Introduction to Mendelian Randomisation

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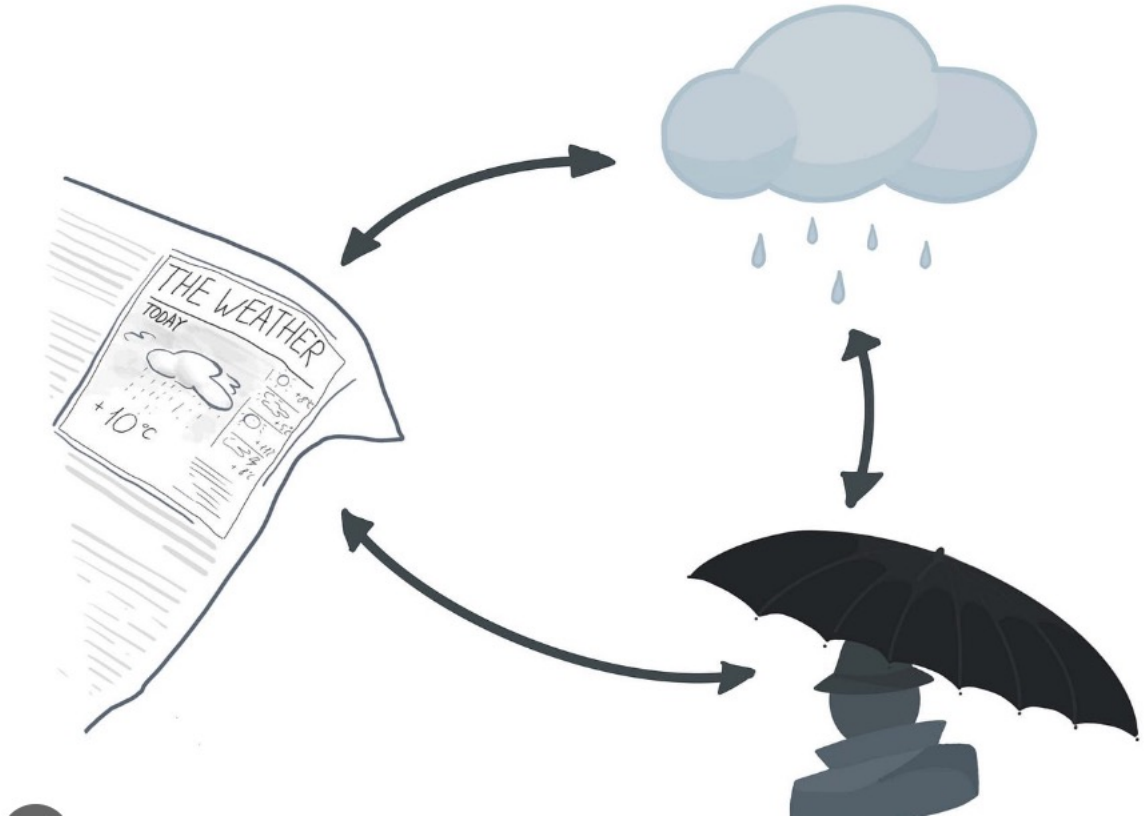
Learning outcomes

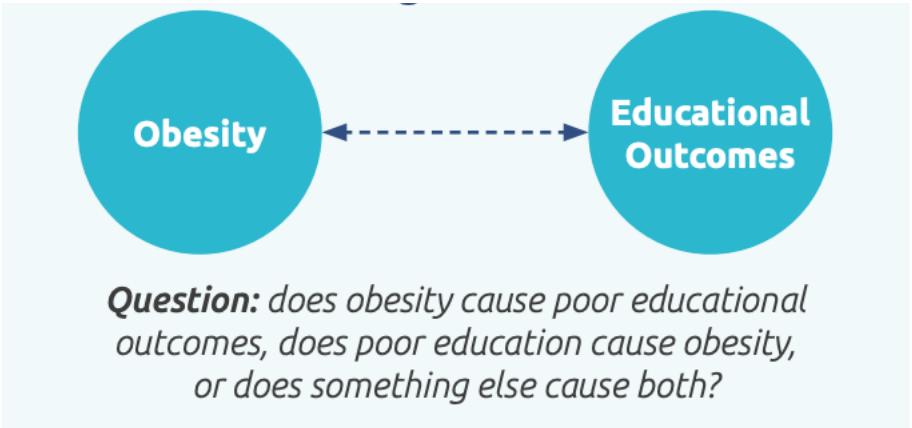
- The participants should be able to understand
  - How RCT is related to MR
  - Principles of MR
  - Limitations of MR
  - Applications of MR is unraveling drug side effects

Correlation or association is not always causal

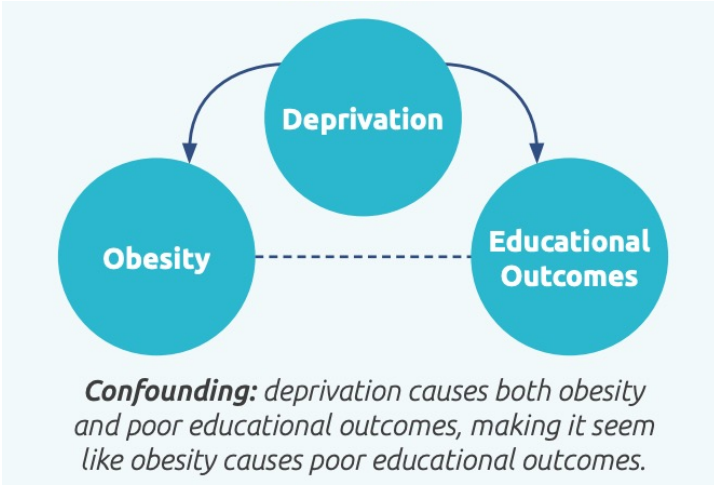
- In health research we are keen to understand relationships of health risks and outcomes
- We can depict associations
- Care is need to evaluate if strength and implications of these relationships



Challenges if unraveling the implications of relationships



Question: *does obesity cause poor educational outcomes, does poor education cause obesity, or does something else cause both?*

