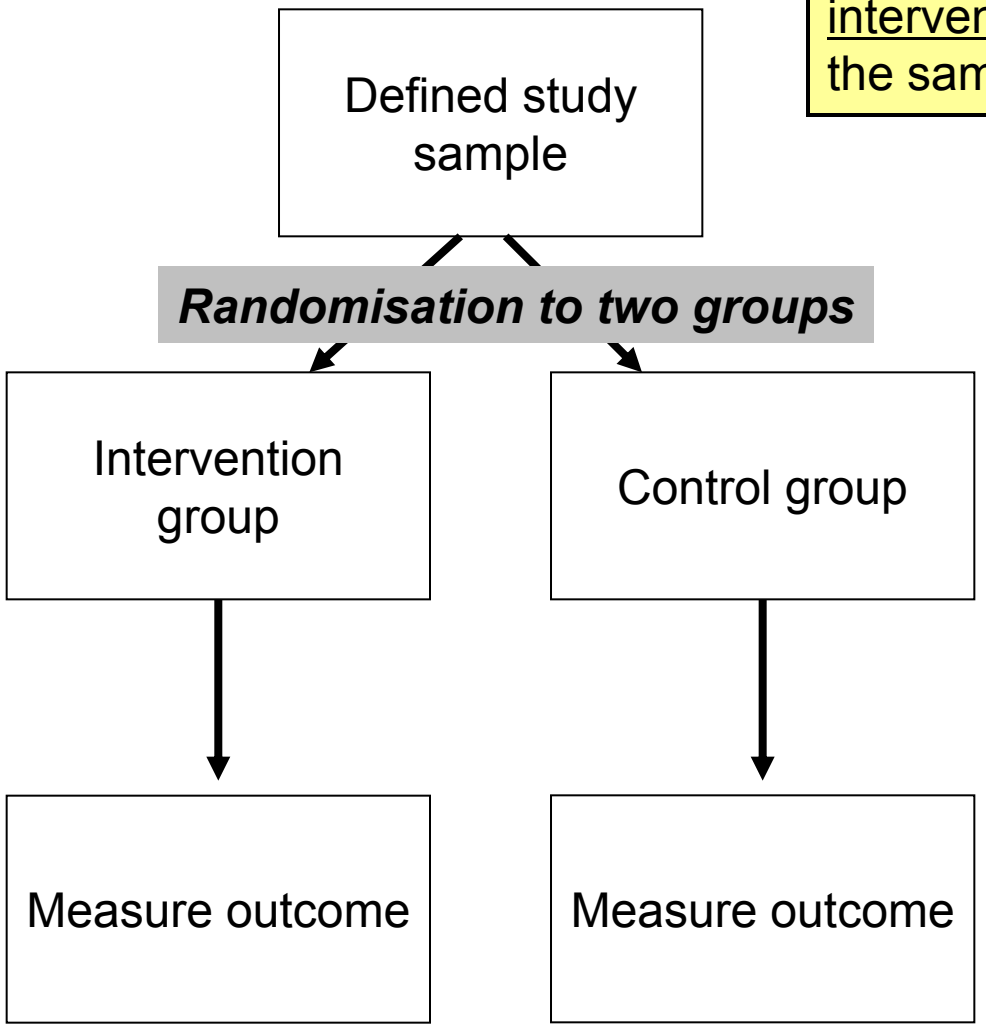
Mendelian randomisation

The RCT concept

Everything except the intervention is (hoped to be) the same in the two groups



Randomisation

- … is allocation of the units of analysis to the different experimental groups or conditions according to chance, such that each unit has an **equal probability of selection into each group**

- Most powerful way of ensuring characteristics **not** systematically allocated to a particular group

- Can randomise in groups (clusters)

The aim of randomisation is to…

create groups that are comparable with respect to known or unknown confounding factors

There are two steps in the process

1. Generating an **unpredictable** allocation sequence e.g. tossing a coin, using a computer random number generator
2. Concealing the allocation sequence from the investigators

Mendelian randomisation studies

Mendelian randomisation studies

- Observational design with (almost) RCT strengths
- Based on Mendel's second law: alleles of different genes assort independently of one another during gamete formation
- Inheritance of one trait should be independent of inheritance of other traits
- Genetic variant used as proxy for exposure is **unrelated** to conventional vascular risk factors and other disease marker

