

# Applications of GWAS: Mendelian Randomization

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# The curse of correlations (and associations)

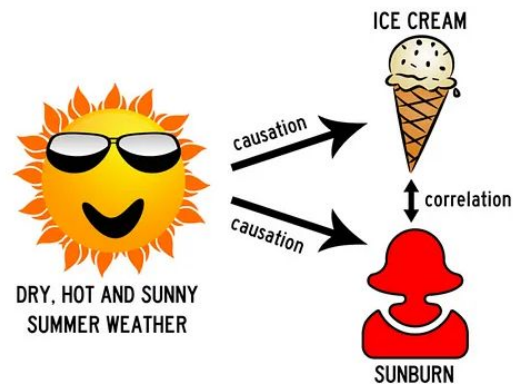
## Correlation is not causation

### Reverse causation

- n. of firemen  $\longleftrightarrow$  size of the fire (the more the firemen, the bigger the fire?)
- smoking  $\longleftrightarrow$  depression (smoking causes depression?)

### Missing variable

- ice cream consumption  $\longleftrightarrow$  n. of sunburn cases
- buying lighters  $\longleftrightarrow$  lung cancer



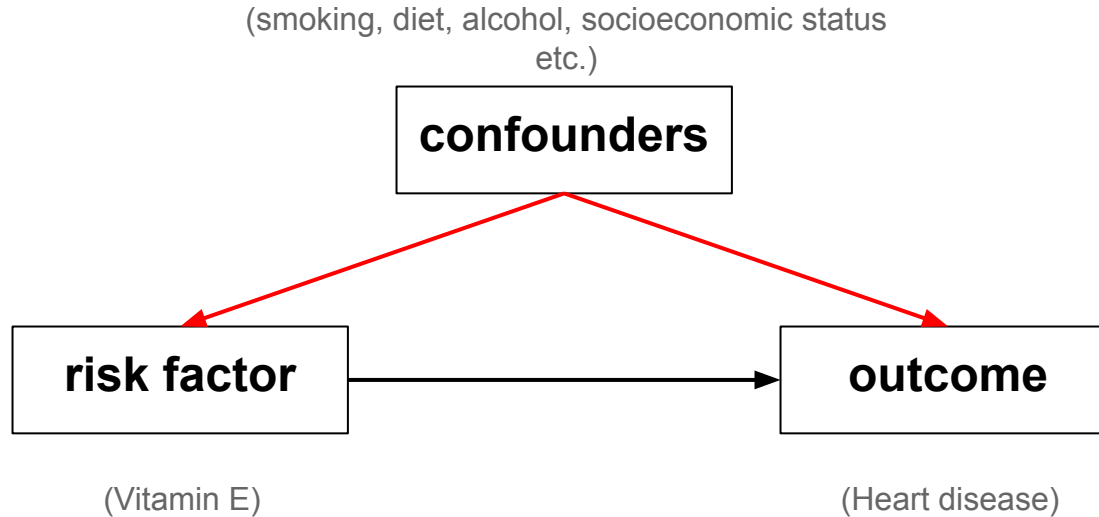
[<https://towardsdatascience.com/>]

# Causation or not causation, that is the question

- post hoc, ergo propter hoc
- strength of correlation
- consistency (different datasets, studies etc.)
- dose-response relationship
- analysis “ceteris paribus” (controlling for confounders, stratifiers etc.)
- **experiments**



# Causation from **observational studies**



- Does the use of vitamin E supplementation reduce the risk of heart disease?
- Is there a causal relationship between dietary assumption of vitamin E and the risk of heart disease?

