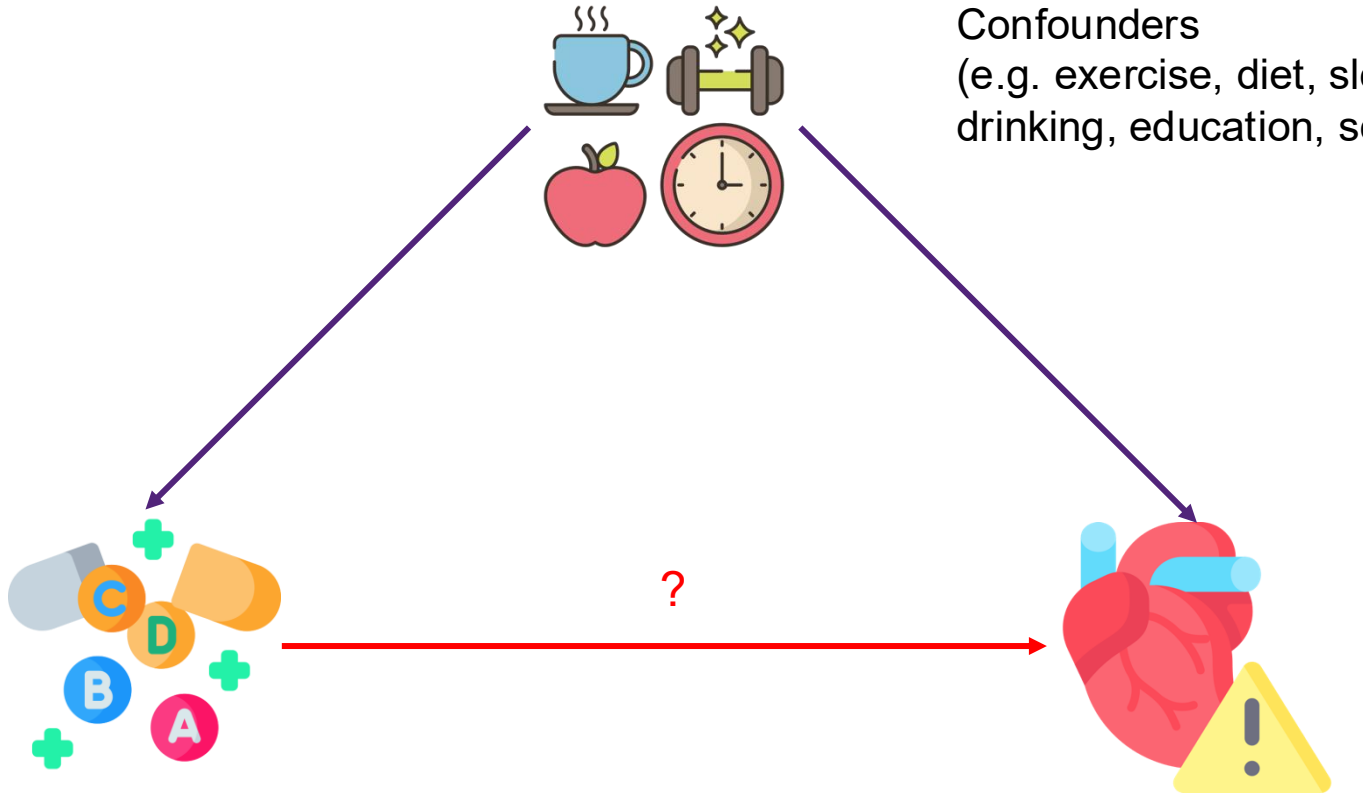
Can women safely take antiseizure drugs during pregnancy?

A recent review of research finds that pregnant women and those trying to conceive should avoid caffeine, as it could result in problems like miscarriage, stillbirth, low birth weight and childhood acute leukaemia. Photo: AFP

Problems of inferring causality using observational data



Confounders
(e.g. exercise, diet, sleep, smoking, alcohol drinking, education, socioeconomic status)

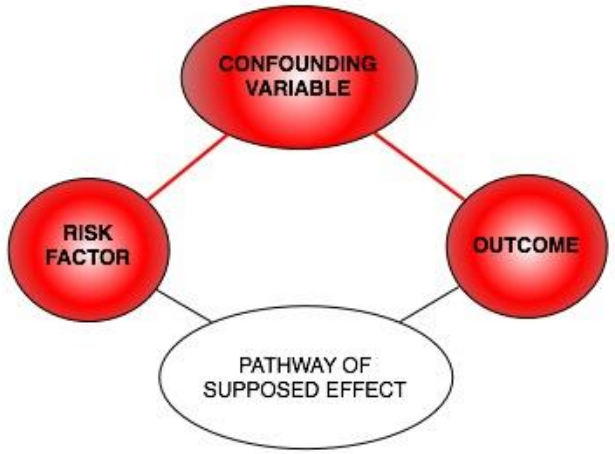
Vitamin supplementation

Heart disease

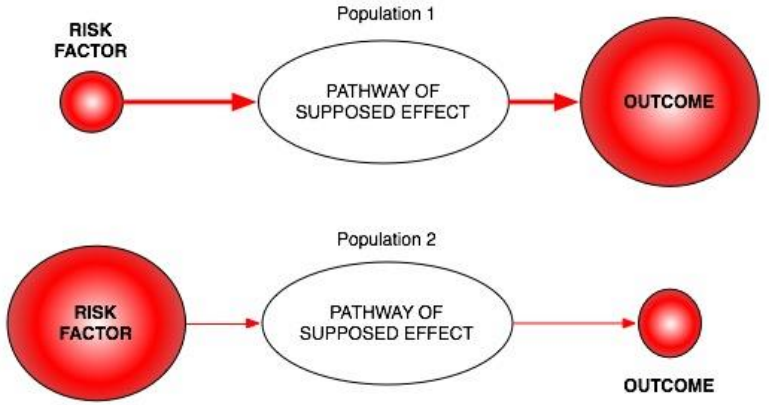
Classic limitations to "observational" science

Reverse Causation

Confounding

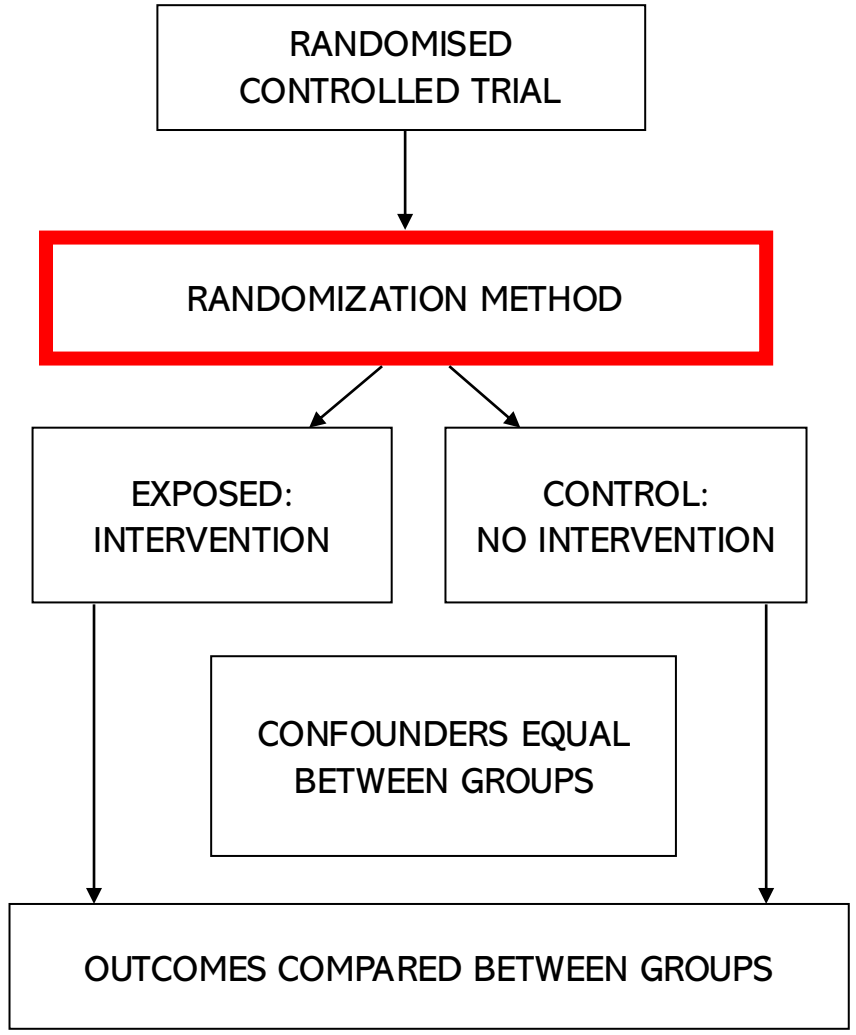


Bias



Randomized Controlled Trials (RCTs)
The Gold Standard in Inferring Causality

Randomization makes causal inference possible



The Need for Observational Studies

Randomized Controlled Trials (RCTs):

- Not always ethical or practically feasible, e.g. anything toxic
- Expensive, requires experimentation in humans, and long follow-up times
- Should only be conducted on interventions that show very strong observational evidence in humans

Observational studies:

- Association between environmental exposures and disease measured in observational designs (non-experimental)
  - e.g. case-control studies or cohort studies
- Reliably assigning causality in these types of studies is ***very limited***

Mendelian Randomization (MR)

A technique that uses genetically informative observational data to inform causality

What does MR do?

1. Assess causal relationship between two variables
   - Useful in genomics studies
2. Estimate magnitude of causal effect
   - Useful in drug development
   - Useful in public health

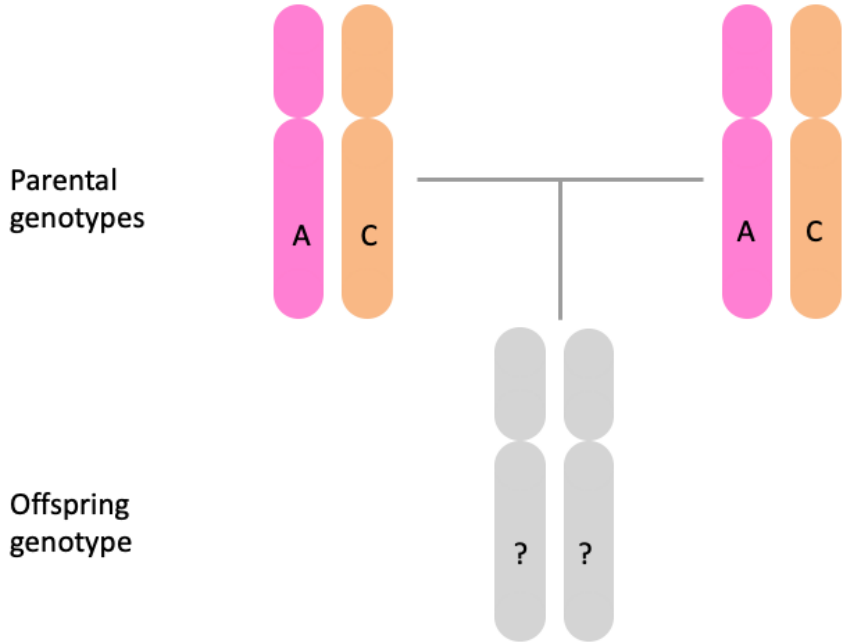
How does MR do this?