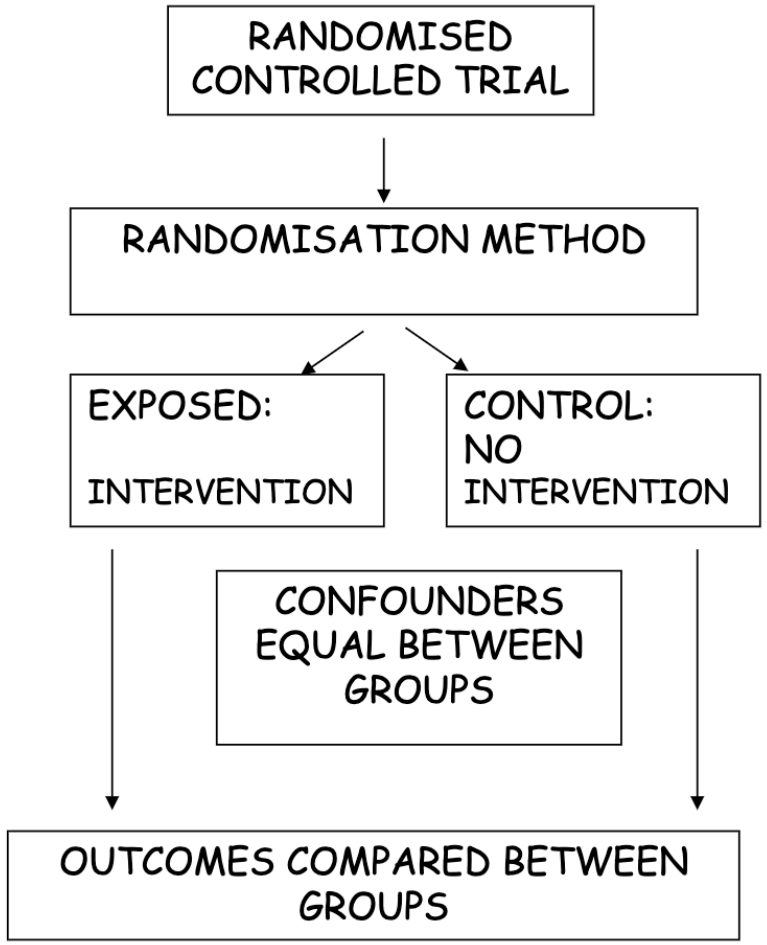


Confounding: *deprivation causes both obesity and poor educational outcomes, making it seem like obesity causes poor educational outcomes.*

Reverse causality: *poor education causes obesity, rather than obesity causing poor educational outcomes.*

Conventional solution is RCT

- This is not always practical.
- Any examples why?



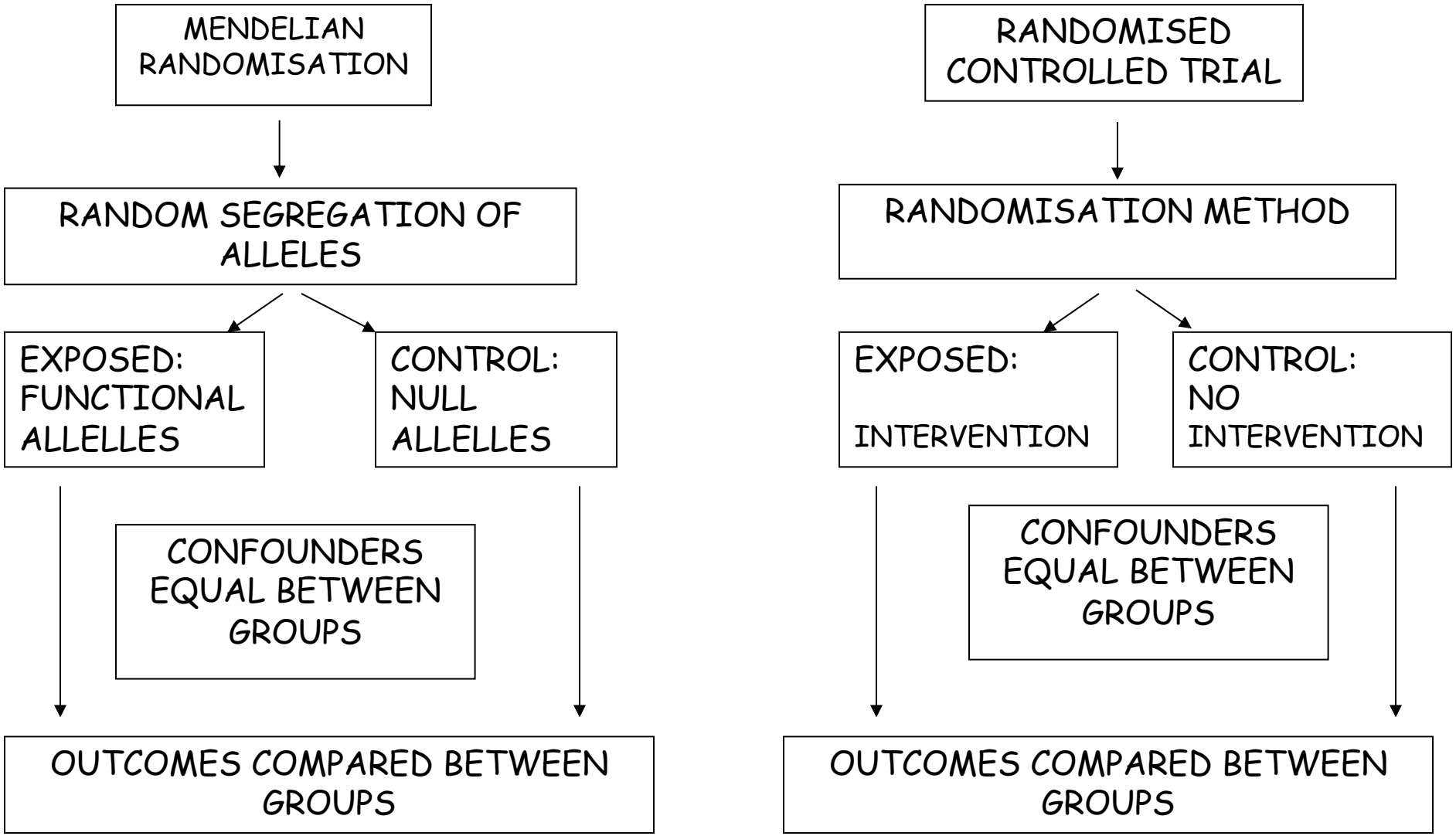
An Alternative to RCTs: Mendelian randomization