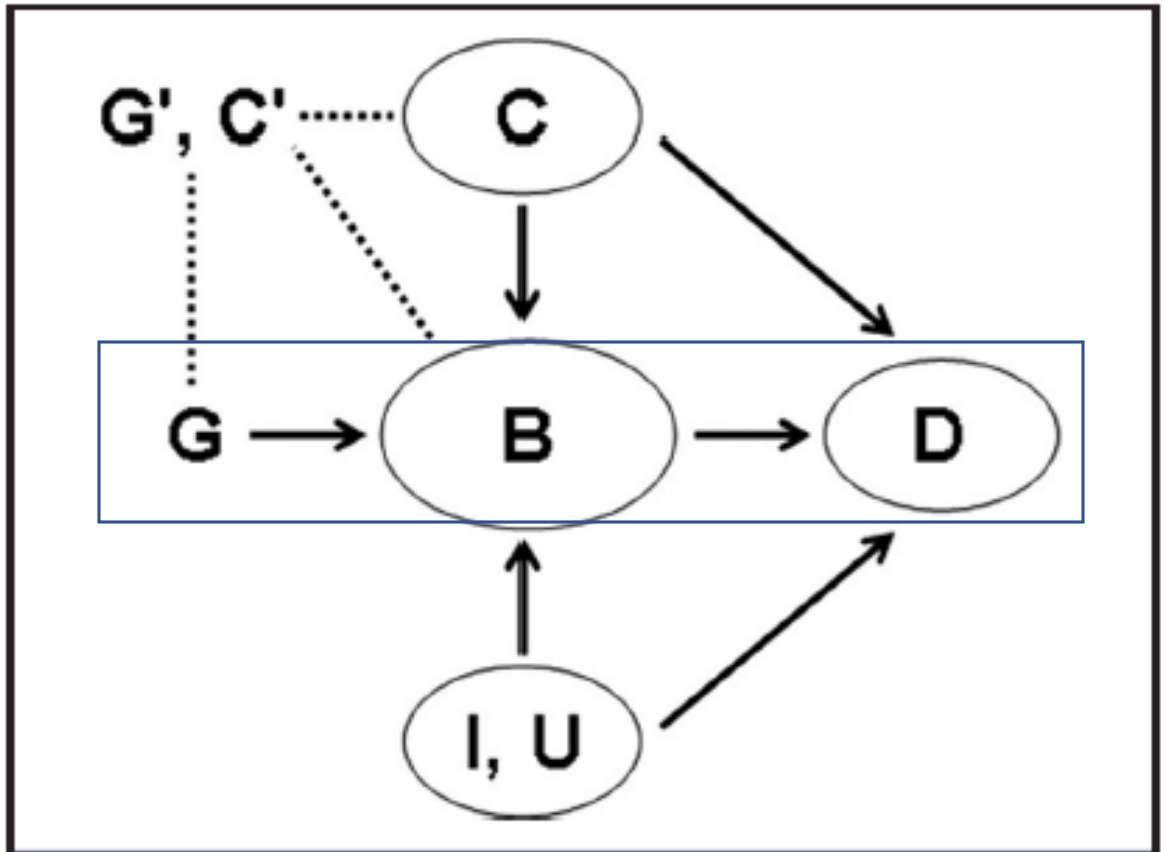
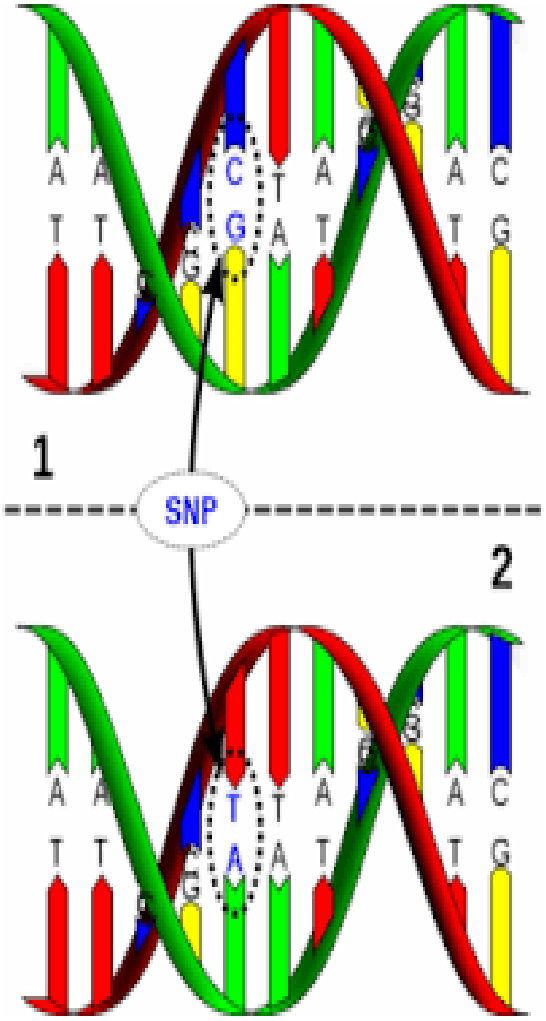