# Causation from **observational studies**

- Confounding: missing variable
- Reverse causation: B causes A, not the other way around as designed/hypothesized
- Bias: the observed sample is not representative of the target population (e.g. different sex ratio, age distribution etc.) [different from random error -variance- which can be reduced by increasing the sample size]

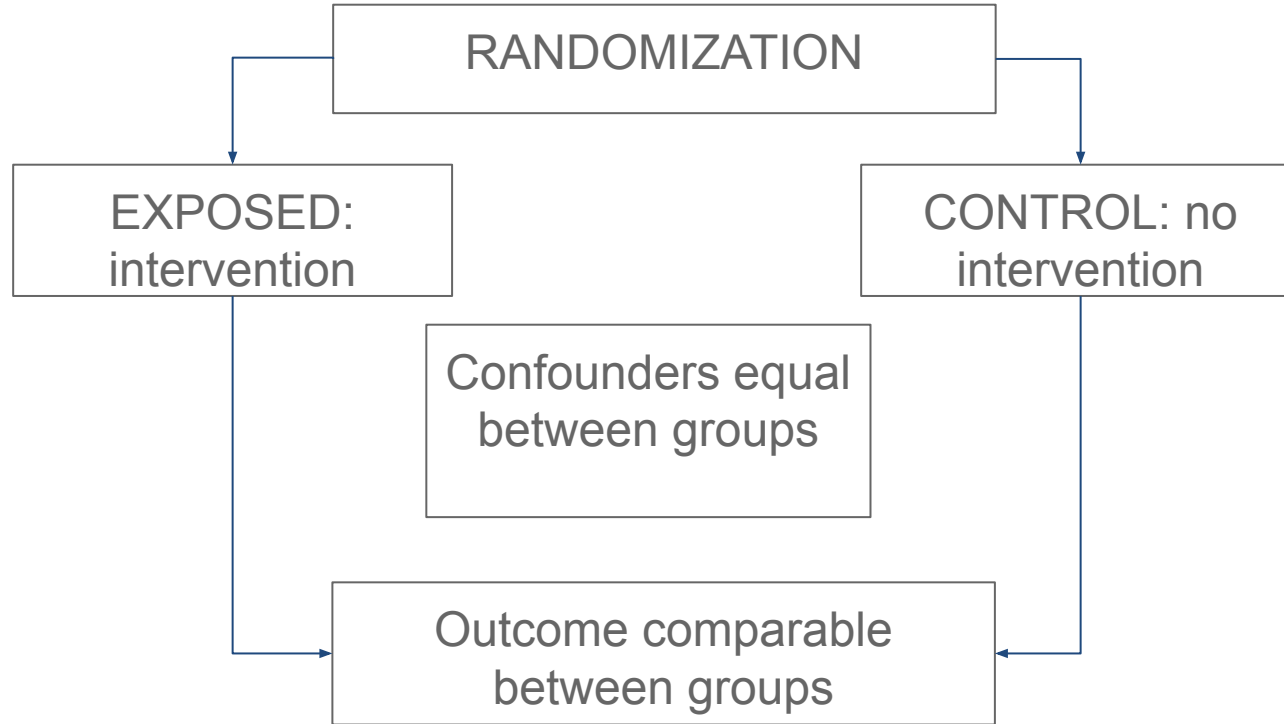


# SNP from GWAS: causal relationship?

- probably not causal mutation, but LD
- post hoc, ergo propter hoc: gene  $\rightarrow$  phenotype
- strength of correlation (p-value, multiple testing adjustments etc.)
- consistency (different datasets, studies etc.)
- dose-response relationship (allele coding)
- analysis “ceteris paribus” (controlling for confounders, stratifiers etc.)
- experiments (follow-up studies, post-GWAS, validation, etc.)



# Randomized trial



# Randomized trial

Randomized trials are the **gold standard for causal inference**

However:

- sometimes not ethical or practical (e.g. toxic exposures)
- expensive and time-consuming
- long follow-up times