Mendel in 1862

In genetic association studies the laws of Mendelian genetics imply that comparison of groups of individuals defined by genotype should only differ with respect to the locus under study (and closely related loci in linkage disequilibrium with the locus under study)

Genotypes can proxy for some modifiable risk factors, and there should be no confounding of genotype by behavioural, socioeconomic or physiological factors (excepting those influenced by alleles at closely proximate loci or due to population stratification)

MR is a classical natural RCT



What is MR

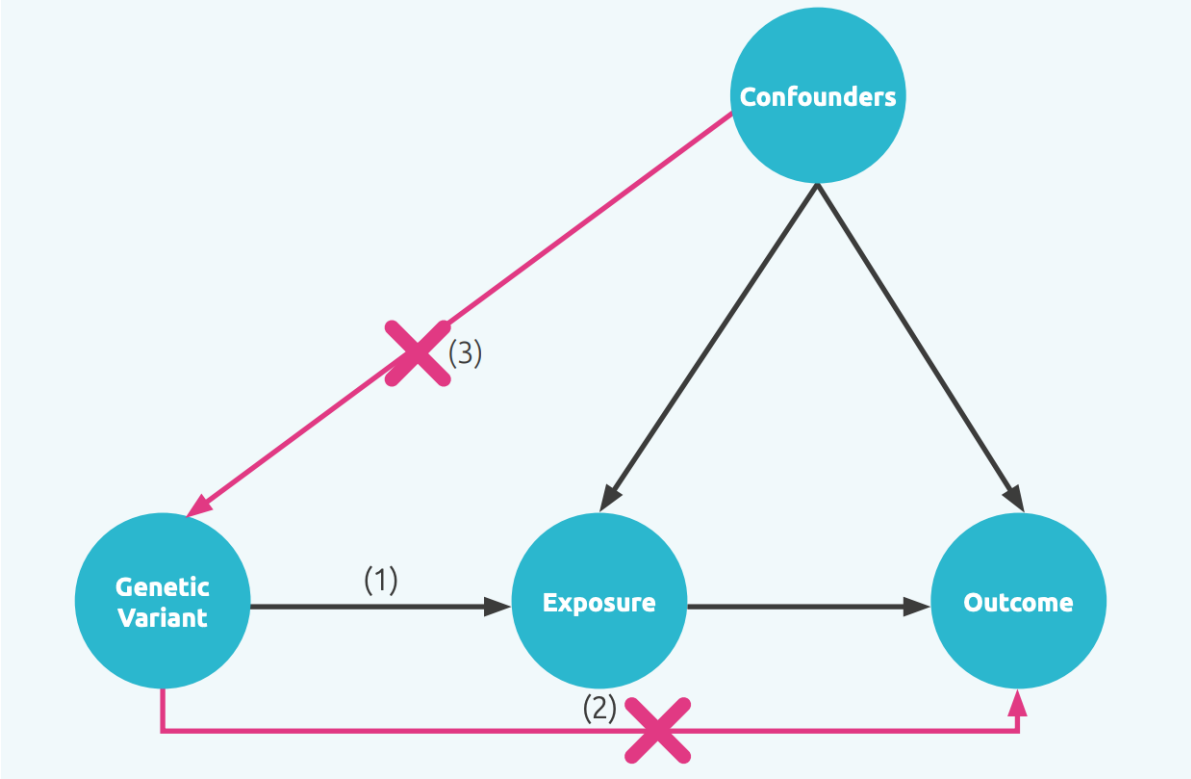
- Approach to test for a causal effect from observational data in the presence of certain confounding factors.
- Uses the measured variation of genes of known function, to

bind the causal effect of a modiable exposure(e.g environment) on a phenotype (e.g disease).

- Fundamental idea is that the genotypes are randomly assigned(due to meiosis).
- This allows them to be used as an instrumental variable.