Fig. 1. Conceptualization of Mendelian randomization with interest in the relationship of a biomarker B with disease D with measured confounding variables C, unmeasured confounding variables U, unmeasured processes I affecting B and D, a polymorphism at a genetic locus G related to B, other genetic variants (G′) possibly related to G and B, and other individual characteristics (C′) possibly related to G, B, and D.

Glynn RJ,
Clinical Chemistry 56:3
388–390 (2010)

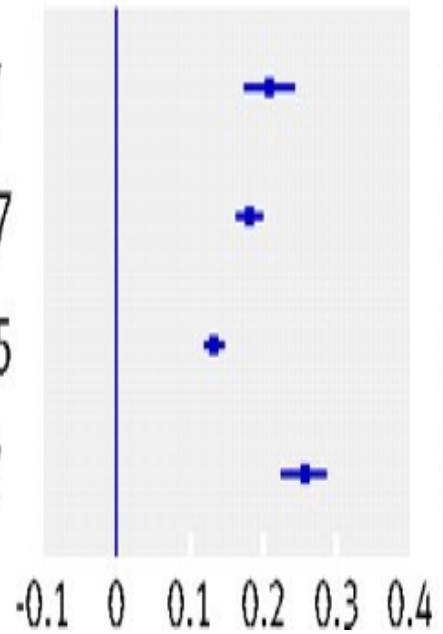
MR studies of biological or behavioural risk factors

- Identify genetic marker (often a SNP)
  - Associated with the risk factor
  - Not associated with the disease via other pathways (i.e. not associated with other risk factors)
- Estimate association between:
  - Genetic markers and RF
  - Observational RF and disease
  - Genetic marker and diseases
- Compare observational and MR associations
- Observational associations can be biased, confounded, MR should be unbiased



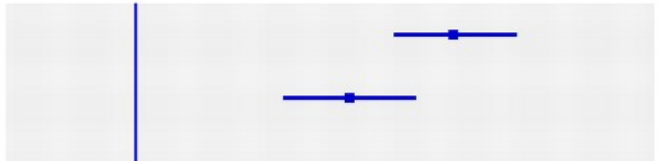
Estimates of association of each single nucleotide polymorphism with ln concentrations of C reactive protein

Single nucleotide polymorphism	Allele frequency*	No of studies/cases /participantst	Per allele higher mean ln CRP (95% CI), mg/L
rs3093077	0.06	19/15 133/96 807	
rs1205	0.67	43/40 527/172 567	
rs1130864	0.30	41/37 145/157 905	
rs1800947	0.94	31/31 636/93 507	



C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) BMJ 2011;342:bmj.d548

Association of (1) circulating concentrations and (2) genetically raised concentrations of C reactive protein (CRP) with risk of coronary heart disease (CHD)

Circulating usual concentrations of CRP	Risk ratio* (95% CI) for CHD per 1 SD higher ln CRP (mg/L)	Risk ratio* (95% CI) for CHD per 1 SD higher ln CRP (mg/L)
Adjusted for age, sex, and ethnicity		1.49 (1.40 to 1.59)
Further adjusted†		1.33 (1.23 to 1.43)

