

# Introduction to Mendelian Randomization: Using genes to inform causality

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# Alcohol and Heart Disease

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## A beer a day keeps the doctor away! Consuming one alcoholic drink daily can reduce your risk of fatal heart disease by up to 20%, study finds

- Harvard experts show benefits to the heart from moderate alcohol consumption
- They looked at data from over 50,000 people all with different levels of intake
- But the researchers stress that exercise is better than alcohol for heart health

By JONATHAN CHADWICK FOR MAILONLINE  
PUBLISHED: 22:00 AEDT, 6 May 2021 | UPDATED: 00:31 AEDT, 7 May 2021

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Consuming a moderate amount of **alcohol** daily can reduce the risk of dying from a major cardiovascular event by up to 20 per cent, scientists reveal.

The researchers have linked moderate alcohol intake – defined as no more than one alcoholic drink for women and two for men per day – with a 20 per cent lower risk of dying from cardiovascular disease (CVD), in a sample of more than 50,000 people.

Interestingly, this percentage decrease was in comparison to people from the sample who had low alcohol intake – defined as less than one drink a week.

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## Drinking a small glass of red wine a day could help avoid age-related health problems like diabetes, Alzheimer's and heart disease, study finds

- Chemical compound called resveratrol is found in skin of grapes and red wine
- In small doses it mimics the hormone oestrogen and associated health benefits
- Imitating the hormone triggers production of key proteins called sirtuins
- These keep the body healthy and prevent development of age-related conditions

By JOE PINKSTONE FOR MAILONLINE  
PUBLISHED: 02:58 AEDT, 4 April 2020 | UPDATED: 10:38 AEDT, 4 April 2020

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Having a small glass of red wine with dinner every night could help fend off age-related diseases, a study suggests.

The tippie is rich in a chemical called resveratrol which, in small doses, imitates oestrogen and triggers production of anti-ageing proteins called sirtuins.

Sirtuins help protect against diseases such as Type 2 diabetes, osteoporosis,

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## Now even sticking to medics' alcohol guidelines is bad for your health! Risk of heart problems could be increased even if you drink less than NHS weekly units, study suggests

- A study of 300,000 people found beer, cider and spirits increased health risks
- Moderate wine drinking appears to slightly reduce risks of cardiovascular events
- Drinking beer, cider and spirits can increase the risk of stroke by 30 per cent

By VICTORIA ALLEN FOR THE DAILY MAIL  
PUBLISHED: 11:05 AEDT, 28 January 2022 | UPDATED: 19:00 AEDT, 28 January 2022

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It is bad news for those who enjoy a swift pint or the occasional gin and tonic.

But even fewer than the **NHS** recommended 14 units of **alcohol** a week could increase the risk of heart problems, if your tippie of choice is beer, cider or spirits.

A study of more than 300,000 people found drinking wine appears to slightly reduce the risk of hospitalisation and death from a cardiovascular event such as a

(A) Alcohol increases risk of heart disease

(C) No causal relationship

(B) Alcohol decreases risk of heart disease

(D) Don't know

# “Bad” LDL Cholesterol and Heart Disease



## 'No evidence' having high levels of bad cholesterol causes heart disease, claim 17 physicians as they call on doctors to 'abandon' statins

- Researchers have warned statins offer no protection to millions of people
- The findings add to the ever-growing row over the cholesterol-busting pills
- High levels of LDL-C has been considered a major cause of heart disease
- The new study, of almost 1.3 million patients, shows there is no such link

By STEPHEN MATTHEWS ASSISTANT HEALTH EDITOR FOR MAILONLINE  
PUBLISHED: 22:07 AEDT, 17 September 2018 | UPDATED: 17:11 AEDT, 18 September 2018



No evidence exists to prove that having high levels of bad cholesterol causes heart disease, leading physicians have claimed.

Researchers have warned statins - cholesterol-busting drugs - offer no protection to millions of people and doctors should 'abandon' them.

The findings add fuel to the ever-growing, controversial row over statins, as cardiologists continue to disagree on whether the cheap pills have any benefit.



## Statins 'may be a waste of time': Controversial report claims there's NO link between 'bad cholesterol' and heart disease

- For decades doctors have prescribed statins to reduce the risk of heart attacks and strokes caused by 'bad' cholesterol in the blood
- But now a team of scientists say taking the pills may be a waste of time
- They found no link between high LDL cholesterol and heart disease

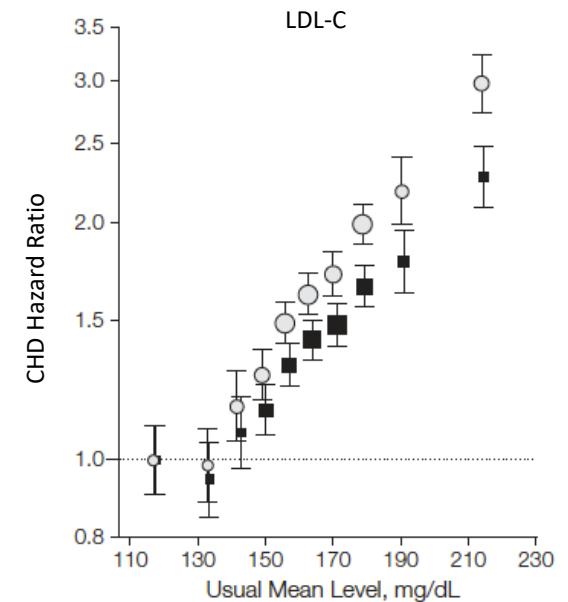
By BEN SPENCER MEDICAL CORRESPONDENT FOR THE DAILY MAIL  
PUBLISHED: 09:03 AEDT, 13 June 2016 | UPDATED: 18:55 AEDT, 13 June 2016



For years doctors have prescribed statins to reduce the risk of heart attacks and strokes caused by 'bad' cholesterol in the blood.

But now a team of scientists say taking the pills may be a waste of time for the over-60s - because they found no link between high levels of LDL cholesterol and heart disease.

In fact, this 'bad' cholesterol may even have a protective effect by warding off infections and disease, including cancer.



(A) High LDL decreases risk of heart disease

(B) High LDL increases risk of heart disease

(C) LDL is not causally related to heart disease

# "Good" HDL Cholesterol and Heart Disease



## Are scientists about to reverse their support for 'good' cholesterol? For years we were told it reduces the risk of a heart attack, but new research may be about to change that advice

- Doctors have been advising patients to take 'good' cholesterol when possible
- They warned against LDL, which is deemed bad and promoted HDL as good
- However, new research indicates that very high HDL levels could be bad
- Patients with too much 'good' cholesterol could be at higher risk of heart attack

By BARNEY CALMAN FOR THE MAIL ON SUNDAY

PUBLISHED: 07:01 AEDT, 14 June 2020 | UPDATED: 18:07 AEDT, 14 June 2020



For decades we've been told there's 'good' cholesterol and there's 'bad' cholesterol.

The bad type, known as LDL, is responsible for damaging blood vessel walls and contributes to the build-up of inflamed fatty deposits known as plaques, which raises the risk of a heart attack or stroke.