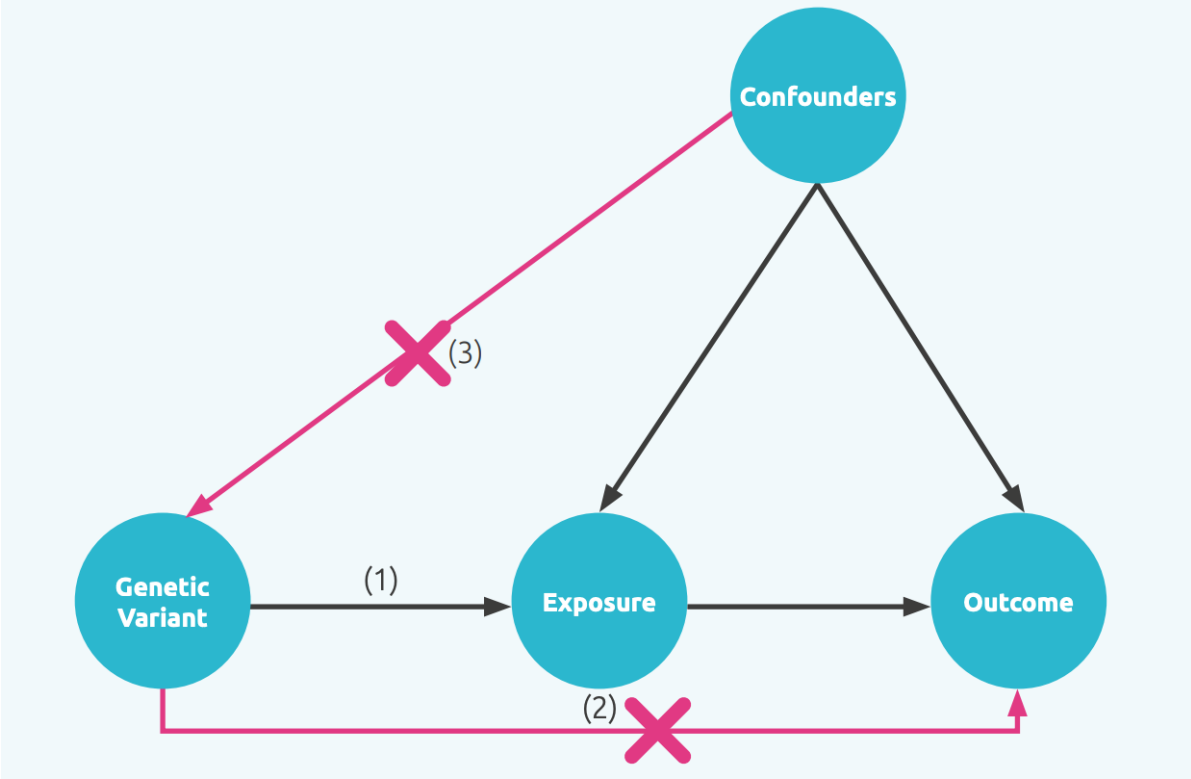
MR Principles

- The genetic variants must be associated with the exposure, (1) This assumption can and should be verified by testing the association between the genetic variants and the exposure within the data being used



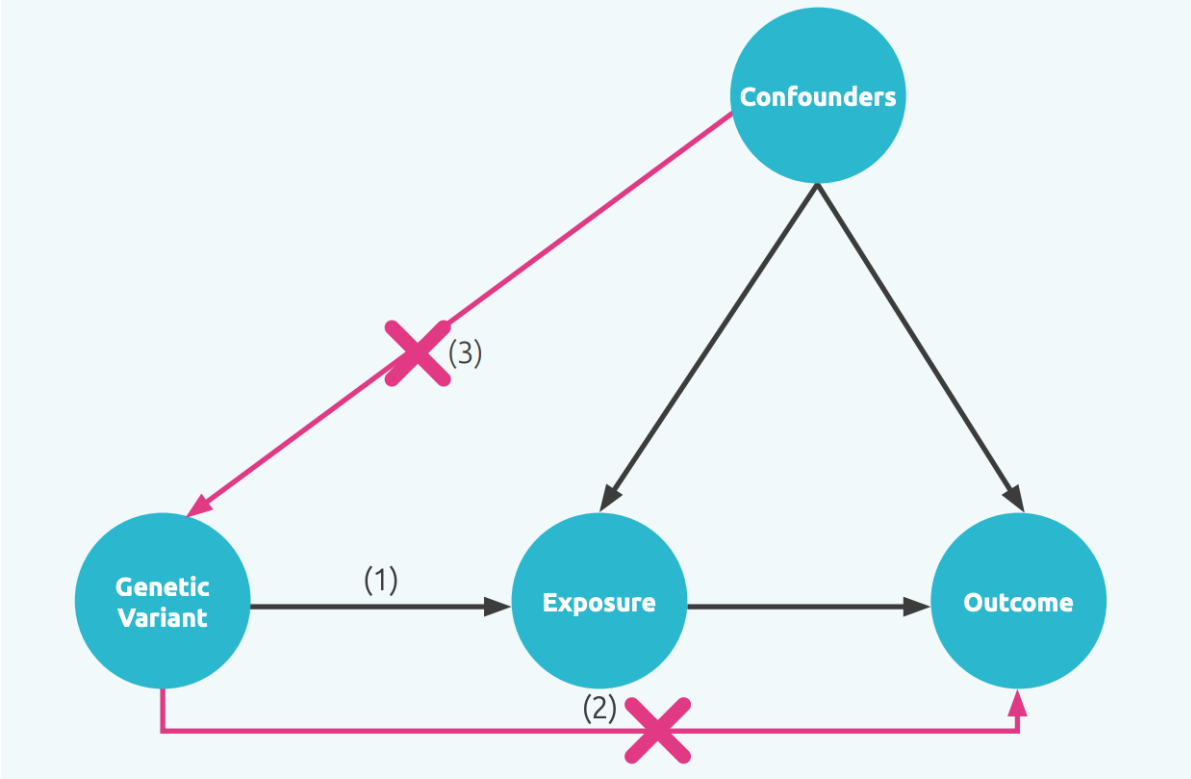
MR Principles

- The genetic variants must not be directly associated with the outcome, (2) We can use biological knowledge about the genetic variants to tell us something about how likely this is, known as horizontal pleiotropy. (There are also a range of sensitivity analyses that can detect and adjust for pleiotropy