By harnessing Mendel's laws of inheritance

Mendel's Laws of Inheritance

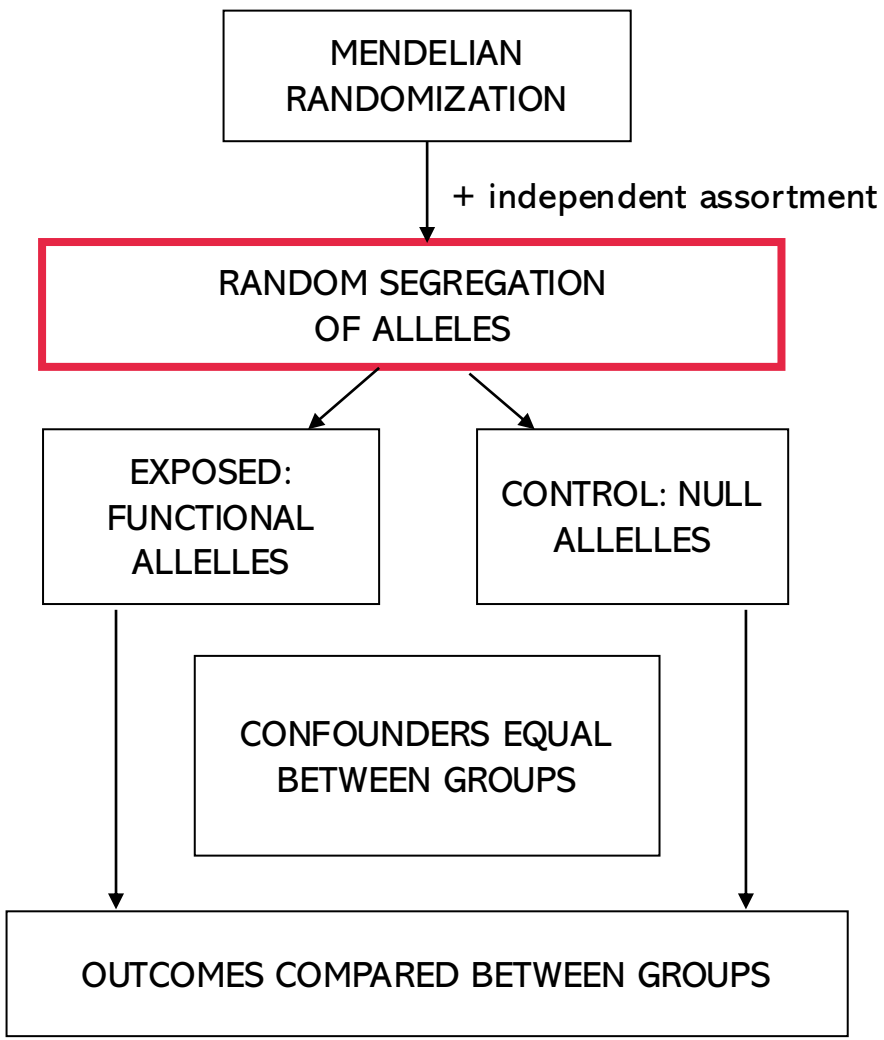
Gregor Mendel in 1862

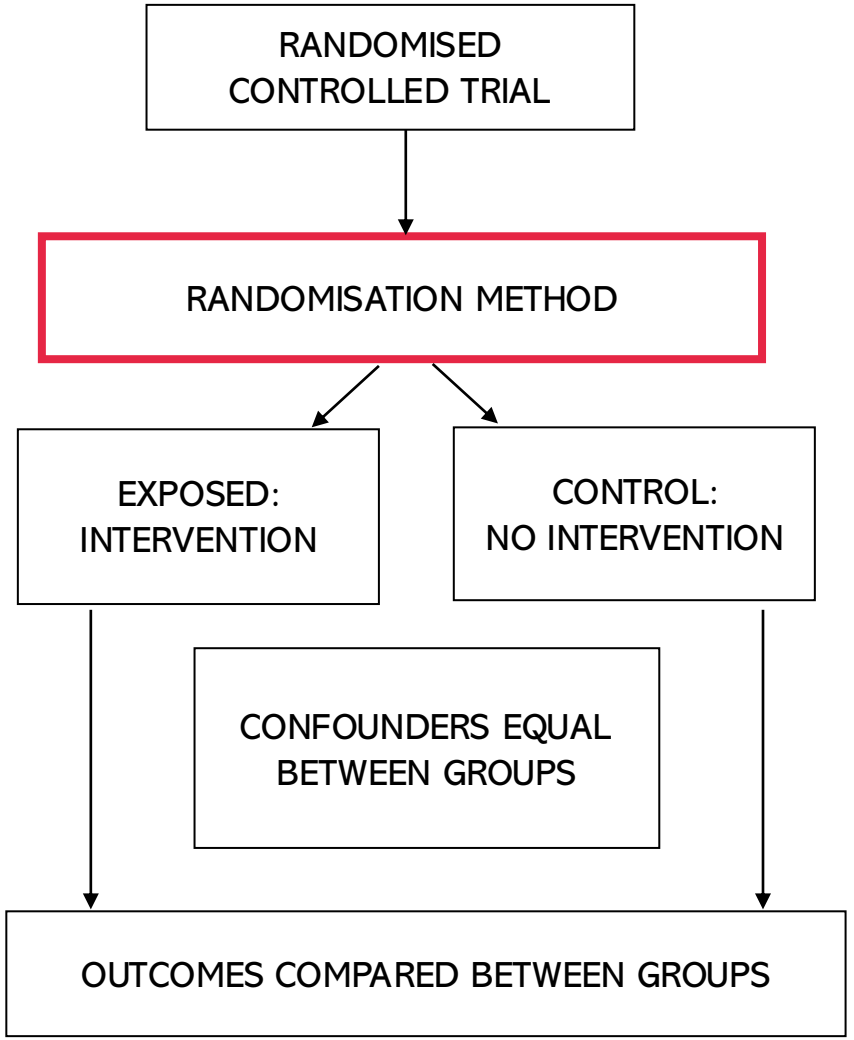
1. **Segregation:** when alleles separate at meiosis, a <u>randomly selected allele</u> is transmitted to offspring



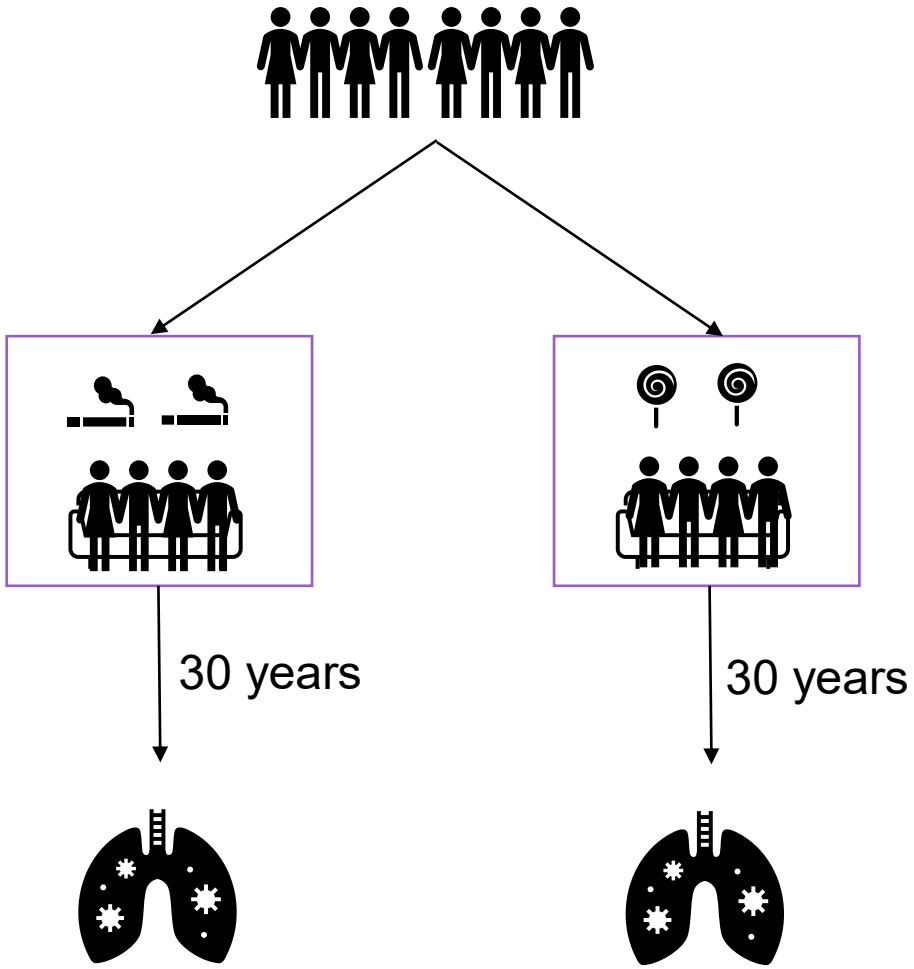
2. **Independent assortment:** alleles at different genetic loci (for different traits) are transmitted <u>independently</u> of one another