The good type, called HDL, does the opposite - clearing away cholesterol in plaques



## 'Good' cholesterol isn't so great after all: NIH study finds higher levels of HDL DON'T reduce heart disease risk

- 'Good' cholesterol helps remove other forms of cholesterol from the blood
- It helps keep risks of heart attack and cardiovascular disease in check
- Too-high HDL levels were not associated with reduced cardiovascular disease

By CASSIDY MORRISON SENIOR HEALTH REPORTER FOR DAILYMAIL.COM

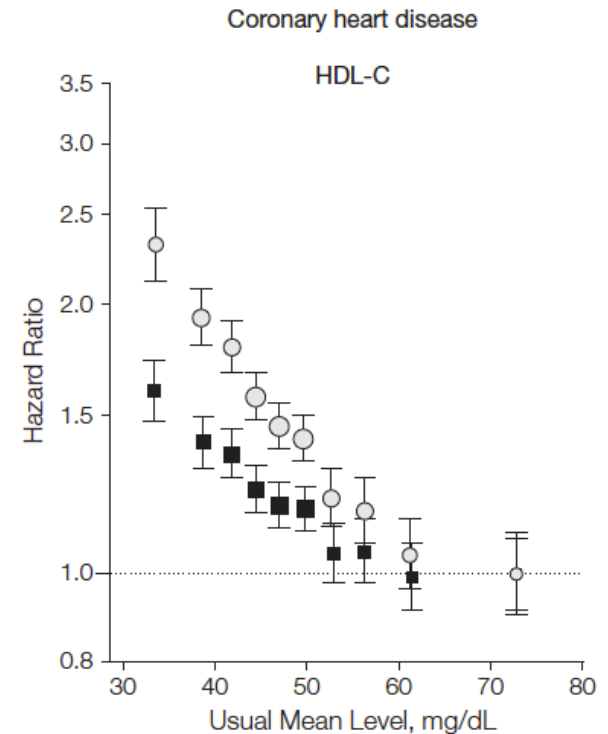
PUBLISHED: 06:51 AEDT, 22 November 2022 | UPDATED: 07:03 AEDT, 22 November 2022



There may be no such thing as 'good' cholesterol after all, a federally-funded study suggests.

Researchers found that high levels of high-density lipoprotein (HDL) were not associated with a lower risk of developing heart disease.

HDL absorbs cholesterol in the arteries and ferries it back to the liver, which then flushes it from the body. For this reason it had been dubbed 'good' cholesterol.



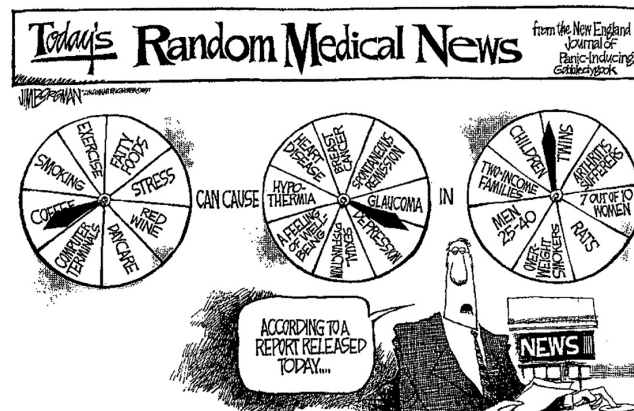
(A) High HDL decreases risk of heart disease

(B) High HDL increases risk of heart disease

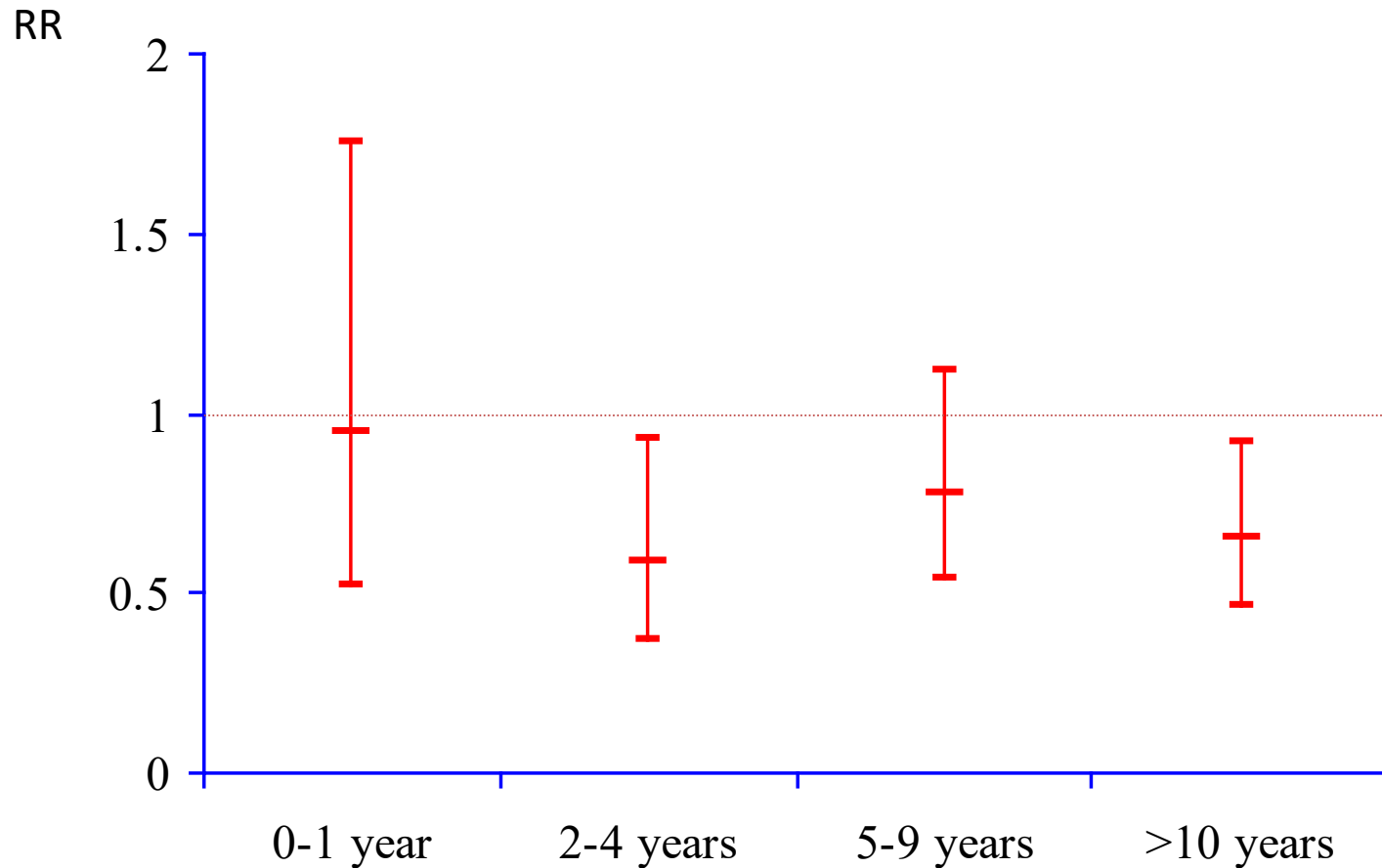
(C) HDL is not causally related to heart disease