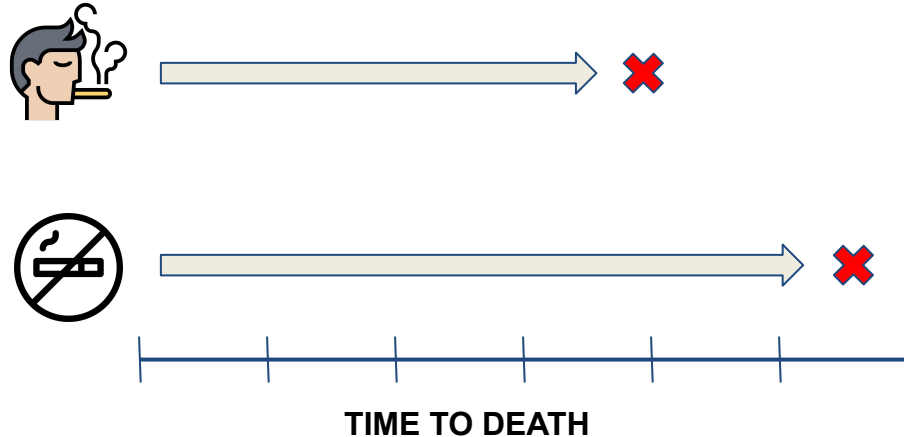


# Enter Mendelian Randomization

- Genes are inherited at the time of conception
- They follow Mendel rules of transmission: **random segregation** and **independent assortment** (e.g. 50% probability that one of two alleles is passed on from parents to their offspring)
- This is not affected by the lifestyle choices of persons, not related to confounding factors



# Enter Mendelian Randomization



Observation: smokers die sooner than non-smokers

Confounders: smokers on average drink more alcohol, less healthy diets

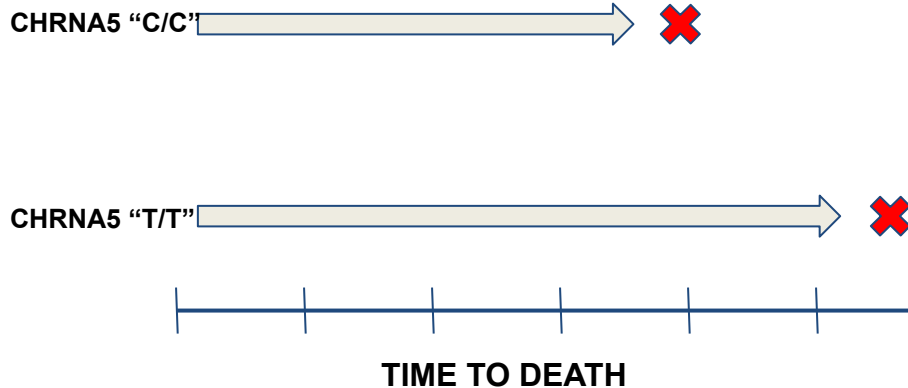
Reverse causation: when smokers get ill they quit smoking: no smoking → higher risk of death (apparently)

# Enter Mendelian Randomization

CHRNA5: acetylcholine receptor subunit alpha 5

→ associated with smoking behavior:

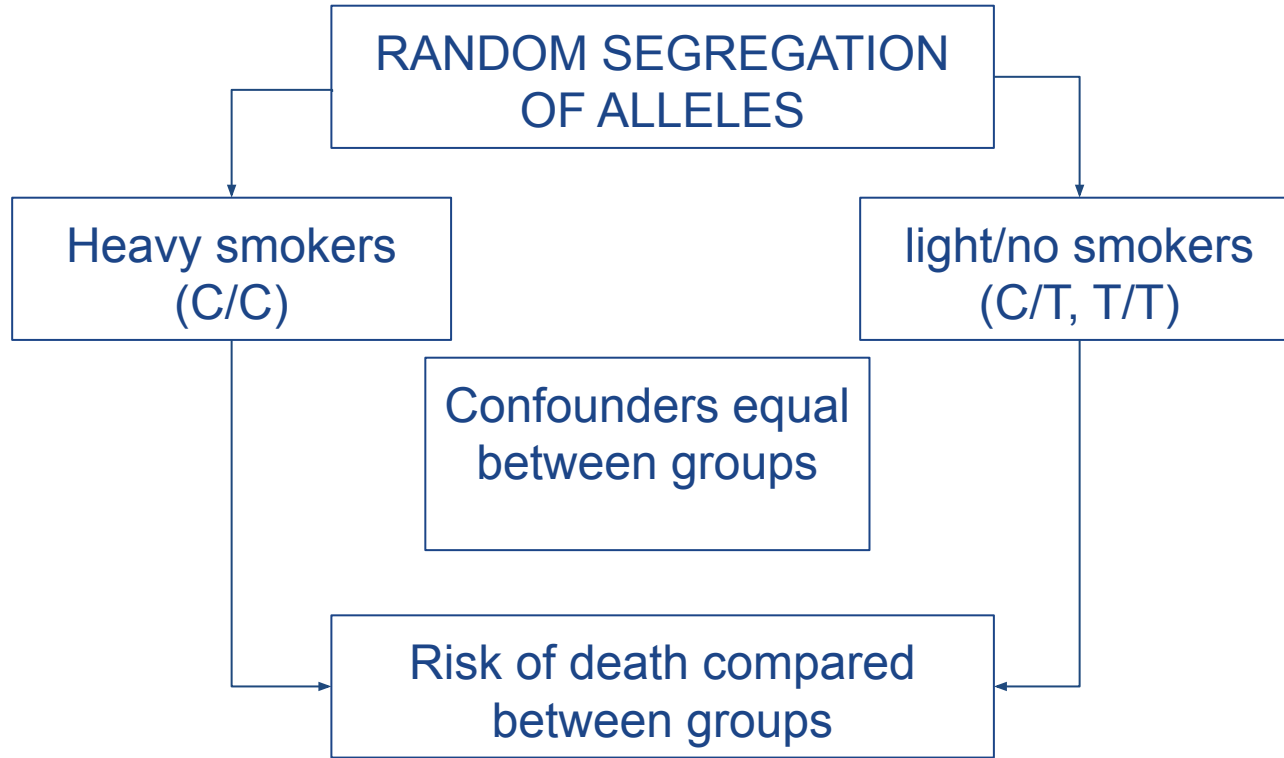
- allele “C” → more smoking (recessive/codominant)
- allele “T” → less smoking



Persons with the allele associated with more smoking die younger (on average)