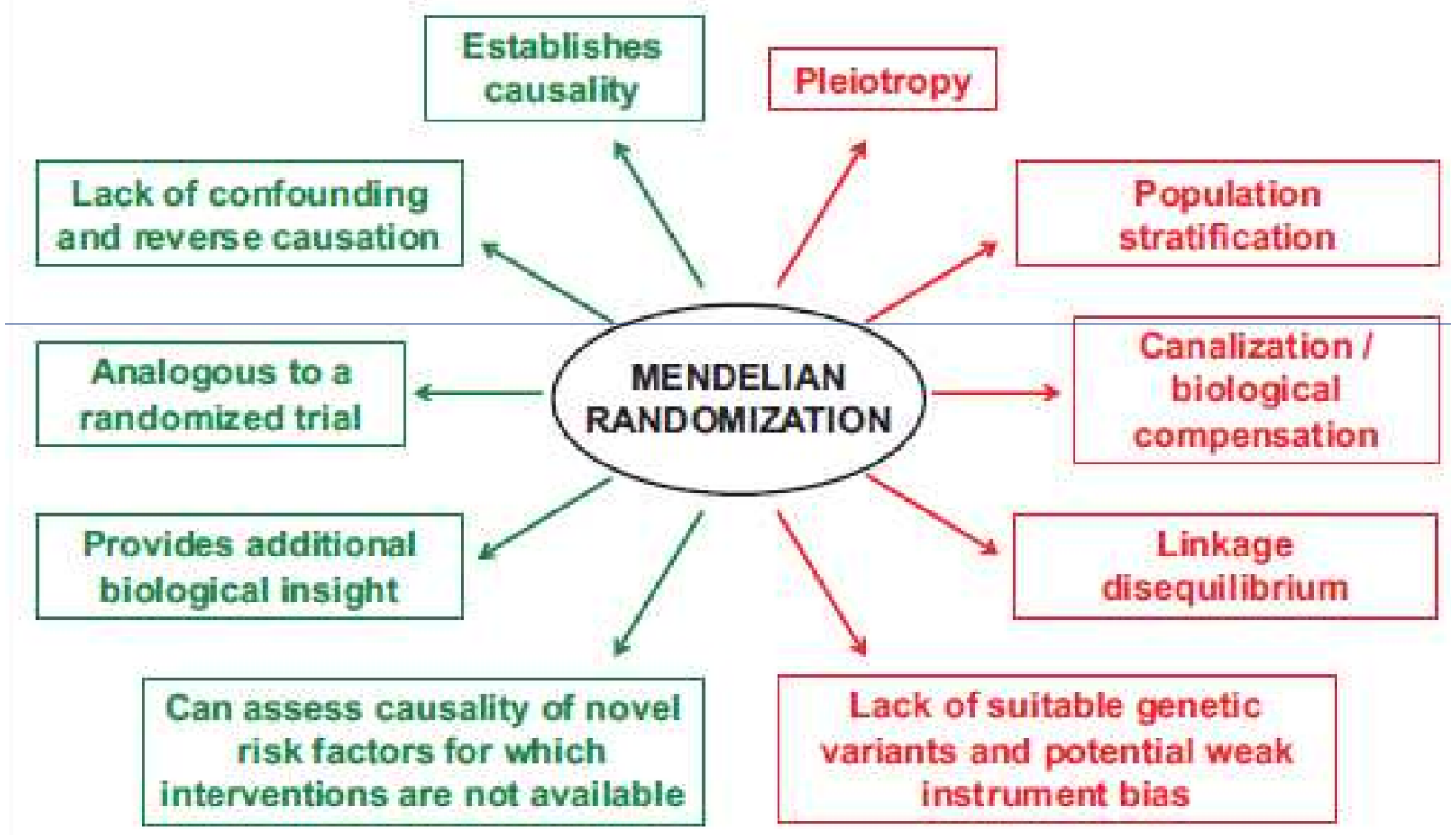


MR Principles

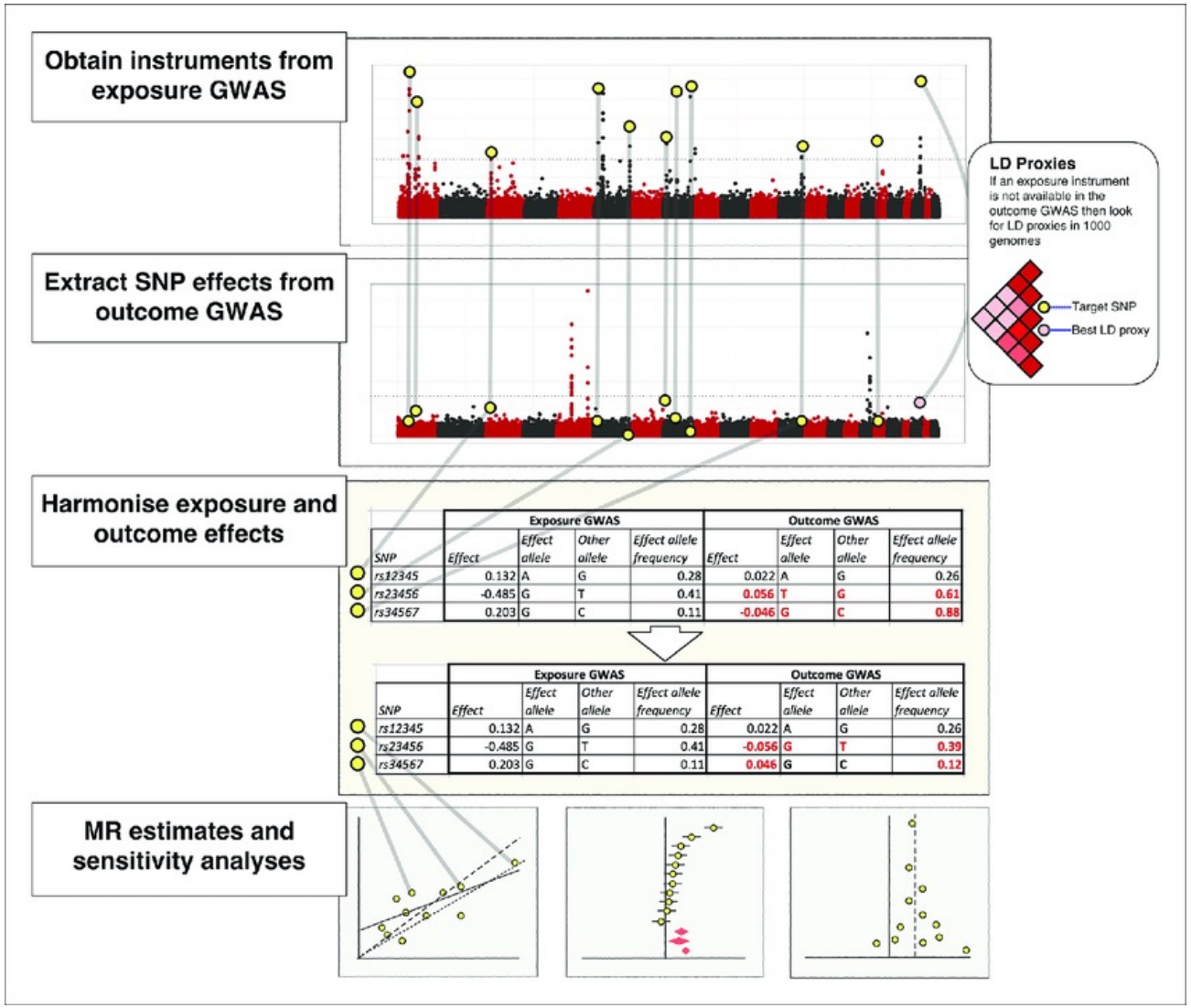
- The genetic variant must not be associated with any potential confounder (3) Confounders can be associated with genetic variants if the choice of partner is non-random, for example if people were more likely to have children with people with similar BMI levels to themselves, or from similar populations (population stratification)