# Problems with inferring causality in observational studies

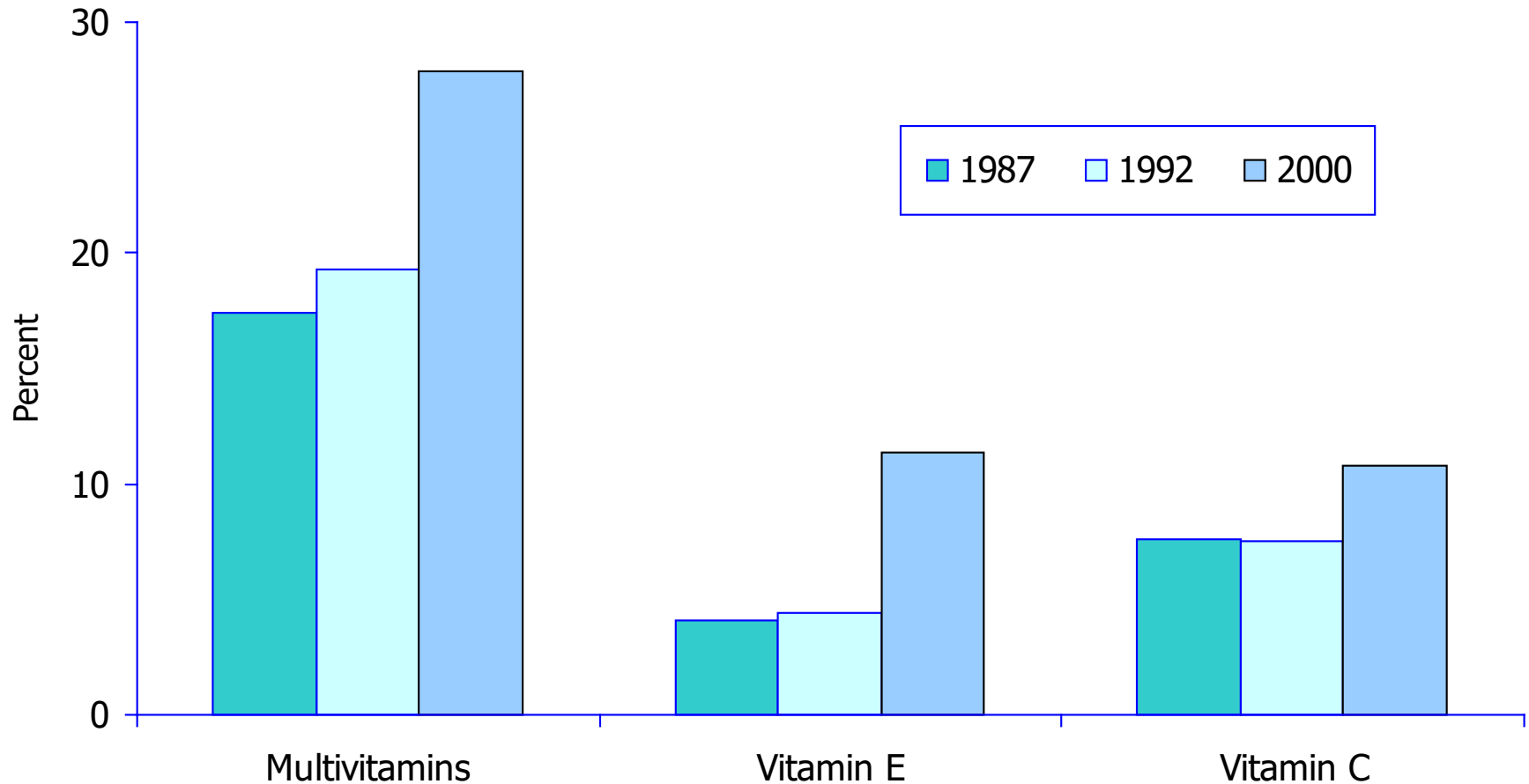


# CHD risk according to duration of current Vitamin E supplement use compared to no use

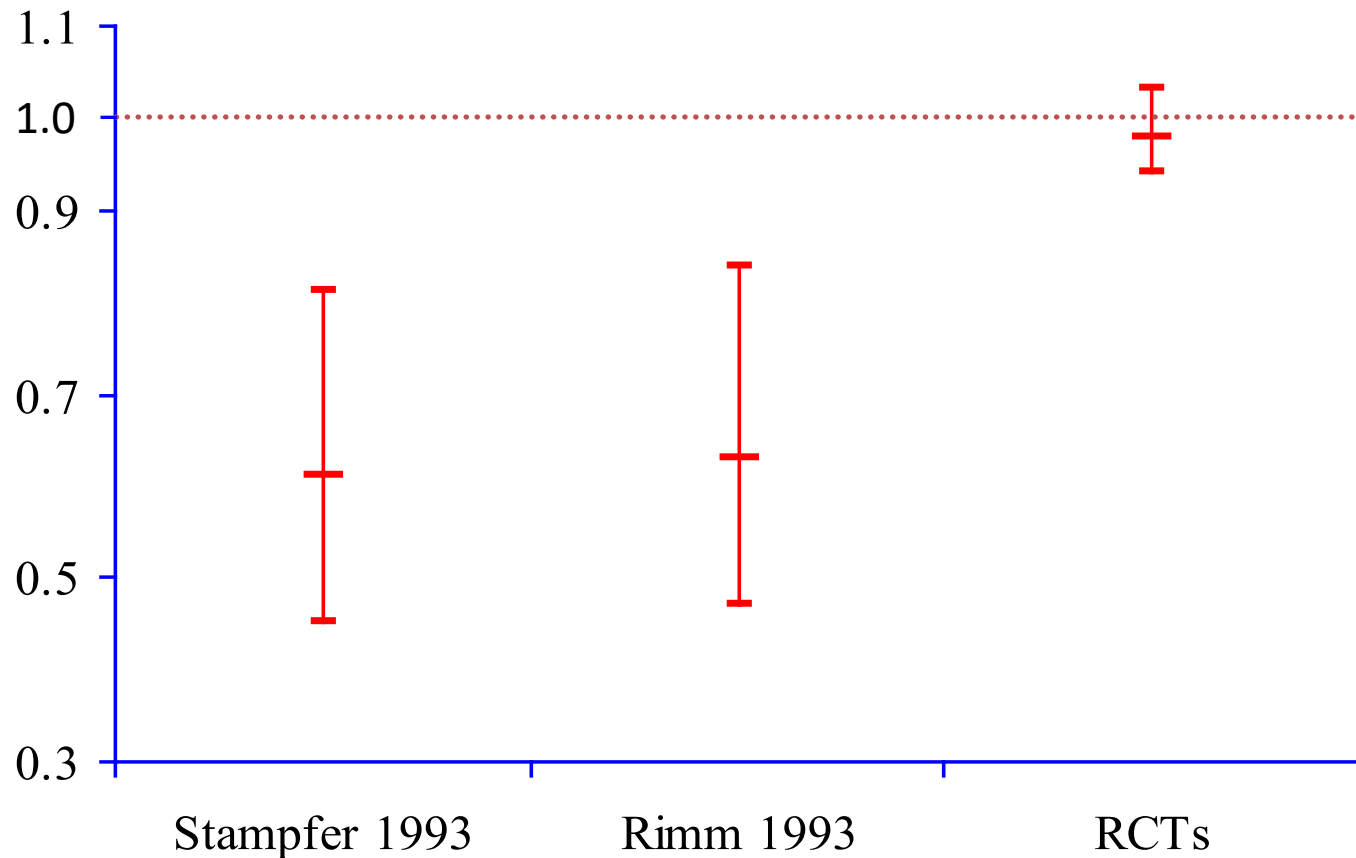


Rimm et al NEJM 1993; 328: 1450-6

# Use of vitamin supplements by US adults, 1987-2000



# Vitamin E supplement use and risk of Coronary Heart Disease



Stampfer et al NEJM 1993; 328: 144-9; Rimm et al NEJM 1993; 328: 1450-6; Eidelman et al Arch Intern Med 2004; 164:1552-6