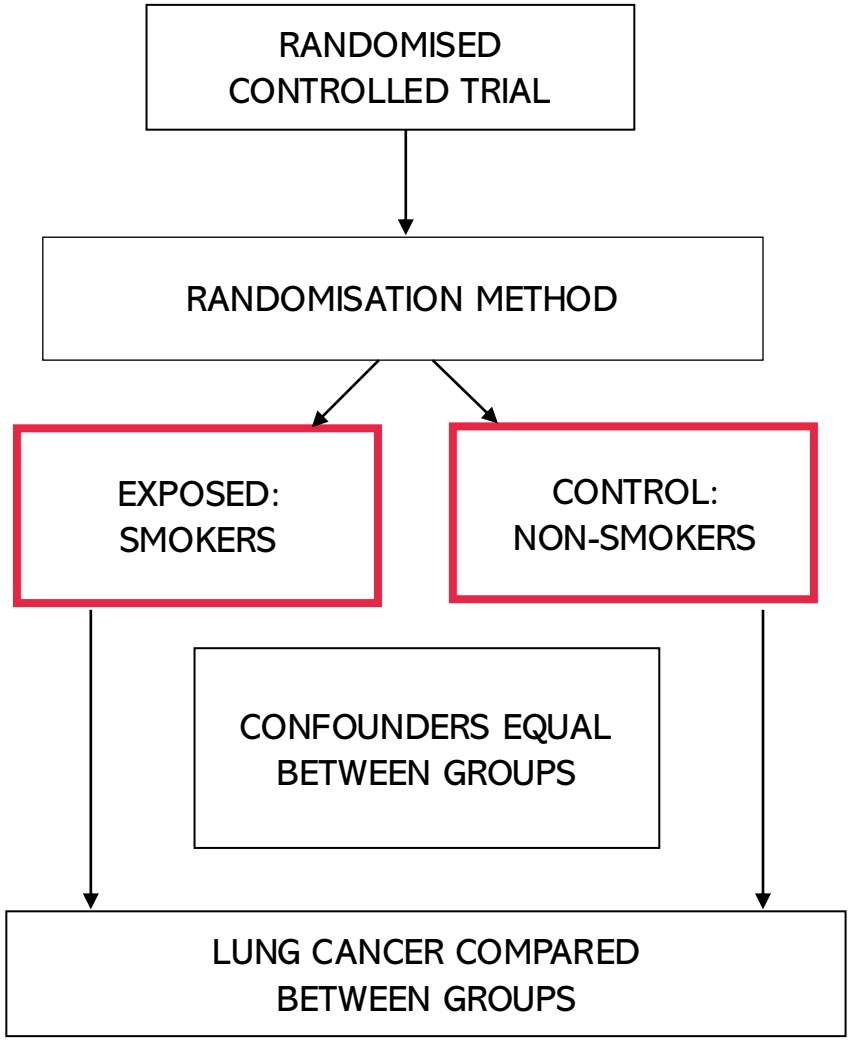
MR vs RCT


MENDELIAN RANDOMIZATION
+ independent assortment
RANDOM SEGREGATION OF ALLELES
EXPOSED: FUNCTIONAL ALLELLES
CONTROL: NULL ALLELLES
CONFOUNDERS EQUAL BETWEEN GROUPS
OUTCOMES COMPARED BETWEEN GROUPS

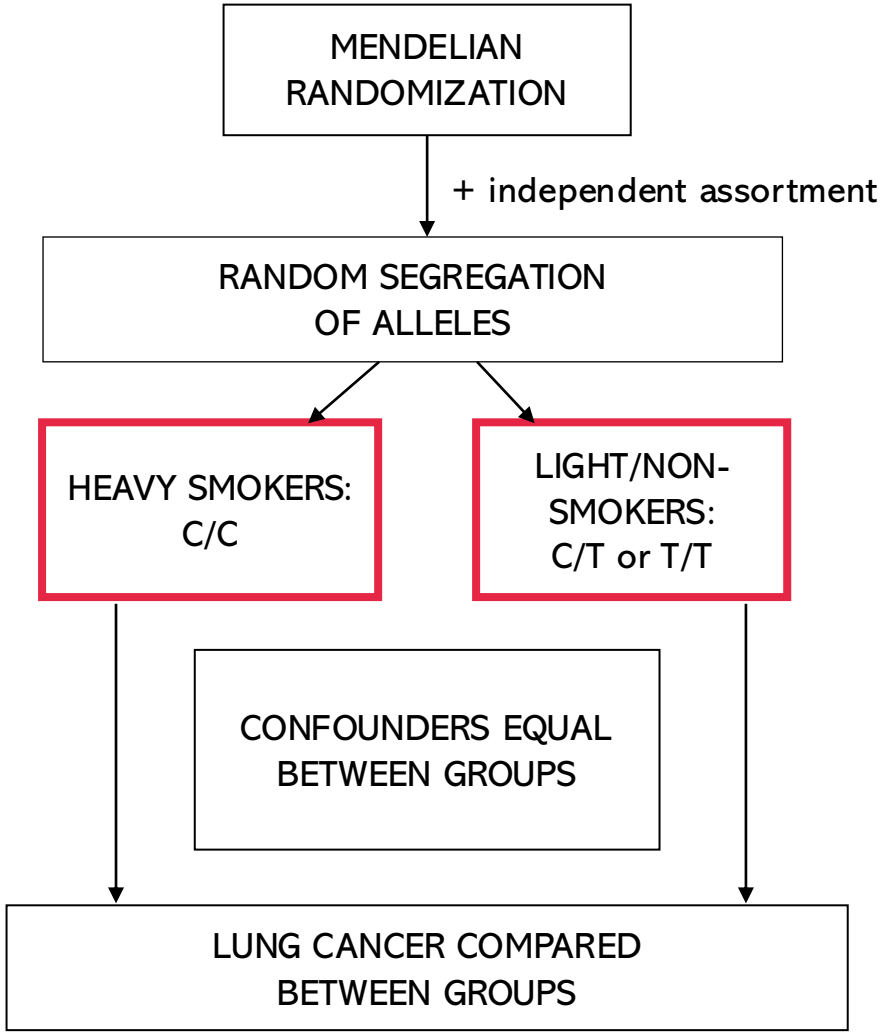

RANDOMISED CONTROLLED TRIAL
RANDOMISATION METHOD
EXPOSED: INTERVENTION
CONTROL: NO INTERVENTION
CONFOUNDERS EQUAL BETWEEN GROUPS
OUTCOMES COMPARED BETWEEN GROUPS

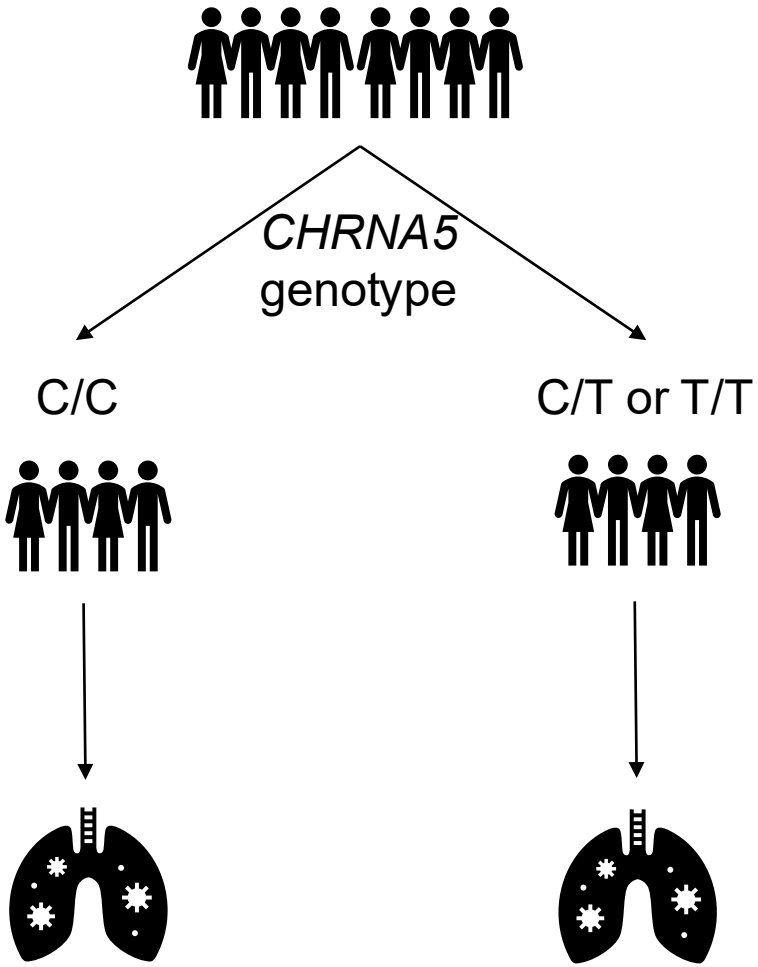
RCT: Smoking and Lung Cancer





MR: Smoking and Lung Cancer





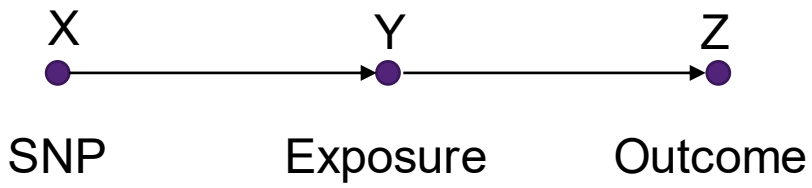
Directed Acyclic Graphs (DAGs)

Purpose of DAGs:

- represent causal assumptions
- identify confounders
- understand collider bias
- understand selection bias
- decide which variables should or should not be adjusted for.

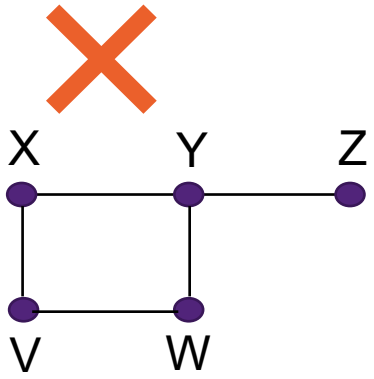
How to construct a DAG?

- A Directed Acyclic Graph (DAG) is a graph that is **Directed (has arrows)** and **Acyclic (no feedback loops)**.
- A path between two nodes X and Z is a sequence of nodes beginning with X and ending with Z in which each node is connected to the next by an edge.
- A “directed path” follows the arrow heads.

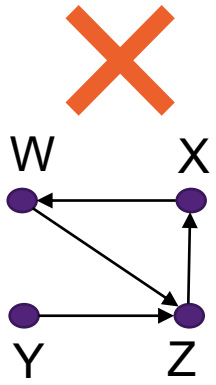


Exercise: DAG or not DAG?

(A)



(B)



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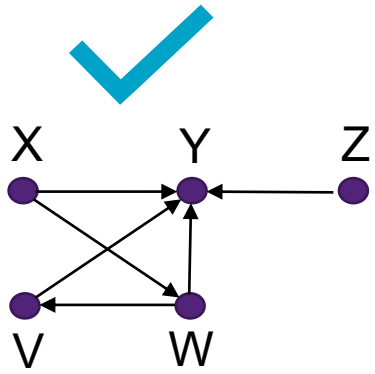

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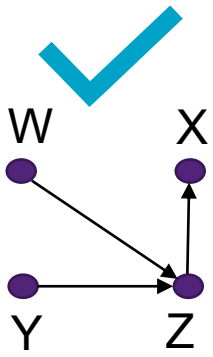

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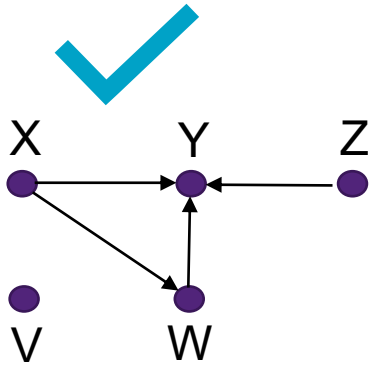

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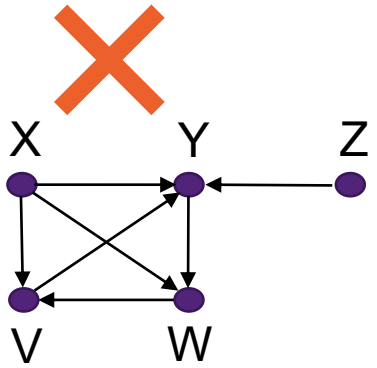


DAGs vs SEMs / Path Models

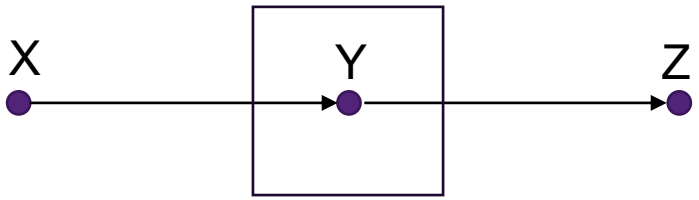
DAGs and path models are related but not the same!