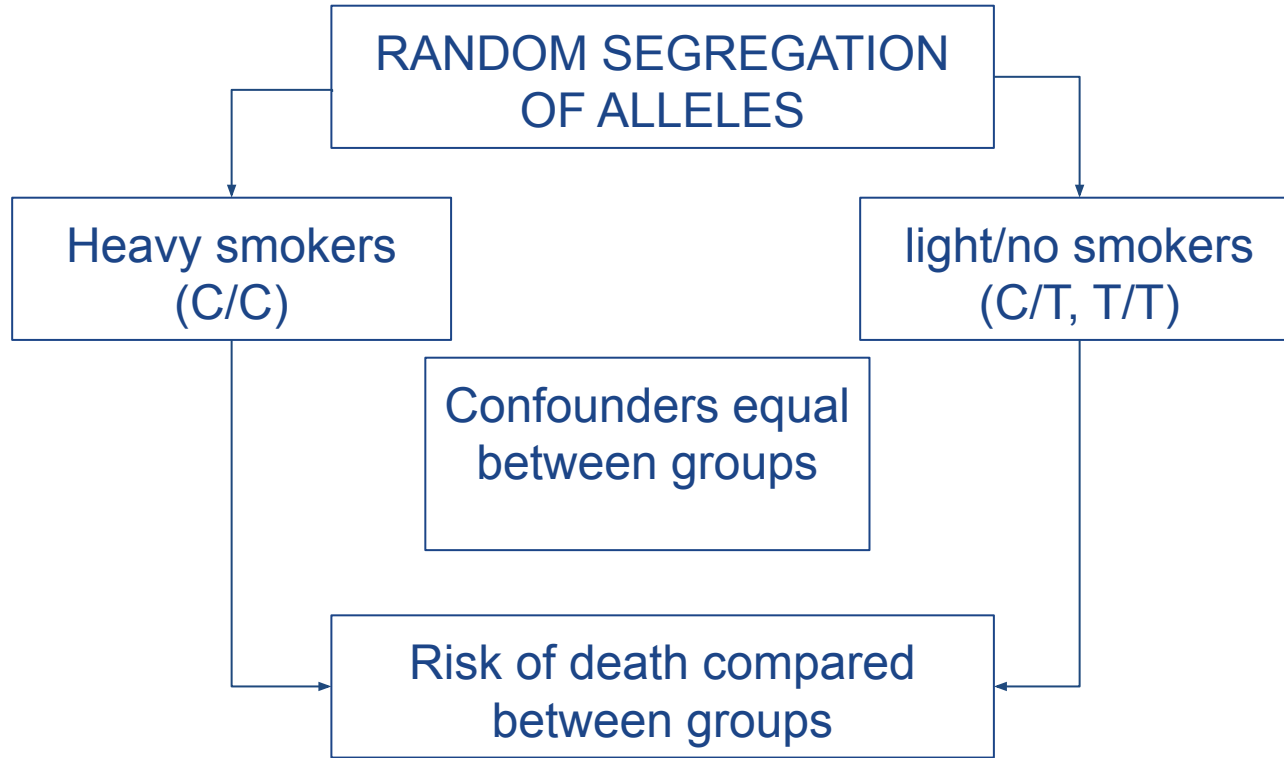


# Enter Mendelian Randomization



- Two groups based on alleles → random segregation
- “Genetic” smokers vs “genetic” non-smokers
- These two groups do not differ for confounders (diet, alcohol, wealth etc.)

# Enter Mendelian Randomization



Maybe *CHRNA5* affects life expectancy in other ways?

If we look only at non smokers, C/C vs C/T + T/T, we observe no effect on the risk of death

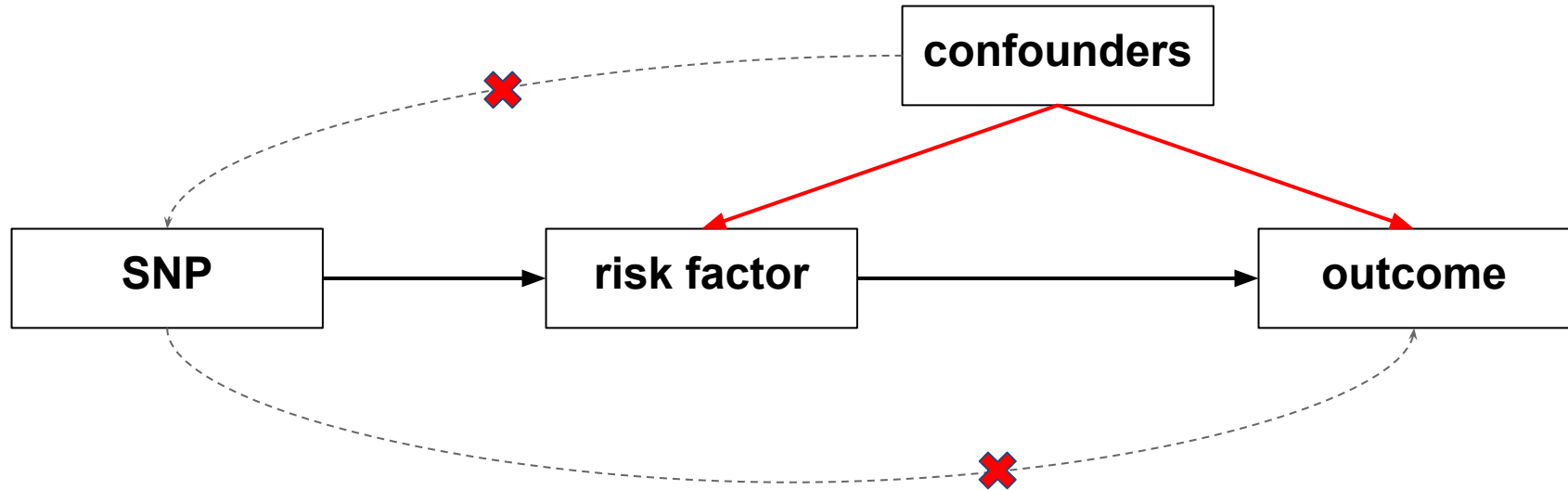
Smoking is the driver for the difference in risk of dying between the two groups

# GWAS and Mendelian Randomization

- GWAS studies produce lots of SNPs associated with phenotypes → IVs!
- This is an important application of GWAS experiments
- Important: the associations must be **true** (not spurious) and **strong**