## **MANY OTHER EXAMPLES**

**VITAMIN C, VITAMIN A, HRT,  
MANY DRUG TARGETS.....**

## **WHAT'S THE EXPLANATION?**

# Vitamin E levels and confounding risk factors:

Childhood SES



Manual social class



No car access



State pension only



Smoker



Obese



Daily alcohol



Exercise



Low fat diet



Height



Leg length

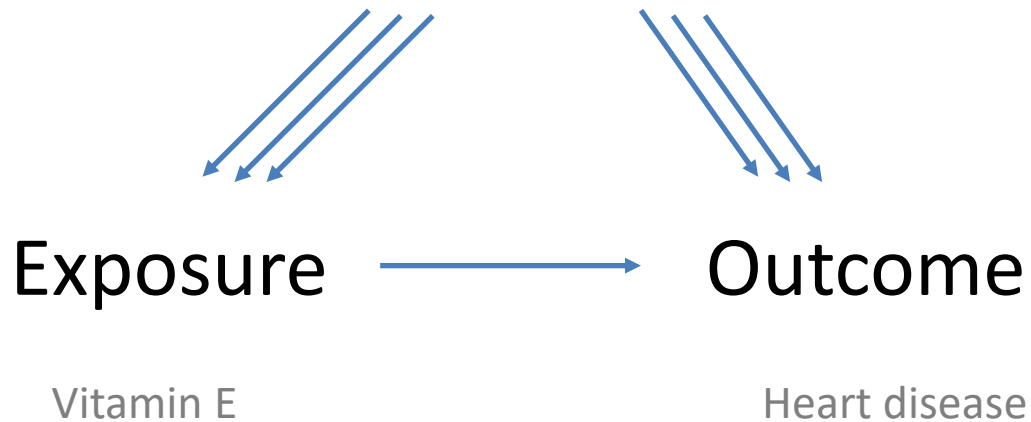


Women's Heart and Health Study  
Lawlor et al, Lancet 2004

# Confounding

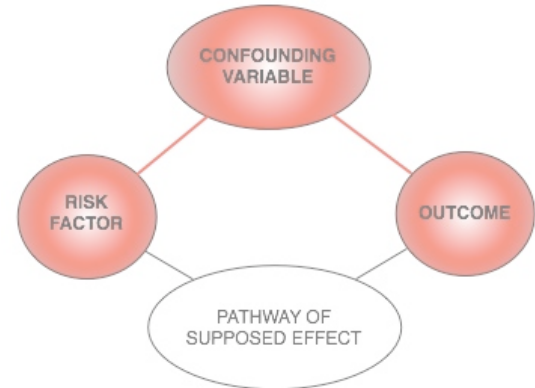
Smoking, diet, alcohol, socioeconomic position....

## Confounders



# Classic limitations to “observational” science

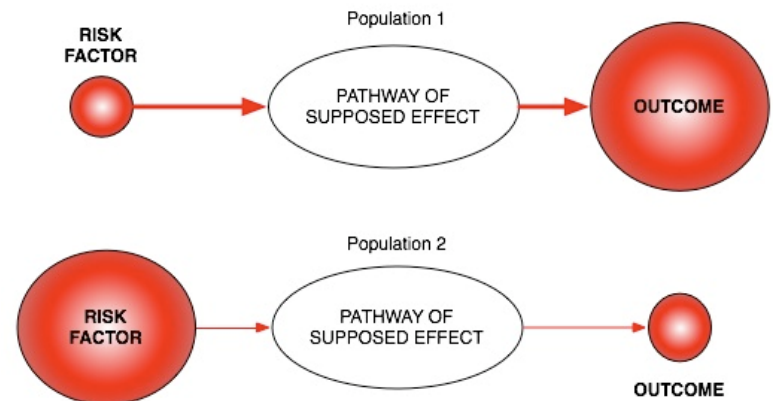
- **Confounding**



- **Reverse Causation**

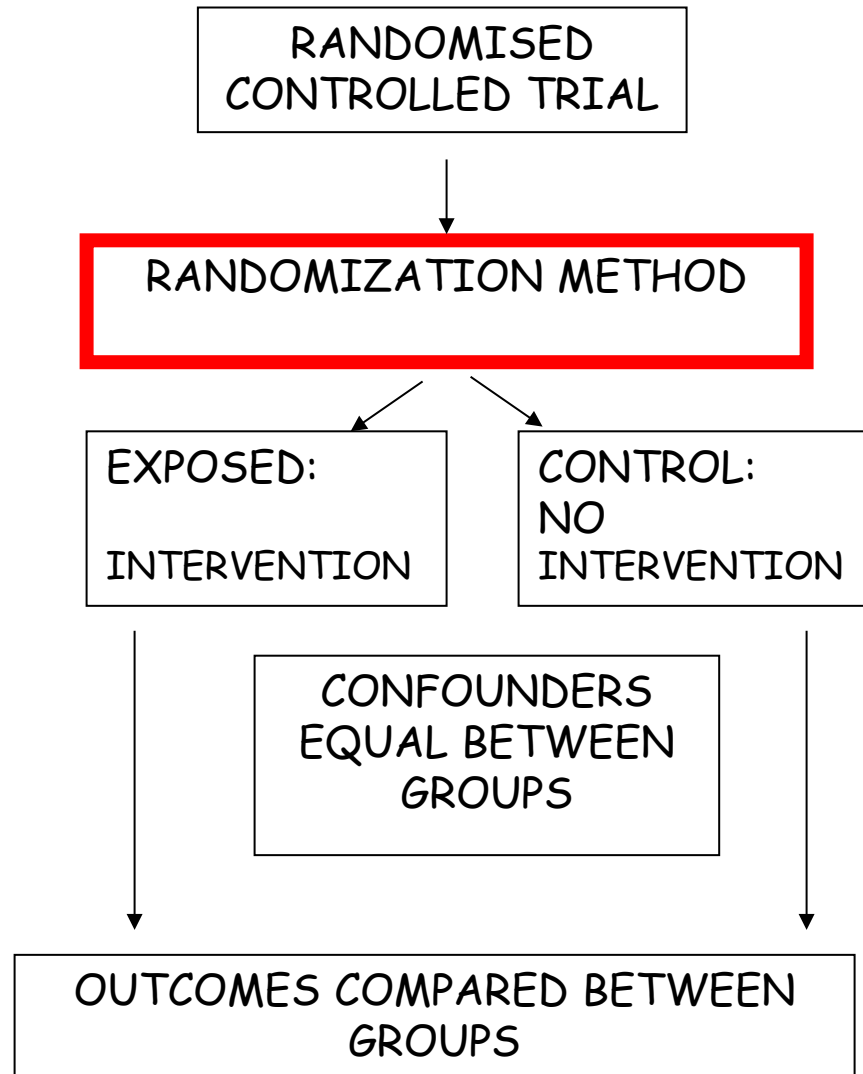


- **Bias**



# 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 eg anything toxic
  - Expensive, requires experimentation in humans
  - Impractical for 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)  
eg case-control studies or cohort studies
  - Reliably assigning causality in these types of studies is *very limited*



How does Mendelian  
randomization work?

# What does MR do?

- **Assess causal relationship between two variables**
- **Estimate magnitude of causal effect**

How does it do this?

By harnessing Mendel's laws of inheritance

# Mendel's Laws of Inheritance



Mendel in 1862

1. **Segregation:** alleles separate at meiosis and a randomly selected allele is transmitted to offspring
2. **Independent assortment:** alleles for separate traits are transmitted independently of one another