Advantages and limitations of MR



From GWAS to MR overview

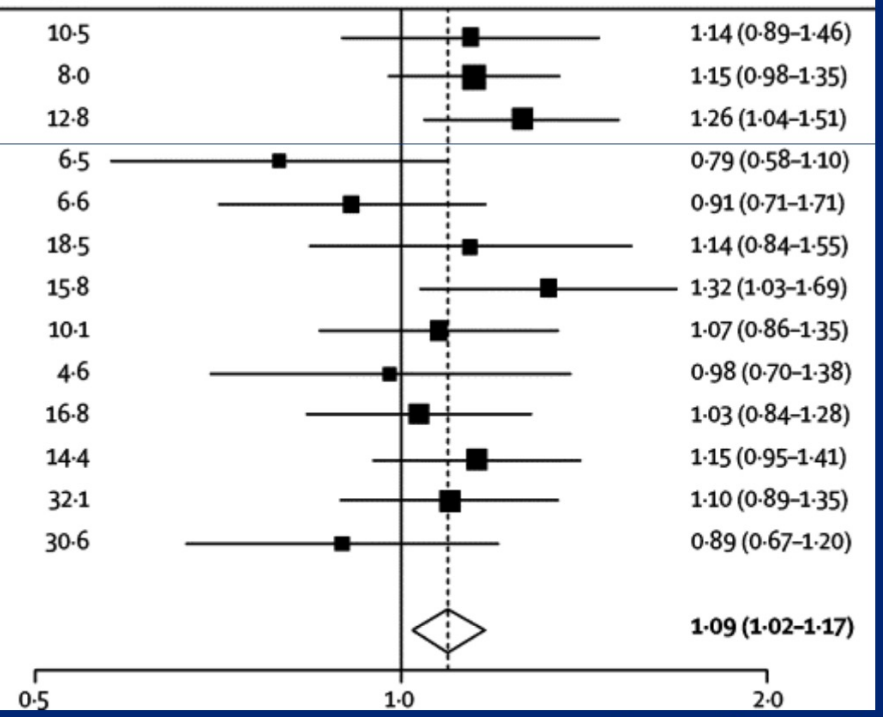


Inconsistent findings of Drug side effects example

Statins and diabetes – the trial evidence

- 91, 140 statin trial participants, of whom 4278 developed diabetes during a mean of 4 years.

	n	Statin		Placebo or control		OR (95% CI)
		Events	Rate	Events	Rate	
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)
Overall (I^2=11·2% [95% CI 0·0–50·2%])						**1·09 (1·02–1·17)**