DAGs	Path Models
Distribution free	Assumes linearity and normality
Implies probabilistic dependencies in model	Implies (linear) covariances and variances in model
One headed arrows only	One headed and two headed arrows
Acylic	Feedback loops allowed
Boxes indicate conditioning	Boxes indicate observed variables

Structure #1 “Chains”

- Y and X are dependent
- Z and Y are dependent
- Z and X are (likely) dependent
- Z and X are independent conditional on Y (one way of thinking about conditioning on Y is like holding Y constant)

Conditioning means:
- including the variable in your analysis (e.g. regression),
- stratifying on it,
- or selecting individuals based on its value.

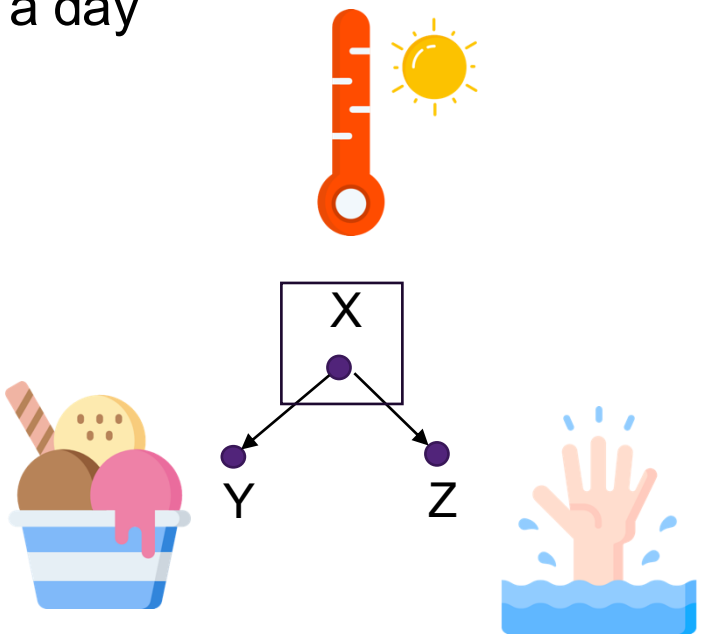


Smoking Blood pressure Stroke

If smoking only affects stroke through increasing blood pressure (i.e. no other pathways), there will be no association between smoking and stroke after conditioning on blood pressure.

Structure #2 “Forks” (Confounders)

- Y = # of ice-cream cones eaten in a day
- Z = # of drownings in a day
- X = Temperature of day



X and Y are dependent

X and Z are dependent

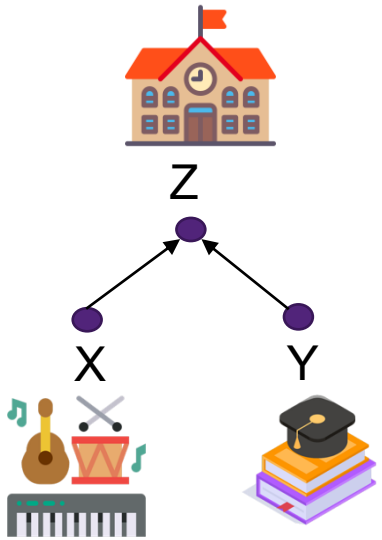
Z and Y are (likely) dependent (i.e. connect through a **backdoor path** X that does not follow the path of the arrows)

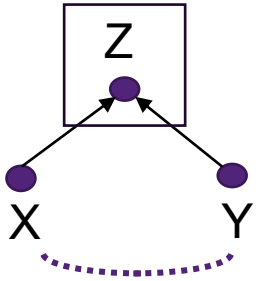
Y and Z are independent conditional on X

In epidemiology, X is a “confounder” that we will often want to control for.

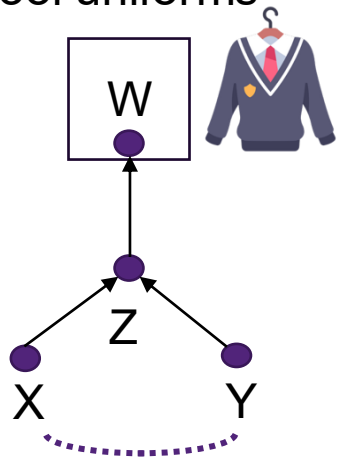
Structure #3 “Colliders”

- Let X be musical ability
- Let Y be academic ability
- Let Z represent admittance to an exclusive school





Wearing elite school uniforms



X and Z are dependent

Y and Z are dependent

X and Y are independent

X and Y are dependent conditional on Z

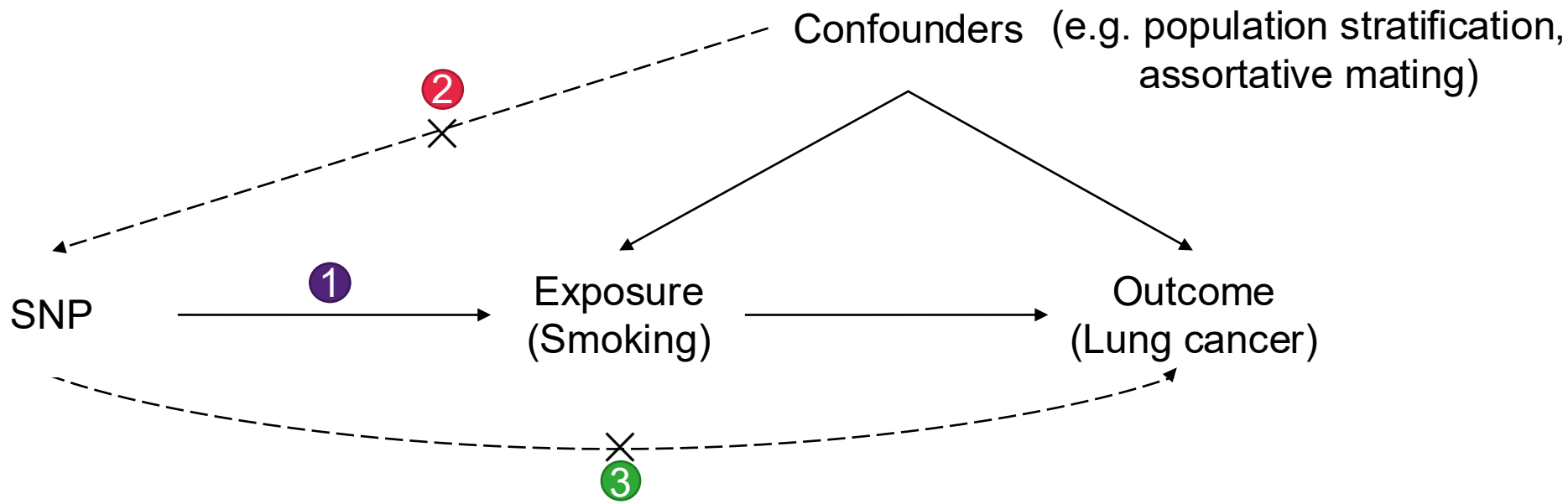
In epidemiology, Z is a “collider” and we often do not want to control for it.

Z may represent missingness, selection into a study, loss to follow up etc.

Break time

Created by Canva AI image generator in 2024

Mendelian Randomization: 3 Core Assumptions



(1) Relevance assumption: SNP is robustly associated with the exposure
(2) Independence assumption: There are no confounders of the association between the instrumental variables (IVs) and the outcome.
(3) Exclusion restriction: SNP is ONLY associated with the outcome through the exposure

SNPs are identified as **good instrumental variables** when the 3 assumptions are met!

Why are genetic associations special?

Robustness to confounding due to Mendel's laws:

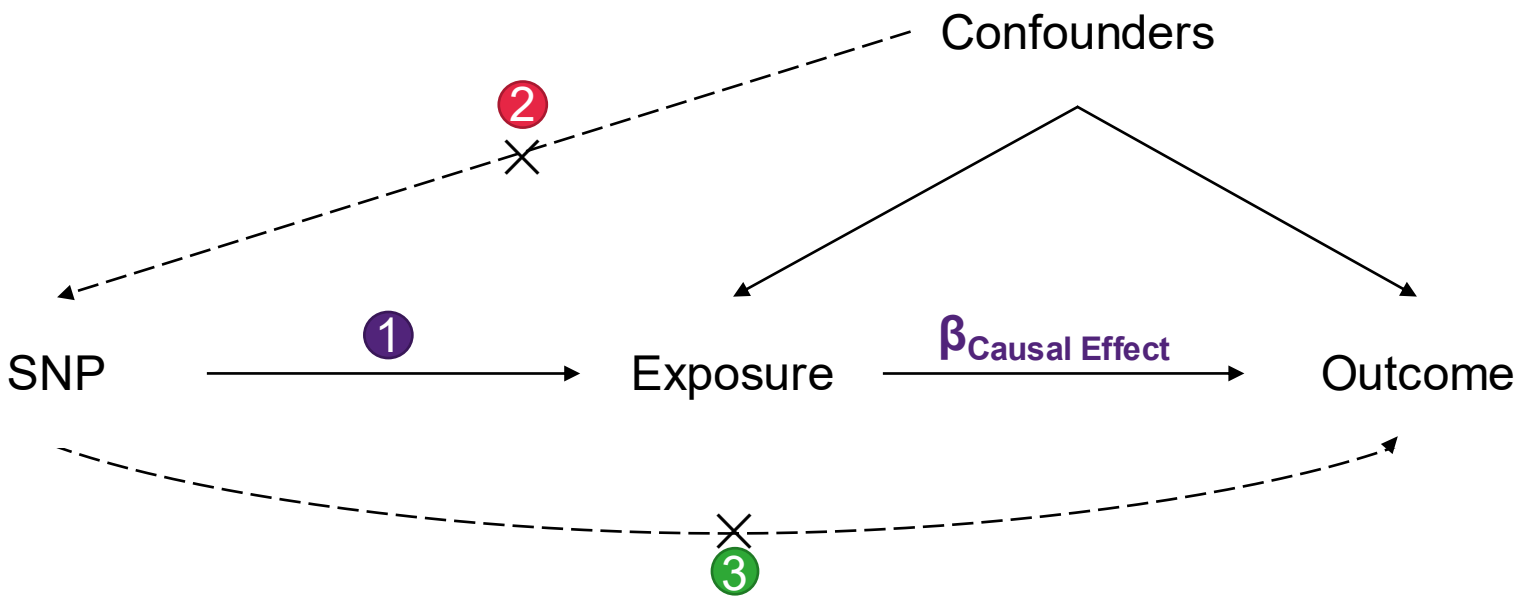
- Law of segregation: inheritance of alleles is random and independent of the environment etc
- Law of independent assortment: genes for different traits segregate independently (assuming not in LD)