# Mendelian randomization and RCTs

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

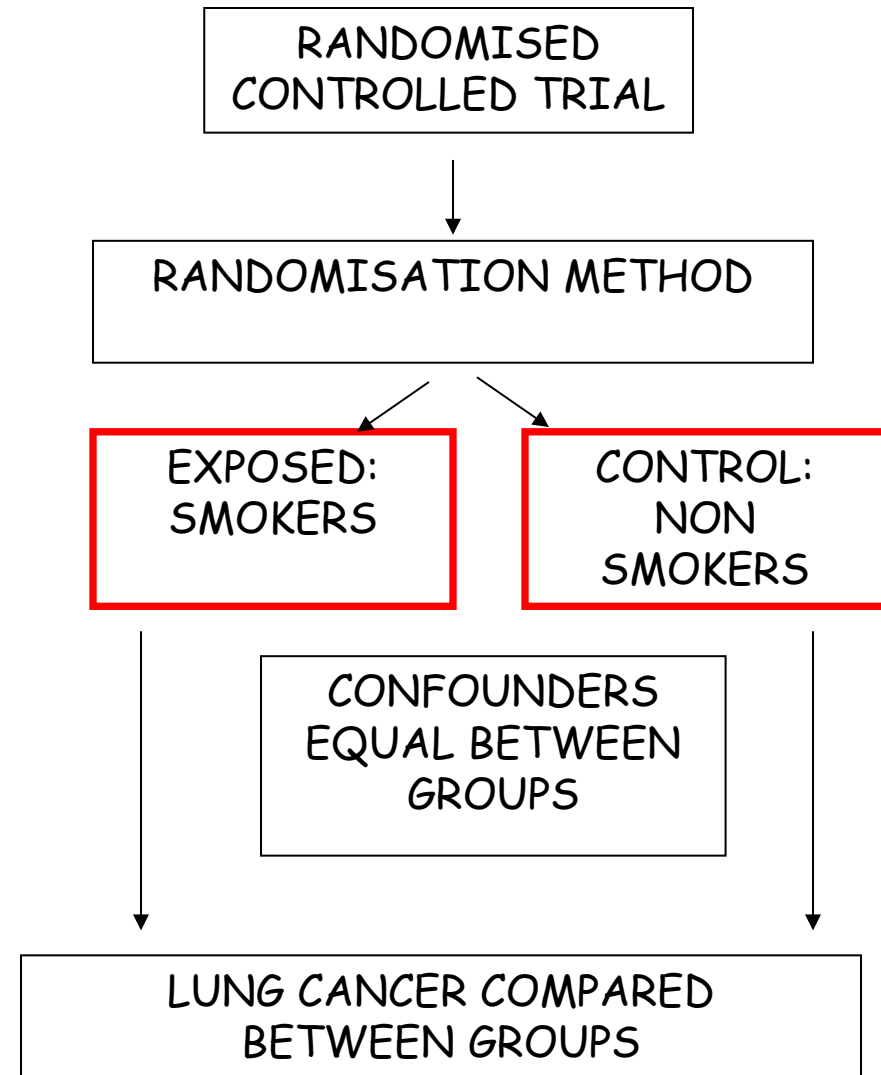
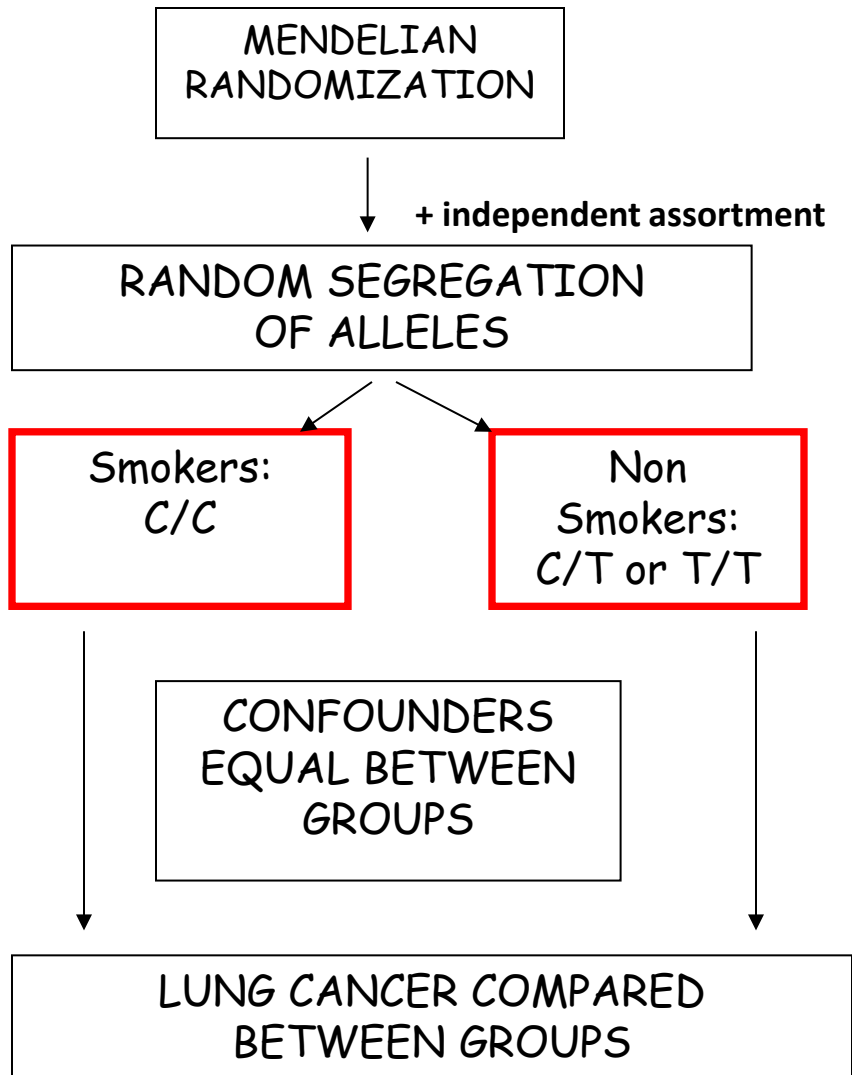
EXPOSED:  
INTERVENTION