*Corrected for regression dilution in C reactive protein and potential confounding factors

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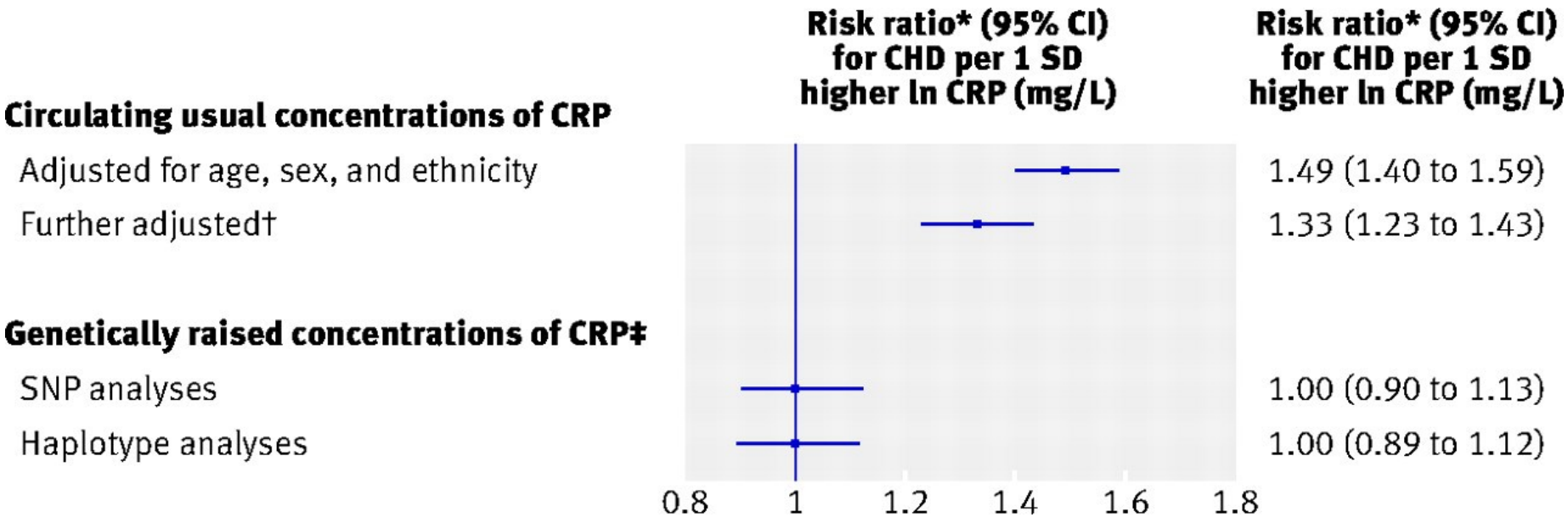
Association of (1) circulating concentrations and (2) genetically raised concentrations of C reactive protein (CRP) with risk of coronary heart disease (CHD)



*Corrected for regression dilution in C reactive protein and potential confounding factors

C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC) BMJ 2011;342:bmj.d548

Assumptions / limitations

- A gene influences disease solely through B. This is unverifiable, as a single gene can influence disease risk through multiple pathways other than B (pleiotropy);
- Other alleles, G', may be correlated with G (linkage disequilibrium) and influence D through other pathways, thereby inducing confounding;
- Other characteristics of individuals at birth, C', that independently predict the development of D can be correlated with G (population stratification) or influence the expression of G (epigenetics),
- Both other alleles and patient characteristics can modify the effect of G on B, the effect of G on D, or both.

Types of comparisons in different types of studies

Study design	Type of comparison
Ecological studies	Comparing disease frequency between populations
Cross-sectional studies	Comparing disease frequency between persons with and without characteristic of interest
Cohort studies	Comparing disease incidence between exposed and unexposed persons
Case-control studies	Comparing frequency of (past) exposure between cases and healthy controls
Interventional studies	Comparing incidence of events in persons exposed to the intervention of interest and in control group
Mendelian randomisation	Comparing frequency of events in persons with and without genotype associated with exposure

hierarchy of major study designs