The direction of causality is known – always from SNP to trait

Genetic variants are potentially very good instrumental variables

Using genetic variants as instrumental variables (IVs) is a special case of IV analysis, known as Mendelian randomization

Calculating Causal Effect Estimates



Two common approaches to calculate causal effects using a single SNP:

- Two-stage least-squares (TSLS) regression
- Wald Estimator

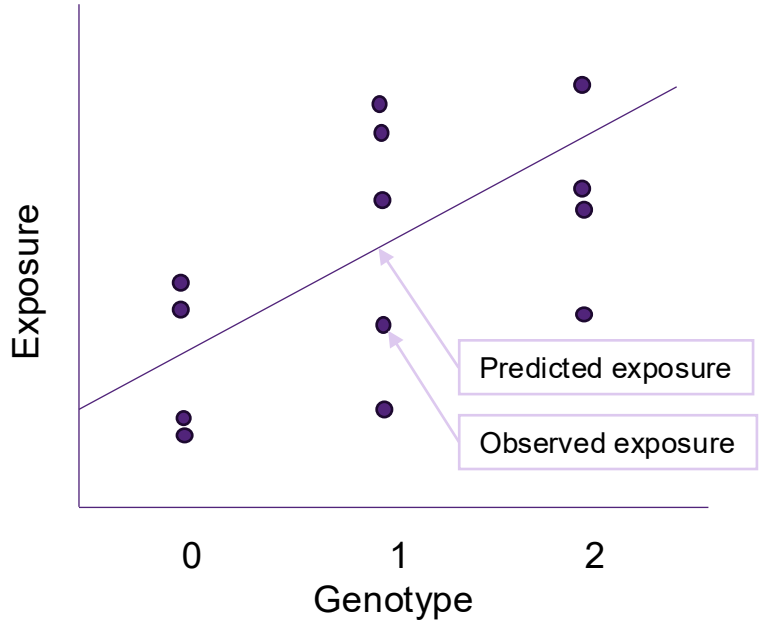
Calculating Causal Effect Estimates: Two-Stage Least Squares

A single sample of individuals with data on the SNP, the exposure and the outcome. Also known as “One sample MR”.

Manual calculation:

1. Regress exposure on SNP and obtain predicted values
2. Regress outcome on **predicted** exposure (from 1st stage regression)

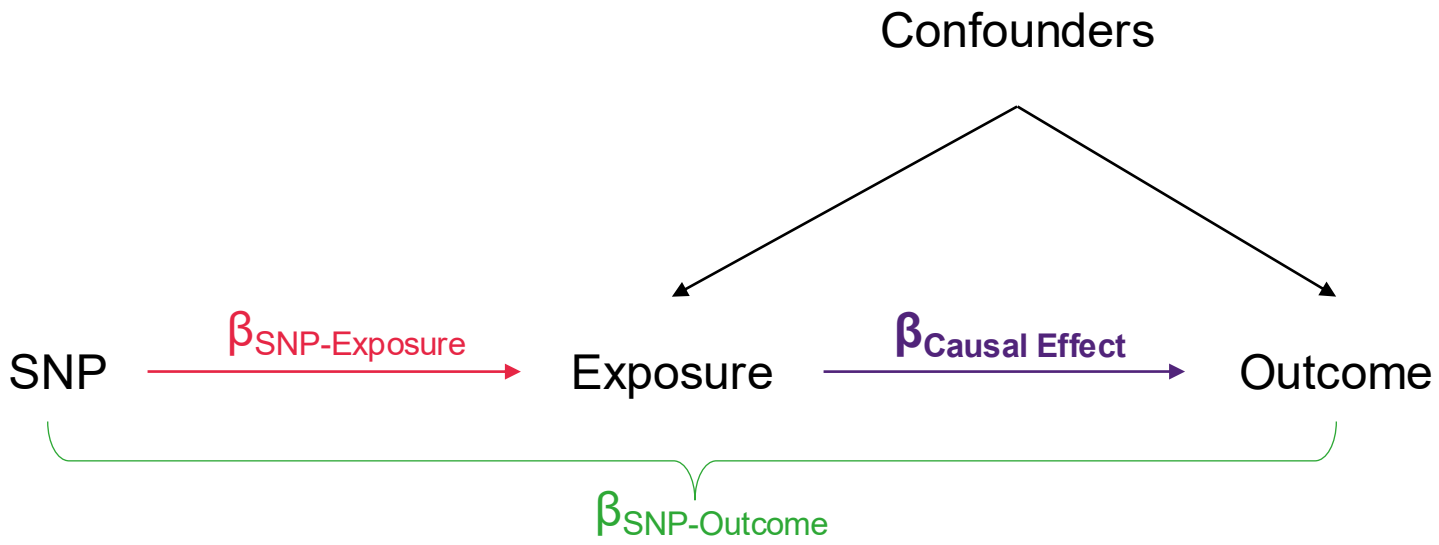
The regression coefficient from the second stage is the estimate of the causal effect of the exposure on the outcome.



This gives you: difference in outcome per unit change in (genetically-predicted) exposure

Genetically determined exposure → “randomized” → can ascribe causality
(if assumptions are met)

Calculating Causal Effect Estimates
Wald Estimator (Wald Ratio)



When there is a linear relationship between SNP, exposure and outcome:

$\beta_{SNP\text{-}Outcome} = \beta_{SNP\text{-}Exposure} \times \beta_{Causal\ Effect}$

$$\beta_{Causal\ Effect}\ (\text{Wald estimator}) = \frac{\beta_{SNP\text{-}Outcome}}{\beta_{SNP\text{-}Exposure}}$$

(change in outcome per unit change in exposure)

Delta method to estimate SE of Wald Estimator (Wald Ratio)

$$Var(\hat{\beta}_{xy}) = Var\left(\frac{\hat{\beta}_{SNP-Outcome}}{\hat{\beta}_{SNP-Exposure}}\right)$$

$$\approx \frac{Var(\hat{\beta}_{SNP-Outcome})}{\hat{\beta}_{SNP-Exposure}^{2}} + \left(\frac{\hat{\beta}_{SNP-Outcome}^{2}}{\hat{\beta}_{SNP-Exposure}^{4}}\right) Var(\hat{\beta}_{SNP-Exposure}) - 2\left(\frac{\hat{\beta}_{SNP-Outcome}}{\hat{\beta}_{SNP-Exposure}^{3}}\right) Cov(\hat{\beta}_{SNP-Exposure}, \hat{\beta}_{SNP-Outcome})$$

$$\approx \frac{Var(\hat{\beta}_{SNP-Outcome})}{\hat{\beta}_{SNP-Exposure}^{2}}$$

$$SE(\hat{\beta}_{XY}) = \hat{\sigma}_{XY} \approx \sqrt{\frac{Var(\hat{\beta}_{SNP-Outcome})}{\hat{\beta}_{SNP-Exposure}^{2}}}$$

$$\approx \frac{\sigma_{SNP-Outcome}}{\hat{\beta}_{SNP-Exposure}}$$

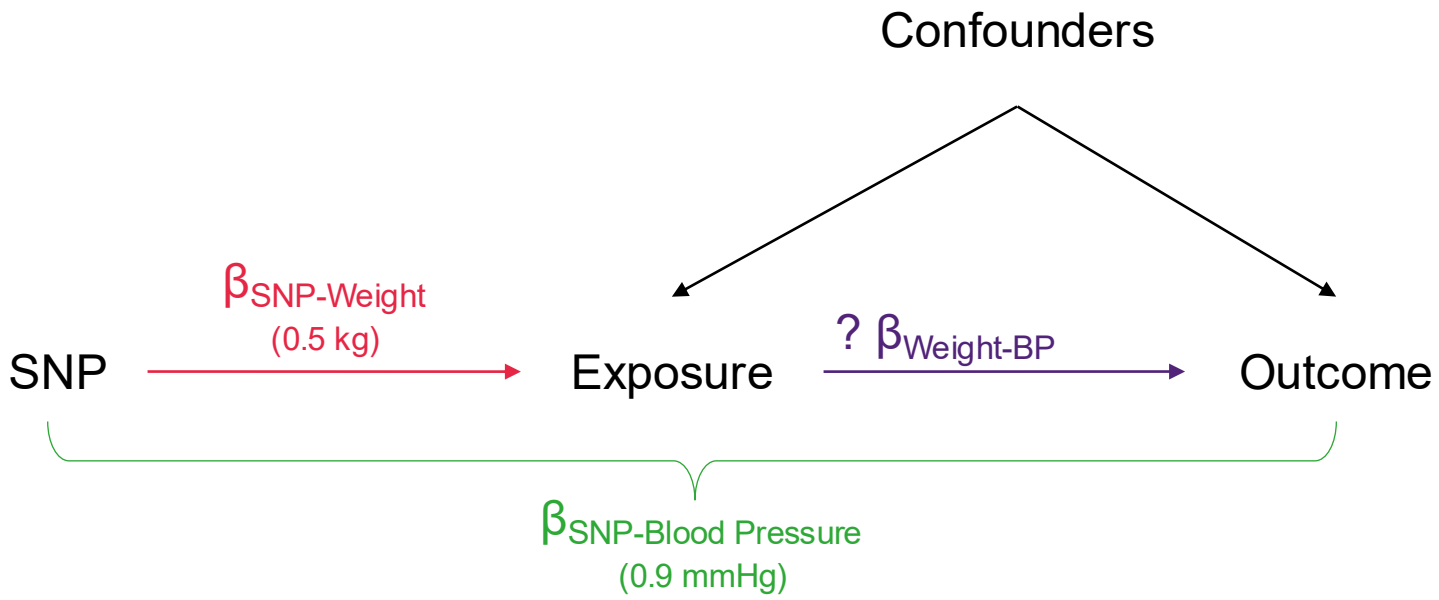
Uncertainty of Wald ratio

If the SNP–outcome estimate is noisy, then the MR estimate will also be noisy.