Sattar et al. Lancet, 2010

Biochemistry insight

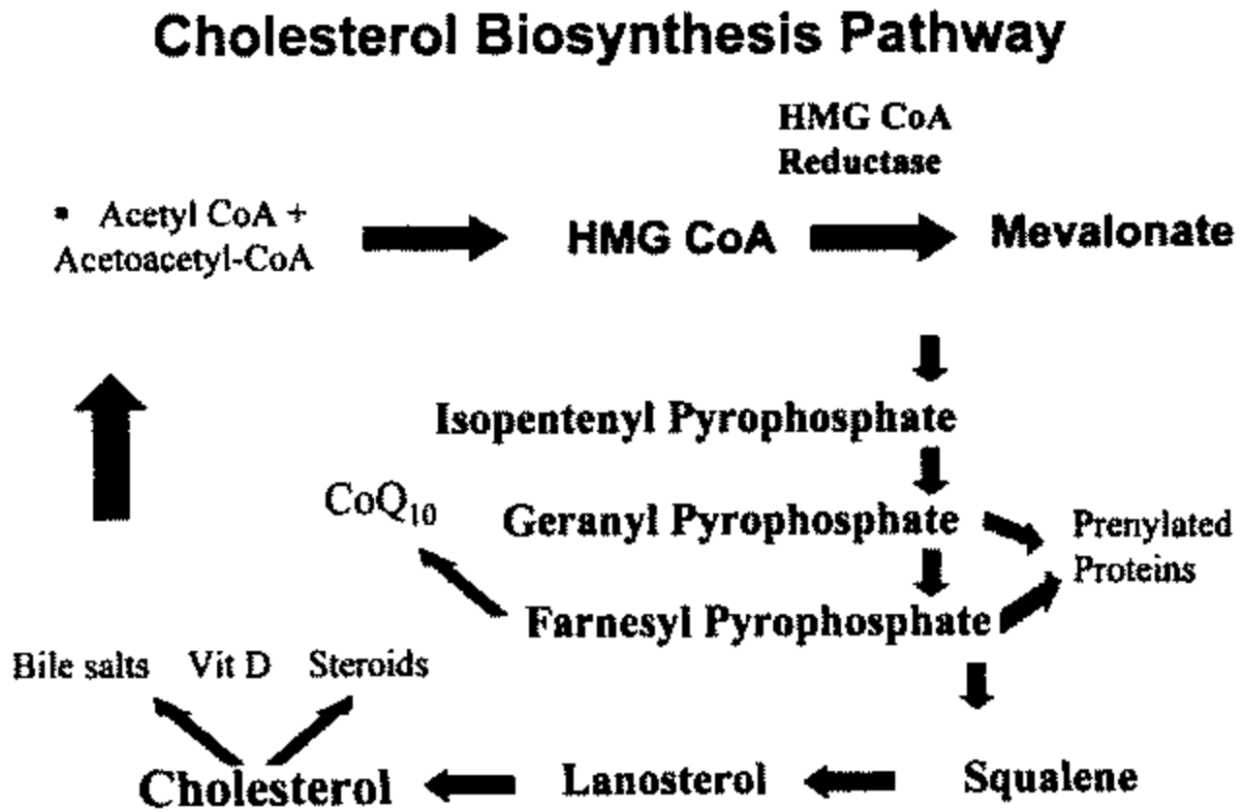
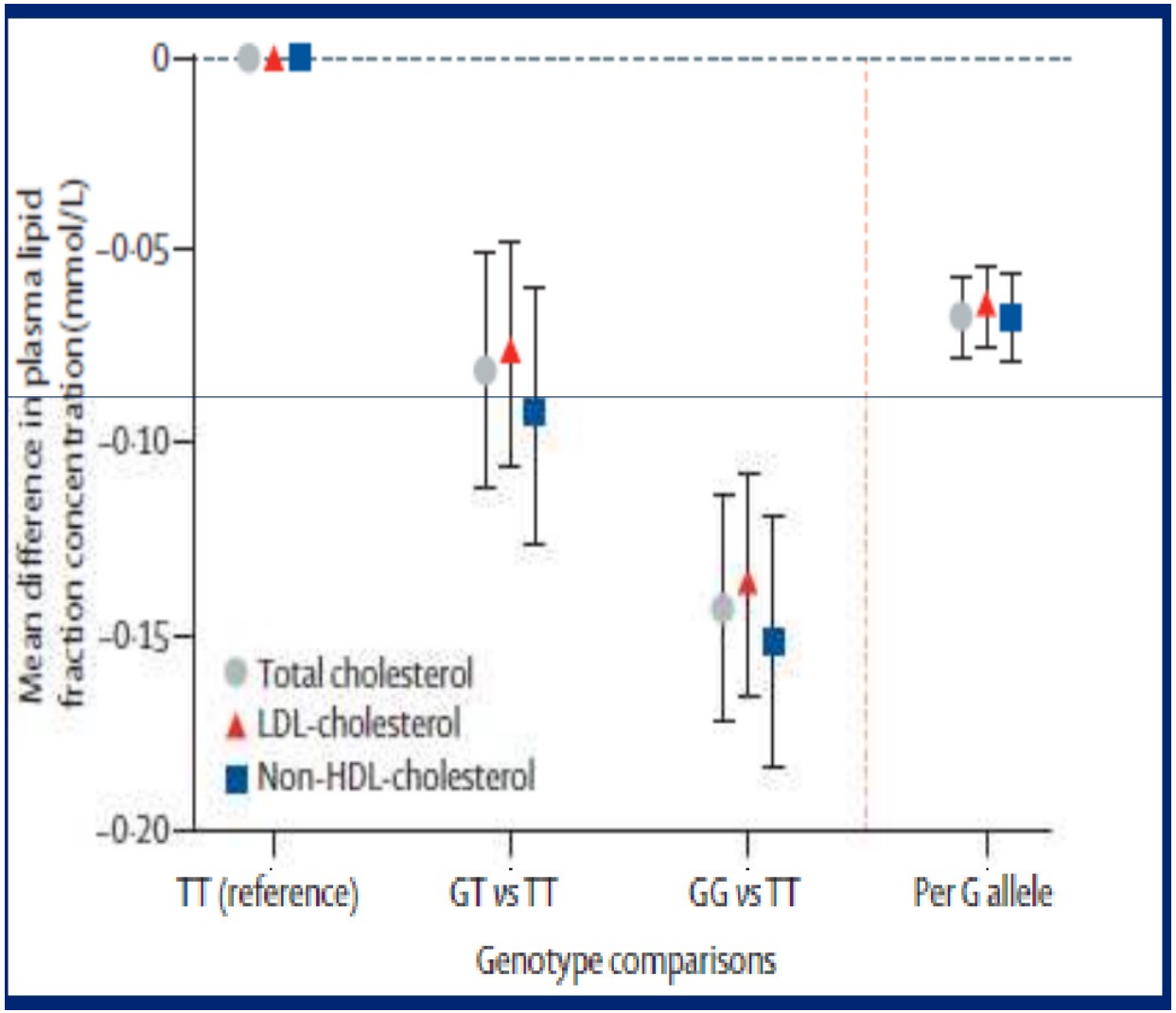


Fig. 1. Cholesterol biosynthesis.