CONTROL:  
NO  
INTERVENTION

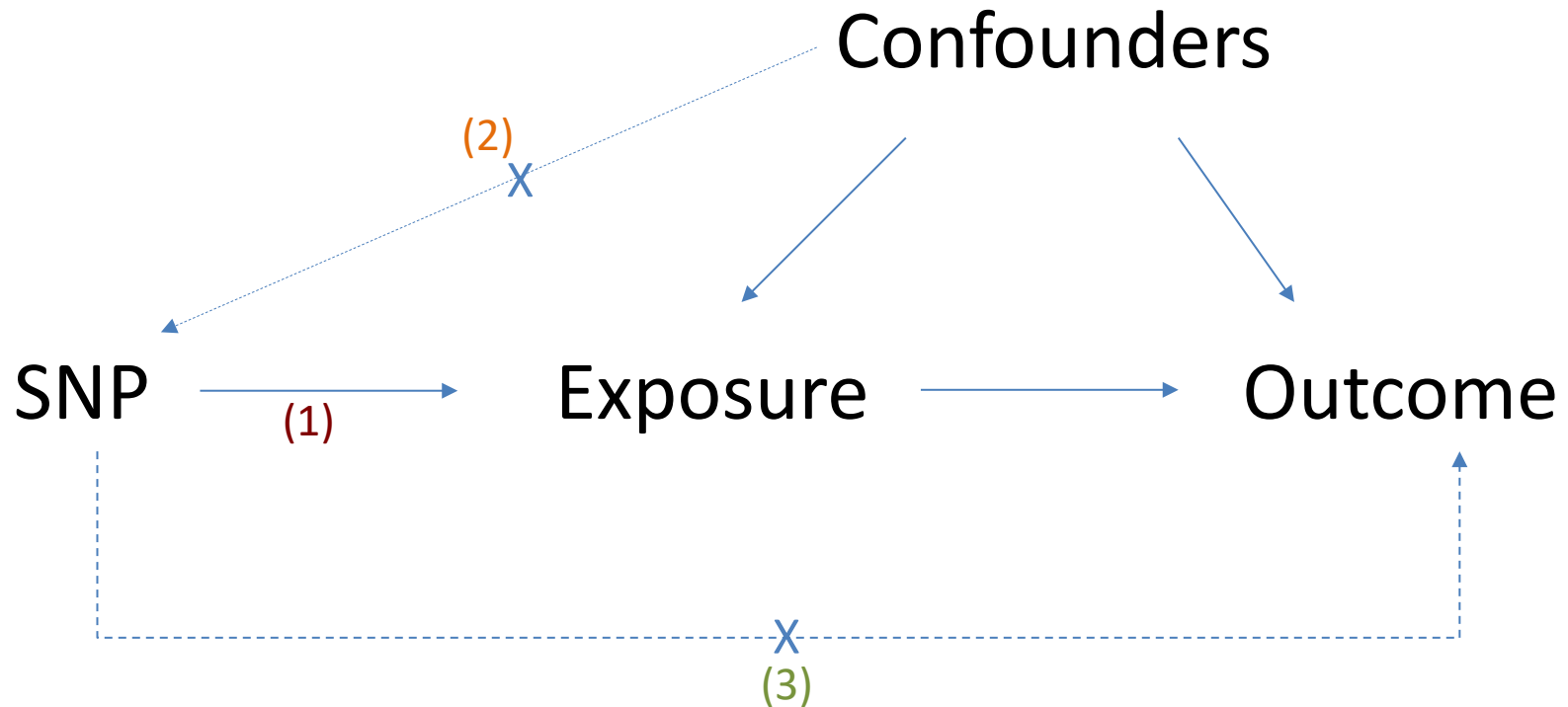
CONFOUNDERS  
EQUAL BETWEEN  
GROUPS

OUTCOMES COMPARED BETWEEN  
GROUPS

# Mendelian randomization: Smoking and Lung Cancer



# Mendelian Randomization: 3 Core Assumptions



(1) SNP is associated with the exposure

(2) SNP is NOT associated with confounding variables

(3) SNP ONLY associated with outcome through the exposure

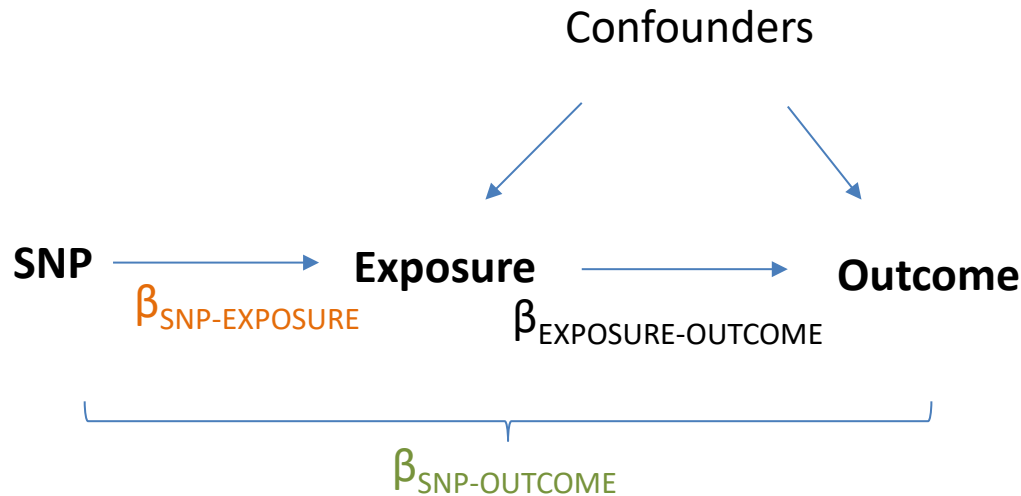


# Why are genetic associations special?

- Robustness 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 are **potentially** very good instrumental variables
- Using genetic variants as IVs is a special case of IV analysis, known as Mendelian randomization

# Calculating causal effect estimates

# Calculating Causal Effect Estimates



After SNP identified robustly associated with exposure of interest:

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

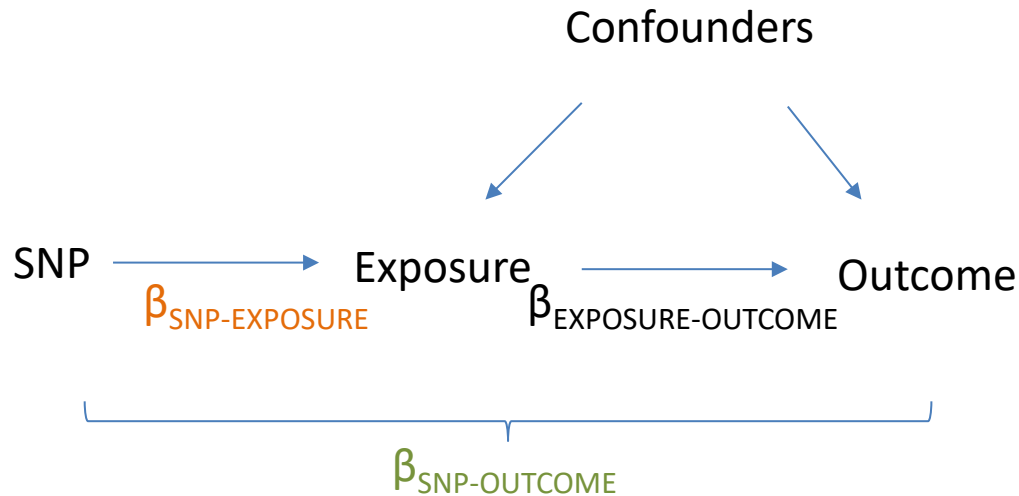
# Calculating Causal Effect Estimates



- (1) Regress exposure on SNP and obtain predicted values of the exposure (STAGE 1)
- (2) Regress outcome on predicted values of the exposure (STAGE 2)
- (3) Adjust standard errors
- (4) Slope of 2<sup>nd</sup> stage regression is the estimate of the causal effect

\*Needs to be done in the one sample ("One sample MR")

# Calculating Causal Effect Estimates



**Causal effect by  
Wald Estimator\* :**

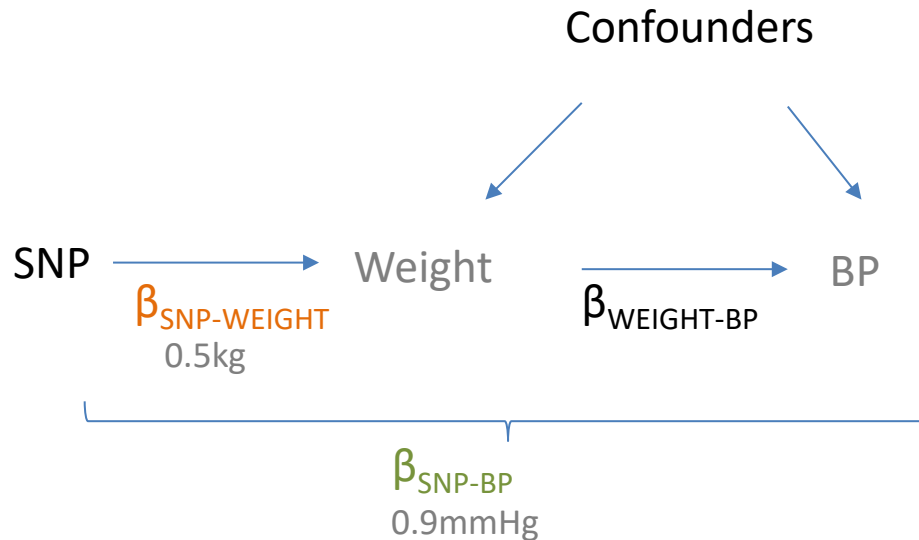
$$\frac{\hat{\beta}_{\text{SNP-OUTCOME}}}{\hat{\beta}_{\text{SNP-EXPOSURE}}}$$

$$\beta_{\text{SNP-OUTCOME}} = \beta_{\text{EXPOSURE-OUTCOME}} \times \beta_{\text{SNP-EXPOSURE}}$$

\*Can be used in different samples (“Two sample MR”)

\*Approximate SEs can be obtained by:  $SE(\beta_{\text{EXPOSURE-OUTCOME}}) \cong \frac{\sigma_{\text{SNP-OUTCOME}}}{\beta_{\text{SNP-EXPOSURE}}}$

# Calculating Causal Effect Estimates



**Causal effect by  
Wald Estimator\* :**

$$\frac{\hat{\beta}_{\text{SNP-OUTCOME}}}{\hat{\beta}_{\text{SNP-EXPOSURE}}}$$

= change in outcome  
per unit change in exposure

BP and weight:

$$\frac{0.9 \text{ mmHg/allele}}{0.5 \text{ kg/allele}}$$

$$= 1.8 \text{ mmHg/kg}$$

\*Can be used in different samples (“Two sample MR”)

\*Approximate SEs can be obtained by:  $SE(\beta_{\text{EXPOSURE-OUTCOME}}) \cong \frac{\sigma_{\text{SNP-OUTCOME}}}{\beta_{\text{SNP-EXPOSURE}}}$



# MR can also be performed using just the results from GWAS

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

# The Wide Applicability of MR

- Traditional Observational Epidemiological Studies
- Behavior Genetics and the Social Sciences
- Molecular Studies
- Pharmacogenomics