The uncertainty is scaled by the square of the SNP–exposure effect. Therefore:

- **strong instrument** (large $\hat{\beta}_{SNP-Exposure}$) → smaller variance
- **weak instrument** (small $\hat{\beta}_{SNP-Exposure}$) → much larger variance

Calculating Causal Effect Estimates
Wald Estimator (Wald Ratio)



When there is a linear relationship between SNP, exposure and outcome:

$\beta_{SNP\text{-}Outcome} = \beta_{Causal\ Effect} \times \beta_{SNP\text{-}Exposure}$

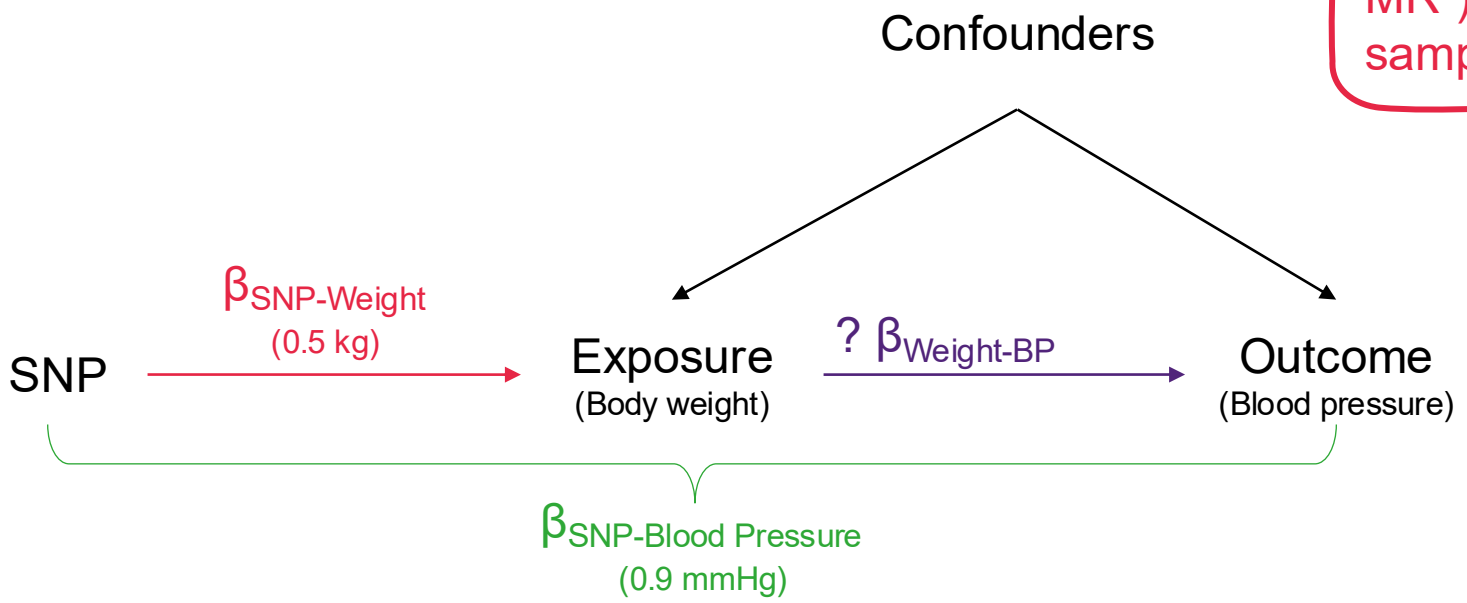
$$\beta_{Causal\ Effect}\ (\text{Wald estimator}) = \frac{\beta_{SNP\text{-}Outcome}}{\beta_{SNP\text{-}Exposure}}$$

$$\beta_{Weight\text{-}BP} = \frac{0.9\ \text{mmHg/allele}}{0.5\ \text{kg/allele}} = 1.8\ \text{mmHg/kg}$$

Interpretation: Each genetically predicted 1 kg increase in weight increases blood pressure by 1.8 mmHg.

Calculating Causal Effect Estimates
Wald Estimator (Wald Ratio)

Wald estimator can be used in one sample ("One sample MR") as well as different samples ("Two sample MR")



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Interpretation: Each genetically predicted 1 kg increase in weight increases blood pressure by 1.8 mmHg.

MR can also be performed using just the results from GWAS

Also known as “two-sample MR”, SMR, or MR with summary data etc

- SNP-exposure associations obtained from GWAS of sample 1
- SNP-outcome associations from GWAS of sample 2

Advantages:

- The data is readily available, non-disclosive, free, open source
- The exposure and outcome might not be measured in the same sample
- The sample size of the outcome variable, key to statistical power, is not limited by requiring overlapping measures of the exposure

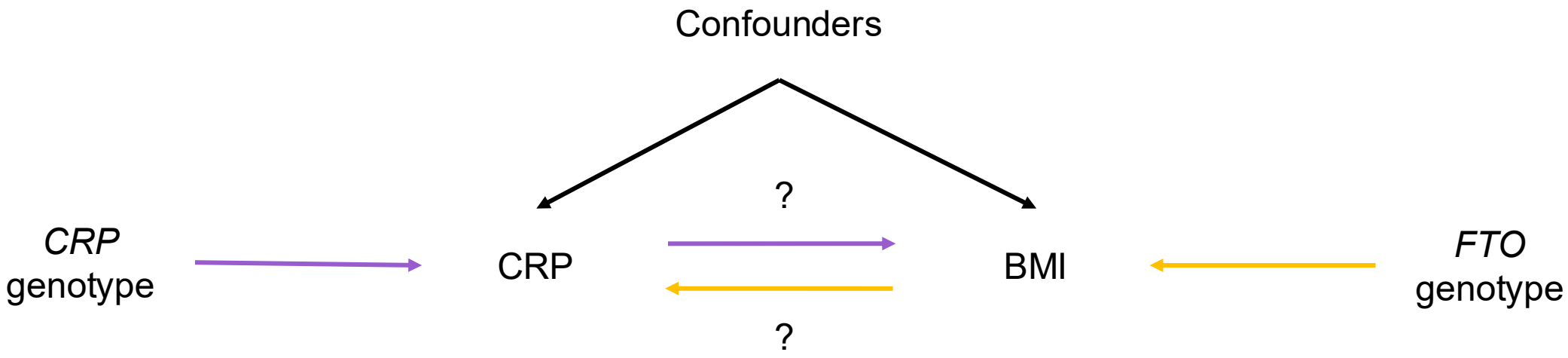
Disadvantages:

- Some extensions of MR not possible, e.g. non-linear MR, use of GxE for negative controls, various sensitivity analyses

MR Example using CRP and BMI

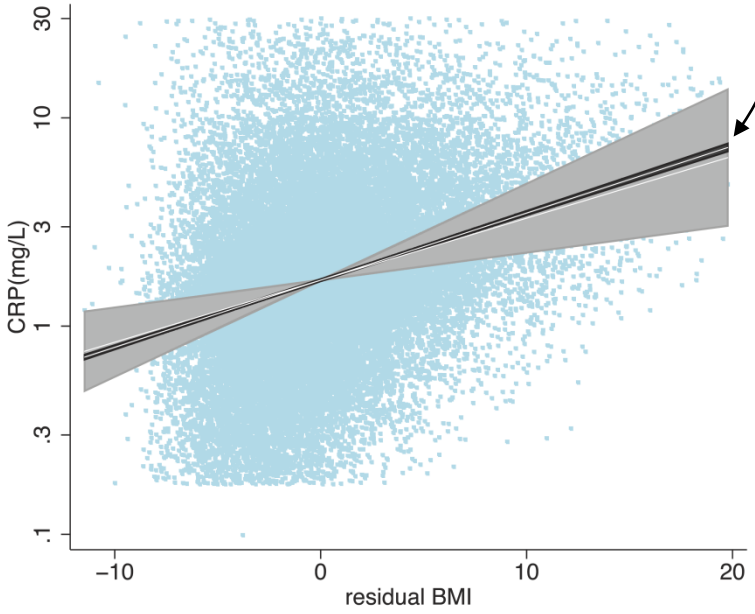
- C-Reactive Protein (CRP) is a biomarker of inflammation
- It is associated with BMI, metabolic syndrome, CHD and a number of other diseases
- It is unclear whether these observational relationships are causal or due to confounding or reverse causality
- This question is important from the perspective of intervention and drug development

“Bi-directional Mendelian Randomization”
Testing causality and reverse causation



“Bi-directional Mendelian Randomization”
Testing causality and reverse causation

	Effect estimates				
Exposure → Outcome	Observational association	Instrumental variable (MR)	P_{IV}	P_{diff}	F_{first}
BMI → CRP	1.075 (1.073, 1.077)	1.06 (1.02, 1.11)	0.002	0.6	50.2



Timpson NJ et al. *Int J Obes* (2011) 35(2):300-308

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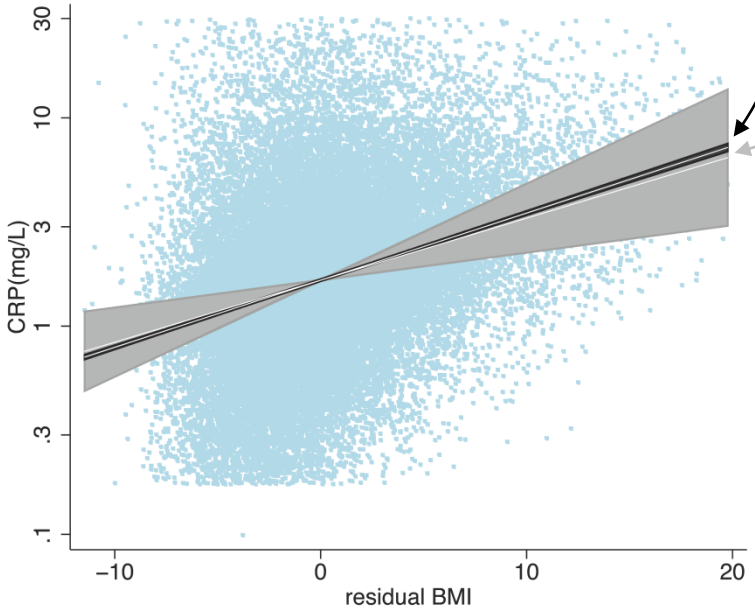

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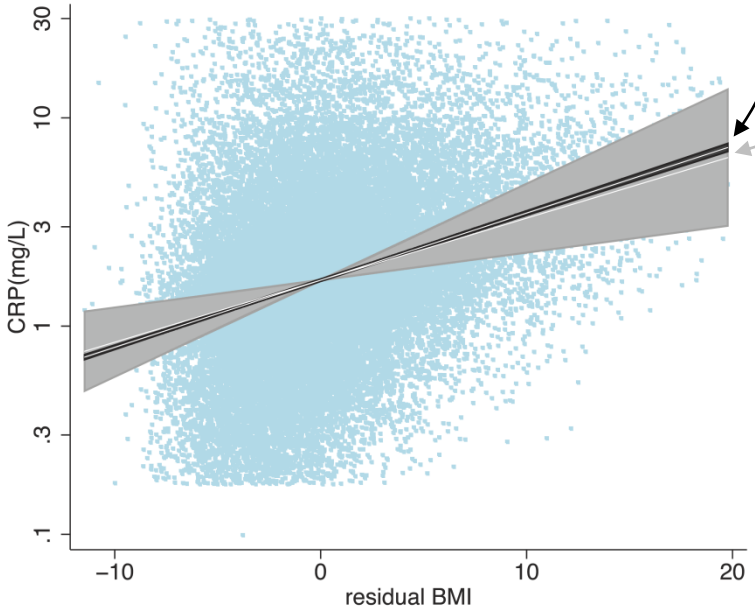

P_{diff} is calculated by conducting a heterogeneity test of the effect estimates from the observational association and instrumental variable analysis.