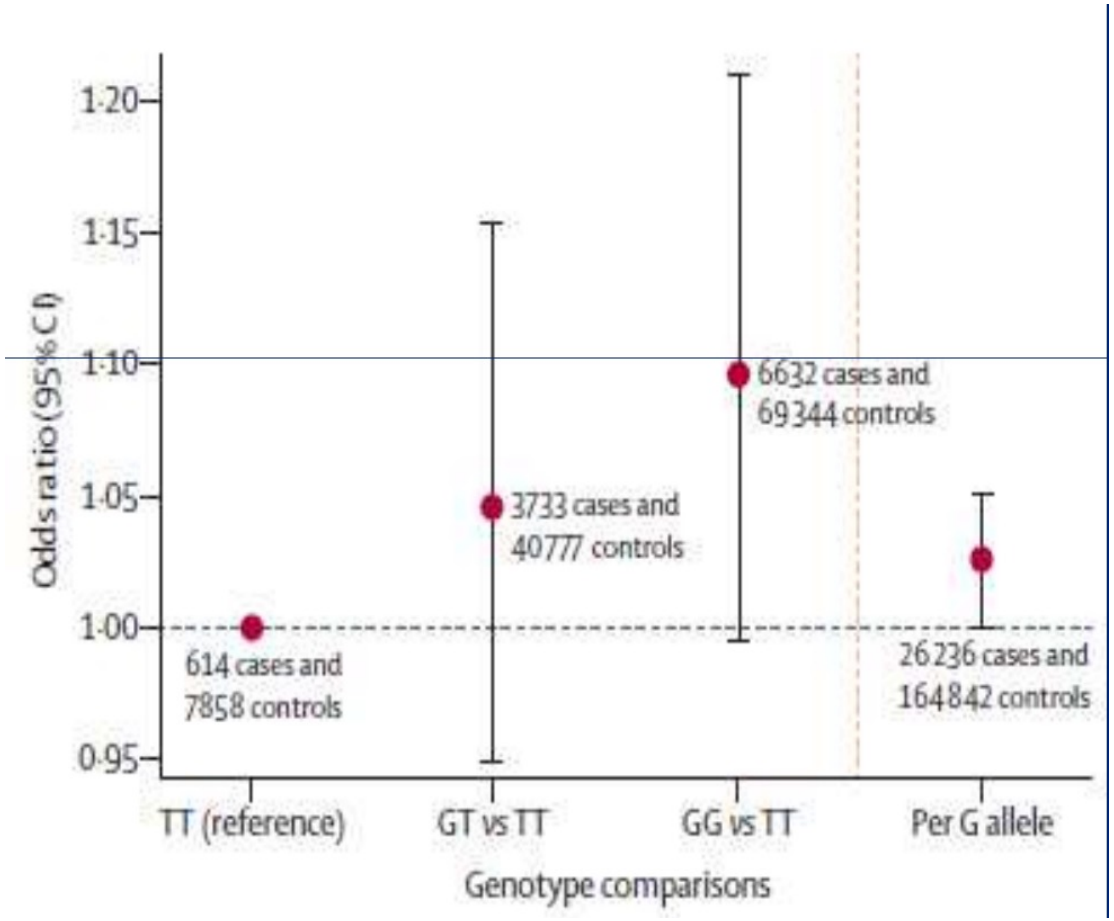
HMGCR variants mimic statins

- Statins exert their action by inhibiting HMGCR, leading to LDL-reduction.
- A HMGCR genetic variant, used as a proxy for statin use, was associated with lower LDL-C

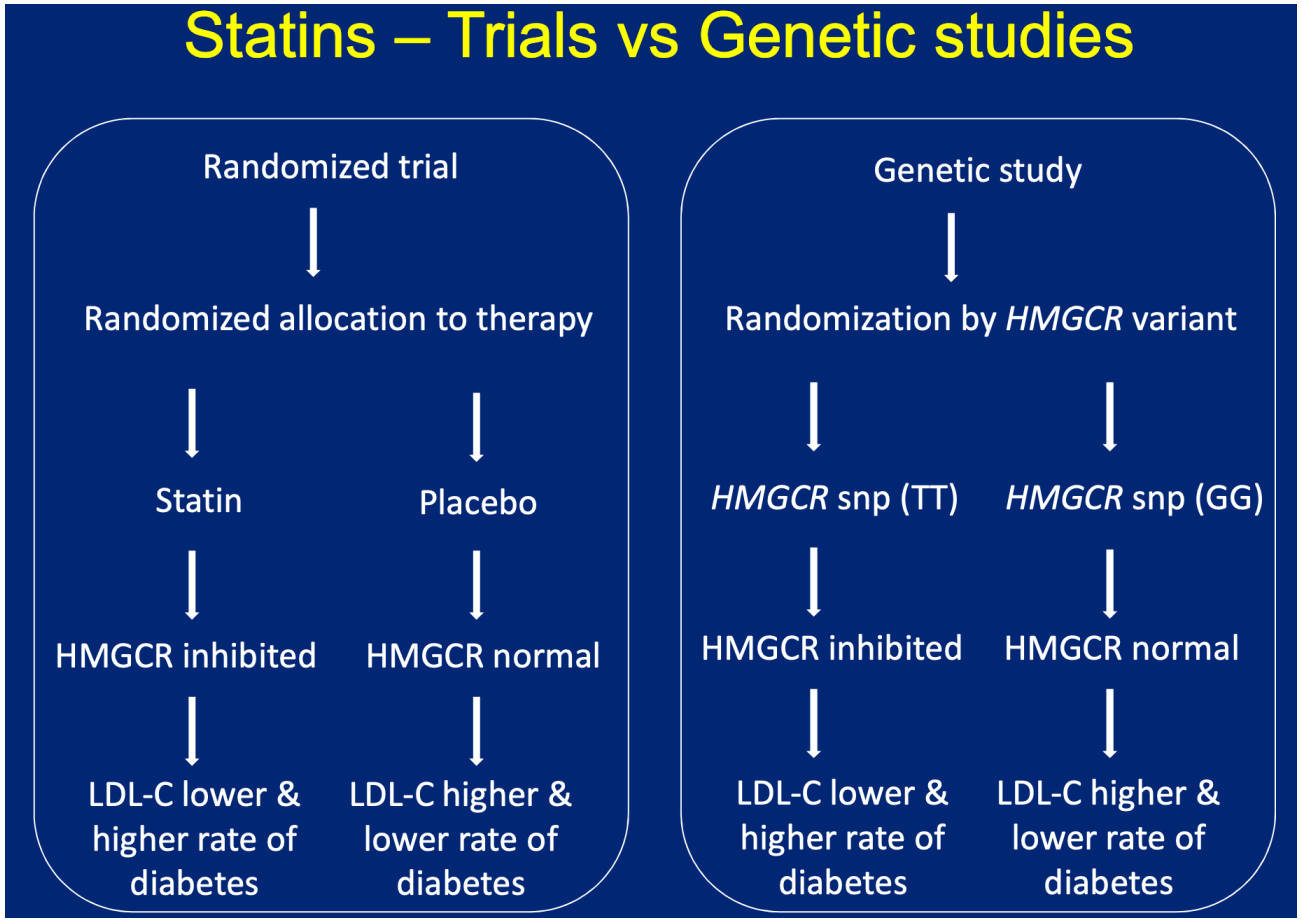


HMGCR and diabetes risk

- The HMGCR genetic variant associated with lower LDL-C was also associated with higher risk of new onset diabetes.
- Impact on diabetes is an on-target effect of HMGCR inhibition.



Statins increase risk of diabetes



Summary

- RCT are not always practical though they are the gold standard
- MR is alternative approach which leverages on Mendelian principle of random assortment
- MR corrects for confounding and not limited by reverse causation
- MR can be applied in multiple causal inference studies such as drug side effects