# An Example using Mendelian randomization

# MR Example using CRP

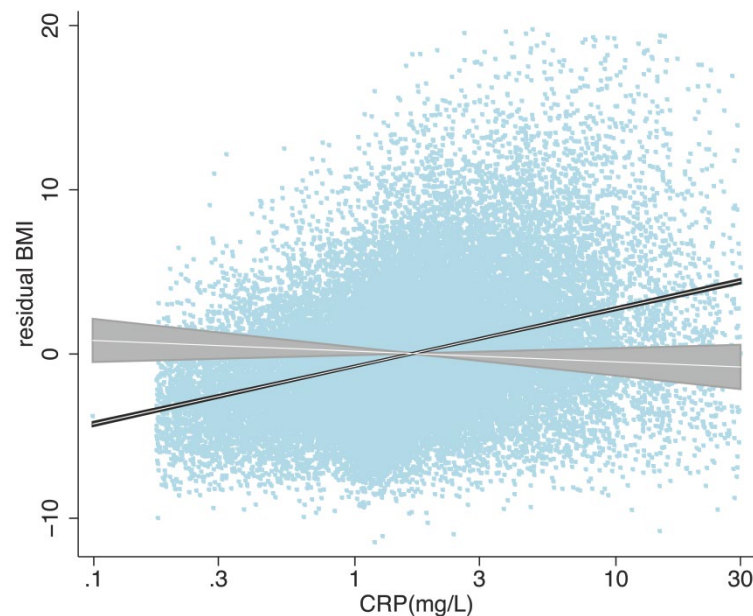
- C-Reactive Protein (CRP) is a biomarker of inflammation
- It is associated with BMI, metabolic syndrome, CHD and a number of other diseases
- It is unclear whether these observational relationships are causal or due to confounding or reverse causality
- This question is important from the perspective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

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



- **NB.** Note that the CRP SNP is an excellent instrument because (1) it is strongly related to CRP levels, and (2) because it is in the CRP gene itself, its effect is more likely to be mediated through changes in the level of CRP (i.e. less potential for horizontal pleiotropy)

	Effect estimates				
	Observational	MR Estimate	$P_{IV}$	$P_{diff}$	$F_{first}$
CRP -> BMI	1.58 (1.53 – 1.62)	-0.30 (-0.78 – 0.18)	0.2	<0.00001	78.3



$P_{IV}$ - Test of whether MR causal effect estimate different from zero

$P_{diff}$ - Test of whether Observational and MR causal effect estimates are different from each other

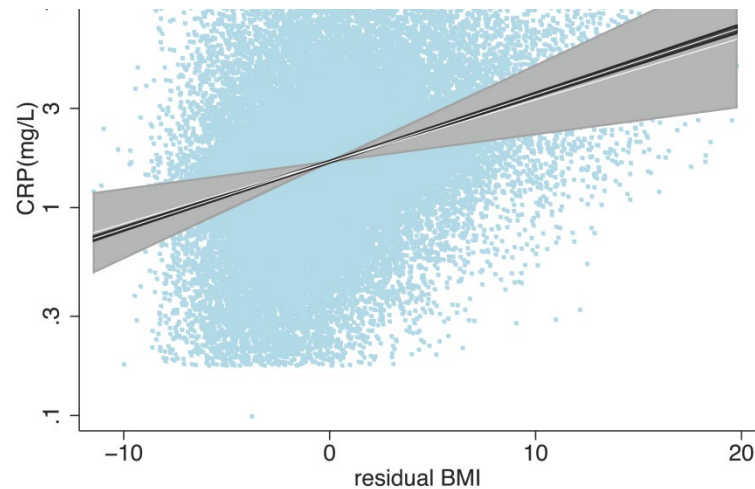
$F_{first}$ - Test of how strong the instrument for CRP is



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



	Effect estimates				
	Observational	MR Estimate	$P_{IV}$	$P_{diff}$	$F_{first}$
BMI -> CRP	1.075 (1.073 – 1.077)	1.06 (1.02 – 1.11)	0.002	0.6	50.2



$P_{IV}$ - Test of whether MR causal effect estimate different from zero

$P_{diff}$ - Test of whether Observational and MR causal effect estimates are different from each other

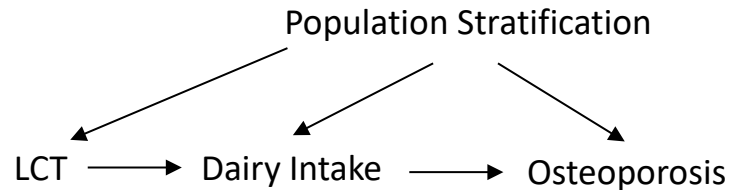
$F_{first}$ - Test of how strong the instrument for BMI is

# Limitations to Mendelian randomization

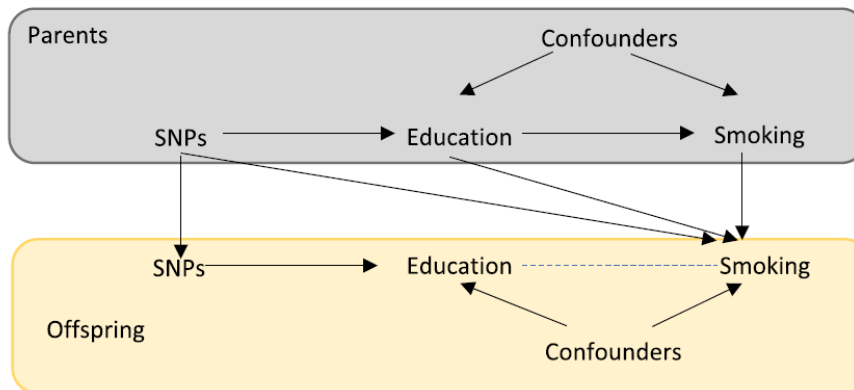
# Limitations to Mendelian Randomization

- 1- Population stratification/Dynastic Effects/Assortative Mating
- 2- Power and “weak instrument bias”
- 3- Pleiotropy

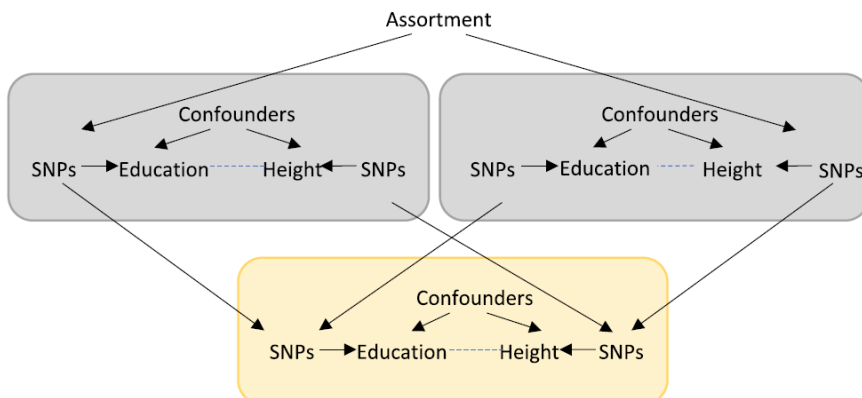
# Pop Strat/Dynastic Effects/Assortment



**Population Stratification**



**Dynastic Effects**



**Assortment**

Davies et al (2019) *Hum Mol Genet*

#### 4 INVITED REVIEW ARTICLE

## Within family Mendelian randomization studies

Neil M Davies<sup>1,2,\*†</sup>, Laurence J Howe<sup>1,2</sup>, Ben Brumpton<sup>1,3,4</sup>,  
Alexandra Havdahl<sup>1,5,6</sup>, David M Evans<sup>1,7</sup> and George Davey Smith<sup>1,2</sup>

<sup>1</sup>Medical Research Council Integrative Epidemiology Unit, University of Bristol, Bristol, BS8 2BN, United Kingdom. <sup>2</sup>Population Health Sciences, Bristol Medical School, University of Bristol, Barley House, Oakfield Grove, Bristol, BS8 2BN, United Kingdom. <sup>3</sup>K.G. Jebsen Center for Genetic Epidemiology, Department of Public Health and Nursing, NTNU, Norwegian University of Science and Technology, Trondheim, Norway <sup>4</sup>Clinic of Thoracic and Occupational Medicine, St. Olavs Hospital, Trondheim University Hospital, Trondheim, Norway <sup>5</sup>Nic Waals Institute, Lovisenberg Diaconal Hospital, Oslo, Norway <sup>6</sup>Department of Mental Disorders, Norwegian Institute of Public Health, Oslo, Norway <sup>7</sup>University of Queensland Diamantina Institute, University of Queensland, Brisbane, 4102, Australia