“Bi-directional Mendelian Randomization”
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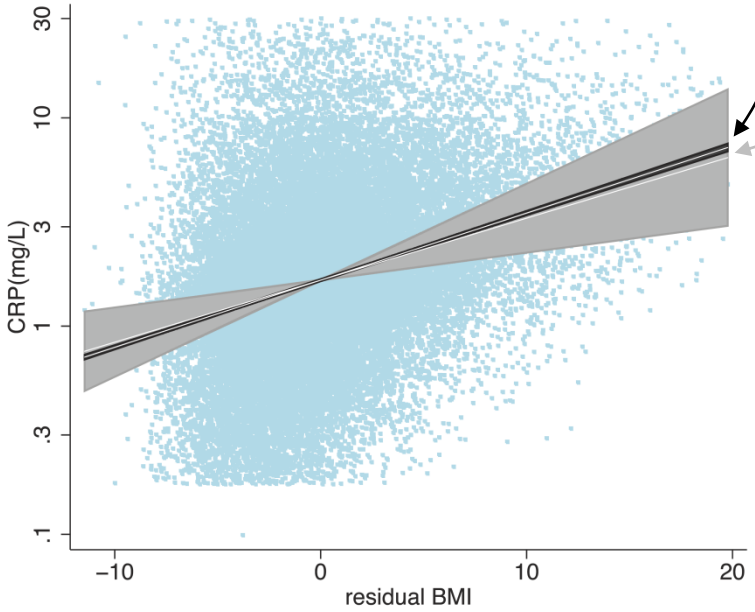


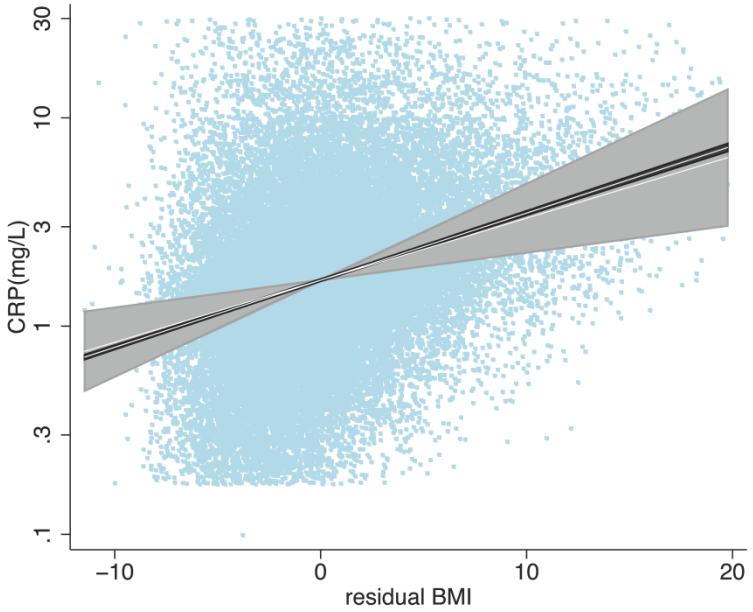
P_{diff} is calculated by conducting a heterogeneity test of the effect estimates from the observational association and instrumental variable analysis.

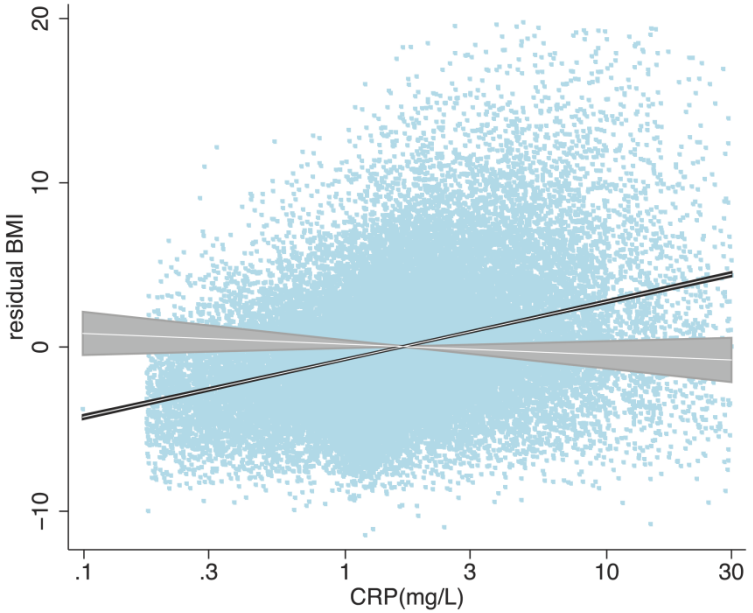
$$F_{first} = \frac{R^2 * (N-1)}{(1-R^2)}$$

R^2 is the variance explained in exposure by the SNP(s)
N is number of individuals in the study.

“Bi-directional Mendelian Randomization”
Testing causality and reverse causation

	Effect estimates				
Exposure → Outcome	Observational association	Instrumental variable (MR)	P_{IV}	P_{diff}	F_{first}
BMI → CRP ✓	1.075 (1.073, 1.077)	1.06 (1.02, 1.11)	0.002	0.6	50.2
CRP → BMI	0.58 (1.53, 1.63)	-0.30 (-0.78, 0.18)	0.2	<0.00001	78.3





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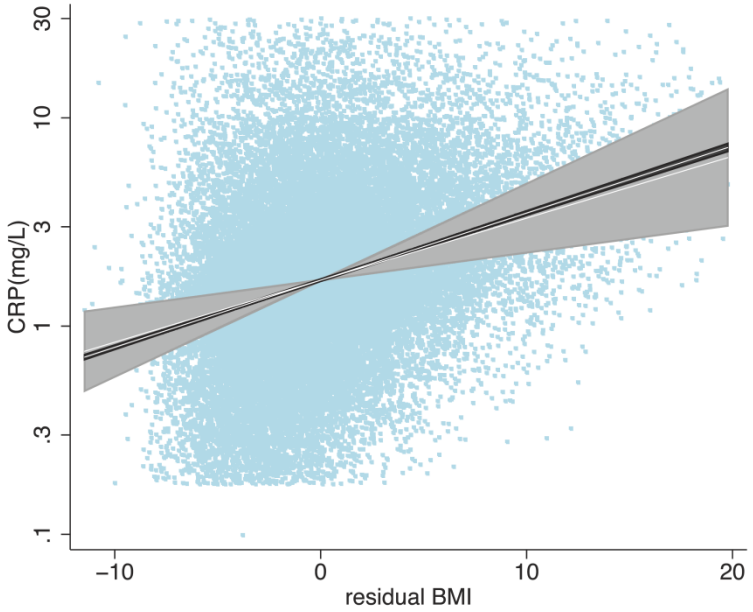
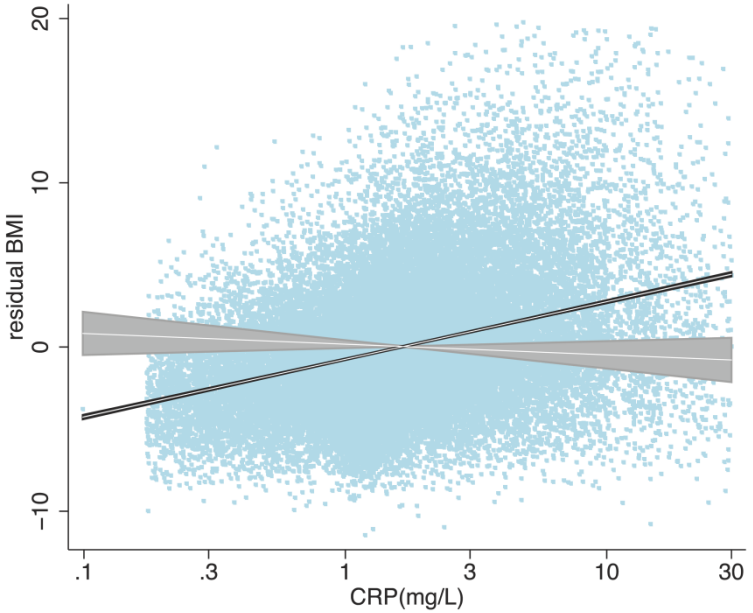




Limitations to Mendelian Randomization

1. Population stratification: ancestry differences can confound genetic associations.

2. Canalization ("Developmental compensation"): biological adaptation may buffer genetic effects, resulting in inaccurate causal estimates.

3. The existence of instruments: suitable genetic variants may not exist.

4. Power (also "weak instrument bias")

5. Pleiotropy

Power and Weak Instruments

Power (Probability of demonstrating a causal effect when one is in fact present):

- Genetic variants explain very small amounts of phenotypic variance in a given trait
- VERY large sample sizes are generally required to demonstrate causal effects

Weak instruments (weak instrument bias):

- Genetic variants that are weak proxies for the exposure (little variance explained, low power)
- Results in biased causal estimates from MR
  - **Single Sample MR:** to the confounded estimate
  - **Two-Sample MR:** to the null

Using Multiple Genetic Variants as Instruments

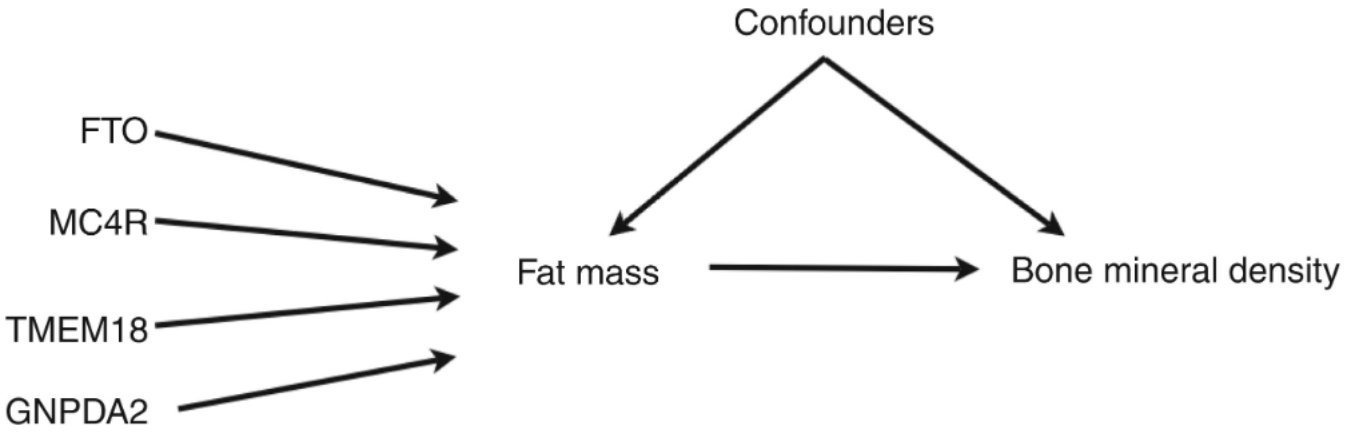


Figure 1. DAG for a Mendelian randomisation analysis using four genetic variants as instrumental variables for the effect of fat mass on bone mineral density.