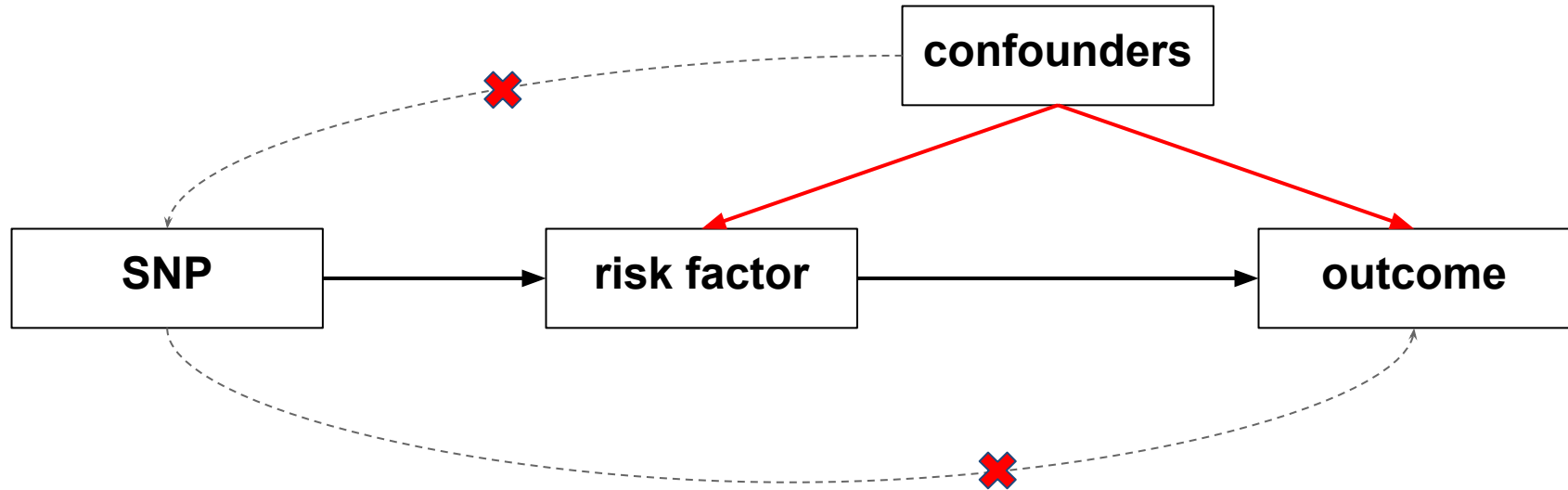


# Mendelian Randomization



1. The SNP is associated with the risk factor

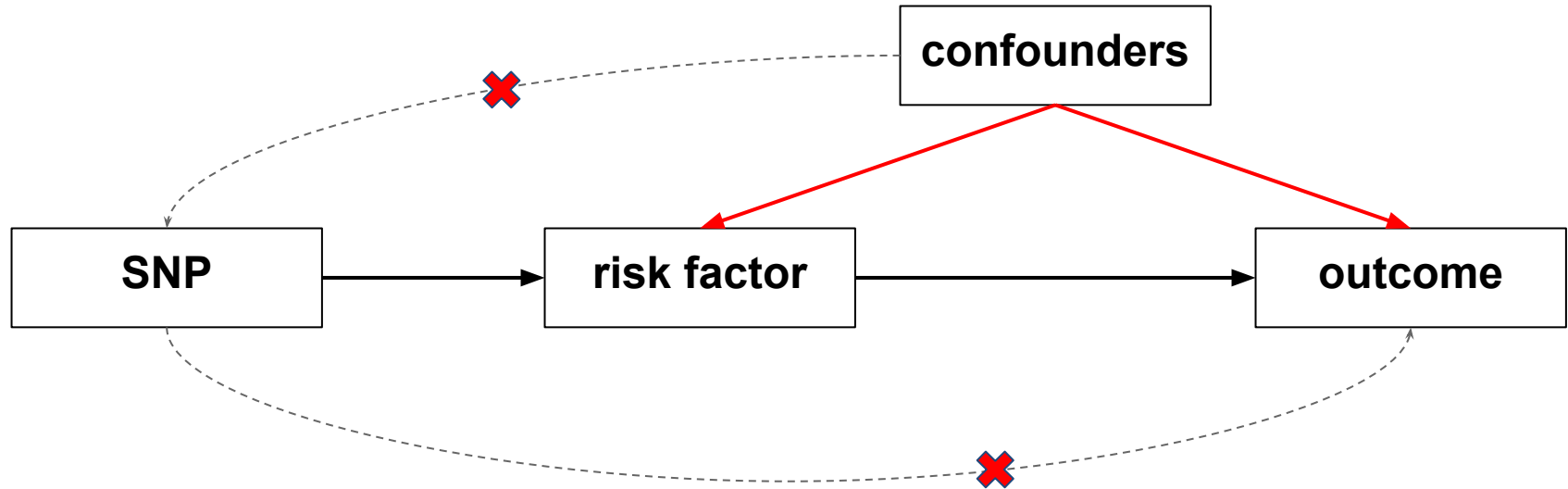
# Mendelian Randomization



2. The SNP is NOT associated with confounders

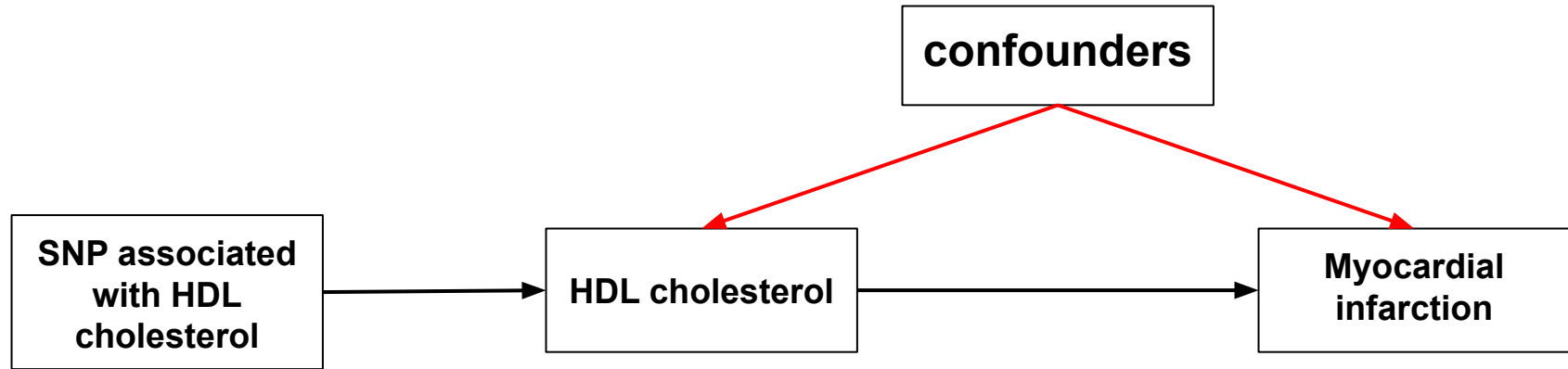


# Mendelian Randomization



3. The SNP is associated with the outcome ONLY through exposure

# Mendelian Randomization: another example



raising HDL cholesterol does not always lower risk of myocardial infarction: interventions (lifestyle or pharmacological) that raise plasma HDL cholesterol cannot be assumed to lead to a corresponding benefit with respect to risk of myocardial infarction ([Voight et al. 2012](#))

# Mendelian Randomization: concluding remarks

- **robust to confounding** due to Mendel's laws:
  - Law of segregation: inheritance of an allele is random and independent of 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 (SNPs) are potentially very **good instrumental variables**
- in most cases, not one single SNP is used, but multiple SNPs assembled into a combined score/IV



# Mendelian Randomization: concluding remarks

- In a different flavor of MR, SNPs (IVs) may also be associated with the outcome to study variation in risk factors (still to study the causal relationship between the two)
- Limitations:
  - population stratification (bias, generalization)
  - pleiotropy
  - power (SNP may explain only a small fraction of the phenotypic variance)



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