- Creating allelic scores using multiple genetic variants
- Testing multiple variants individually and then meta-analysing individual SNPs

Palmer et al (2011) Stat Method Res

Calculating Power in Mendelian Randomization Studies (https://shiny.cnsgenomics.com/mRnd/)

mRnd: Power calculations for Mendelian Randomization

Input

Calculate:

- (●) Power
- ( ) Sample size

Provide:

Sample size

1000

α

0.05

Type-I error rate

β_{yx}

0

The regression coefficient β_{yx} for the true underlying causal association between the exposure (X) and outcome (Y) variables

β_{OLS}

0

The regression coefficient β_{OLS} for the observational association between the exposure (X) and outcome (Y) variables

R^2_{xz}

0.01

Proportion of variance explained for the association between the SNP or allele score (Z) and the exposure variable (X)

$\sigma^2(x)$

1

Variance of the exposure variable (X)

Continuous outcome | Binary outcome | Binary outcome derivations | Citation | About

Two-stage least squares

Power	0.05	
NCP	0.00	Non-Centrality-Parameter
F-statistic	11.10	The strength of the instrument

Power or sample size calculations for two-stage least squares Mendelian Randomization studies using a genetic instrument Z (a SNP or allele score), a continuous exposure variable X (e.g. body mass index [BMI, $\frac{kg}{m^2}$]) and a continuous outcome variable Y (e.g. blood pressure [mmHg]).

YZ association

Power	0.05	
NCP	0.00	Non-Centrality-Parameter

Power or sample size calculations for the regression association of a genetic instrument Z (e.g. a BMI SNP), with a continuous outcome variable Y (blood pressure).

Working Example

If we are interested in calculating the minimum required sample size for performing a Mendelian Randomization (MR) study ascertaining the causal effects of body mass index (BMI) on systolic blood pressure (SBP) in children, the required parameters for this online calculator could be taken from, for example, results from a published observational epidemiology study reporting associations between BMI and SBP and a SNP instrument that is reliably associated with BMI.

In an observational study reporting the association of BMI and SBP in children[1], the regression coefficients for the association between BMI and SBP (averaged coefficients for boys and girls) was observed to be $1.41\frac{mmHg}{SD}$ (no confounder-adjustment) and $1.30\frac{mmHg}{SD}$ [*] (adjusted for confounders). The SD for SBP in this sample (from the paper's online supplementary data) was 10.8, with an SD (standard deviation) of 1 for BMI.

Assume that the causal effect of BMI on SBP is $1.30\frac{mmHg}{SD}$ [*] and that the population regression coefficient of BMI on SBP, including the effects of confounders, is $1.41\frac{mmHg}{SD}$. Also assume that for the MR study we have a genetic instrument that explains $R^2_{xz} = 0.01$ of variation in BMI (based on e.g. FTO SNP, which explains $\sim 1\%$ of the variation in BMI)[2]. Then we can calculate the power of an MR study using the following parameters:

$\beta_{OLS} = 1.41\frac{mmHg}{SD}$

$\beta_{yx} = 1.3\frac{mmHg}{SD}$ [*]

$\sigma^2(x) = 1$

$\sigma^2(y) = 10.8^2 = 116.6\ mmHg^2$

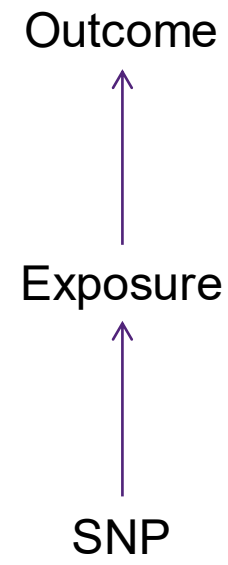
For an α of 0.05 and power of 0.8, the calculated minimum sample size for the Mendelian Randomization study is $N = 53,218$. The reason why this sample size is so large is because BMI explains a small amount of variation in SBP in this case and because the genetic instrument explains a small proportion of variance in BMI.

$*\ \beta_{yx}$ refers to the unknown true causal association between X and Y (between BMI and blood pressure, in this example) and therefore instead of 1.3 mmHg one could potentially use any value of β_{yx} deemed plausible or, for example, inspect the power/sample size calculations for a range of hypothetical values of β_{yx}.

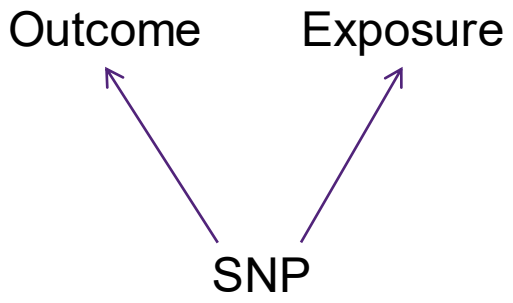
1. Lawlor DA, Benfield L, Logue J et al. Association between general and central adiposity in childhood, and change in these, with cardiovascular risk factors in adolescence: prospective cohort study. BMJ 2010; 341: c6224.

2. Frayling TM, Timpson NJ, Weedon MN et al. A Common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science 2007; 316(5826): 889-894.

Pleiotropy: Genetic variant influences more than one trait



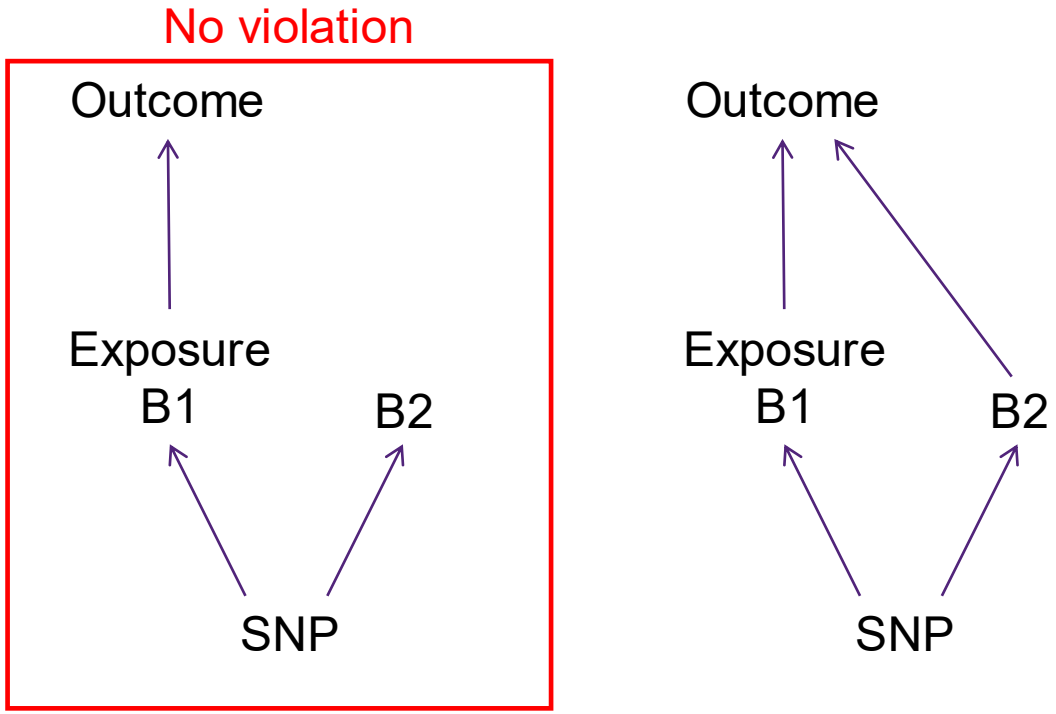
Vertical pleiotropy



Horizontal pleiotropy

Horizontal Pleiotropy

Pleiotropy only violates MR's assumptions if it involves a pathway outside that of the exposure and is a pathway that affects your outcome.



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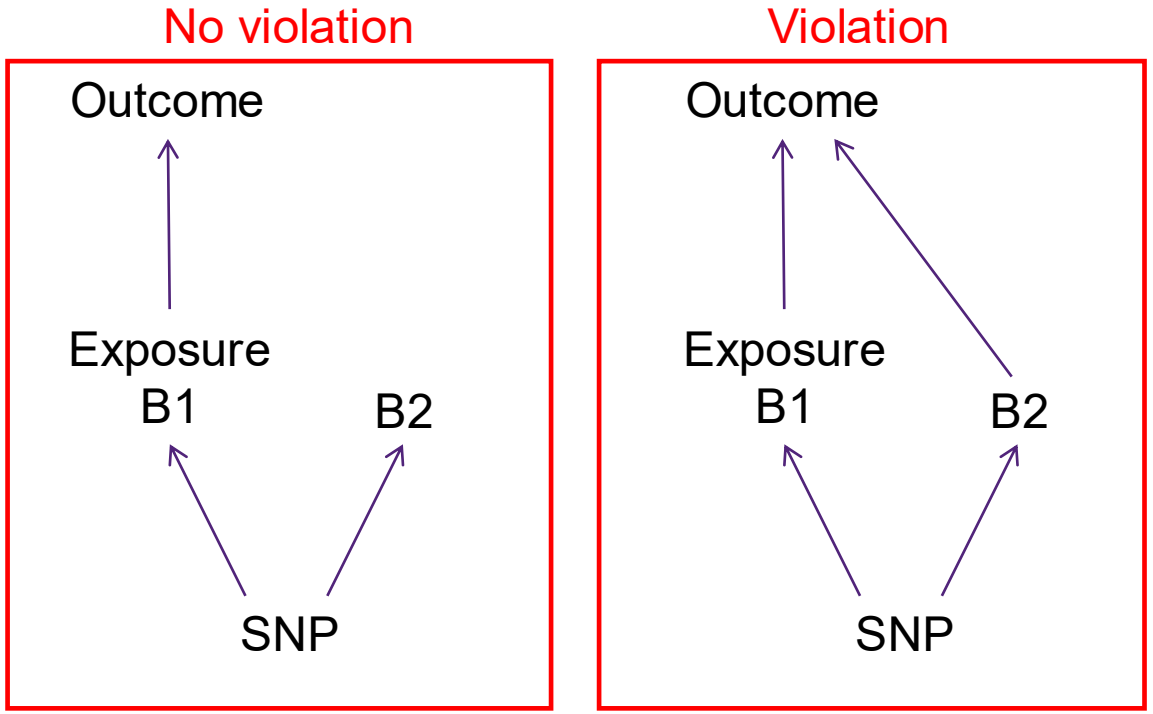

Key take-home messages

Association does not imply causation. Observational studies are vulnerable to confounding, reverse causation, and bias.

MR uses genetic variants as natural experiments. Because alleles are randomly allocated at conception, MR can approximate the causal inference of an RCT when its assumptions hold.

Understand DAGs. The chain, fork (confounder), and collider are the three fundamental structures for reasoning about causal relationships and deciding which variables to adjust for.

Always assess the three MR assumptions. Relevance, independence, and exclusion restriction determine whether a genetic variant is a valid instrumental variable.

Horizontal pleiotropy is the main threat to validity. Much of the next lecture focuses on methods to detect and account for it.

Useful References

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