\*To whom correspondence should be addressed at: IEU Admin team. Tel: 0117 3310099; Fax: 0117 3314052; Email: neil.davies@bristol.ac.uk

### Abstract

Mendelian randomization (MR) is increasingly used to make causal inferences in a wide range of fields, from drug development to etiologic studies. Causal inference in MR is possible because of the process of genetic inheritance from parents to offspring. Specifically, at gamete formation and conception, meiosis ensures random allocation to the offspring of one allele from each parent at each locus, and these are unrelated to most of the other inherited genetic variants. To date, most MR studies have used data from unrelated individuals. These studies assume that genotypes are independent of the environment across a sample of unrelated individuals, conditional on covariates. Here we describe potential sources of bias, such as transmission ratio distortion, selection bias, population stratification, dynastic effects and assortative mating that can induce spurious or biased SNP–phenotype associations. We explain how studies of related individuals such as sibling pairs or parent–offspring trios can be used to overcome some of these sources of bias, to provide potentially more reliable evidence regarding causal processes. The increasing availability of data from related individuals in large cohort studies presents an opportunity to both overcome some of these biases and also to evaluate familial environmental effects.

# Power and Weak Instruments

- Power:
  - Genetic variants explain very small amounts of phenotypic variance in a given trait
  - VERY large sample sizes are generally required
- Weak instruments:
  - Genetic variants that are weak proxies for the exposure
  - Results in biased causal estimates from MR
- Different impact of the bias from weak instruments:
  - **Single Sample MR:** to the confounded estimate
  - **Two-Sample MR:** to the null

# Using Multiple Genetic Variants as Instruments

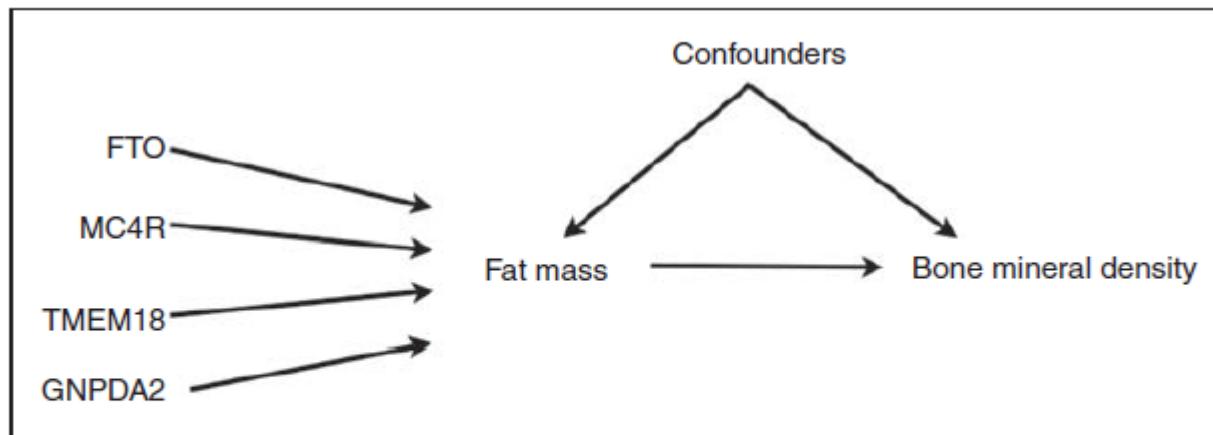


Figure 1. DAG for a Mendelian randomisation analysis using four genetic variants as instrumental variables for the effect of fat mass on bone mineral density.

*Palmer et al (2011) Stat Method Res*

- Allelic scores
- Testing multiple variants individually
- Meta-analyse individual SNPs



# Calculating Power in Mendelian Randomization Studies



## mRnd: Power calculations for Mendelian Randomization

### Input

Calculate:

- ☒ Power  
☐ Sample size

Provide:

**Sample size**

1000

$\alpha$

0.05

Type-I error rate

$\beta_{YZ}$

0

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

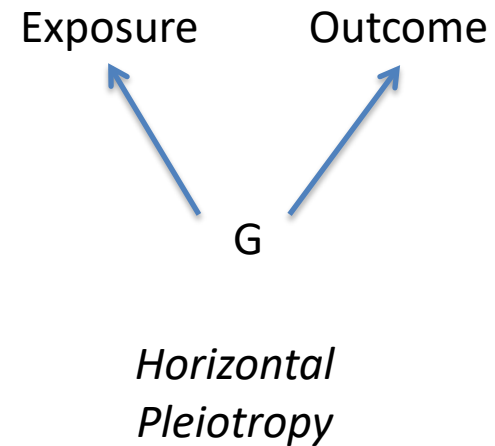
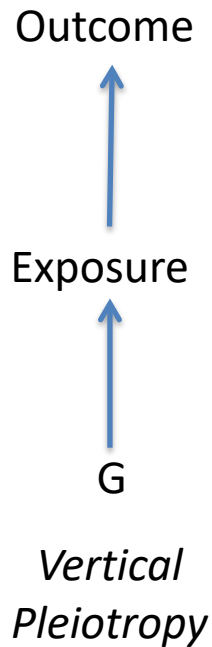
Power	0.05	
NCP	0.00	Non-Centrality-Parameter

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).



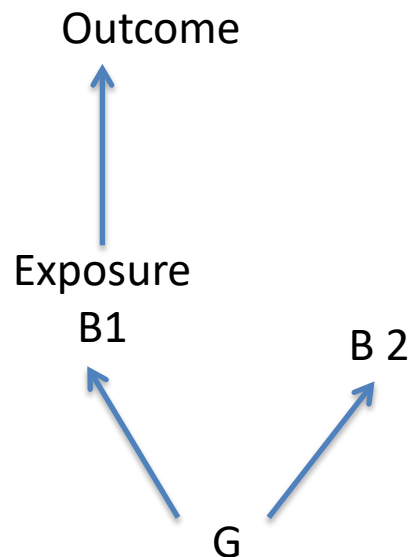
# Pleiotropy

- Genetic variant influences more than one trait
- Horizontal vs Vertical pleiotropy

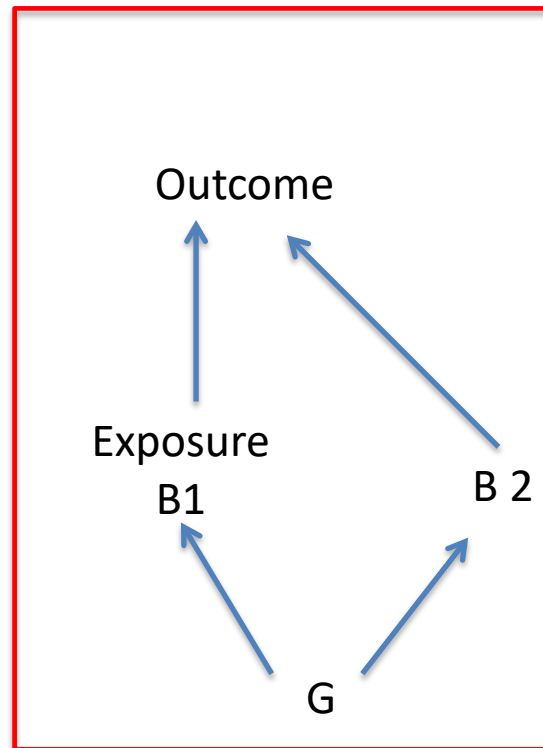


# Pleiotropy

- Genetic variant influences more than one trait
- Pleiotropy only violates MR's assumptions if it involves a pathway outside that of the exposure and is a pathway that affects your outcome



Violation





# MR Base

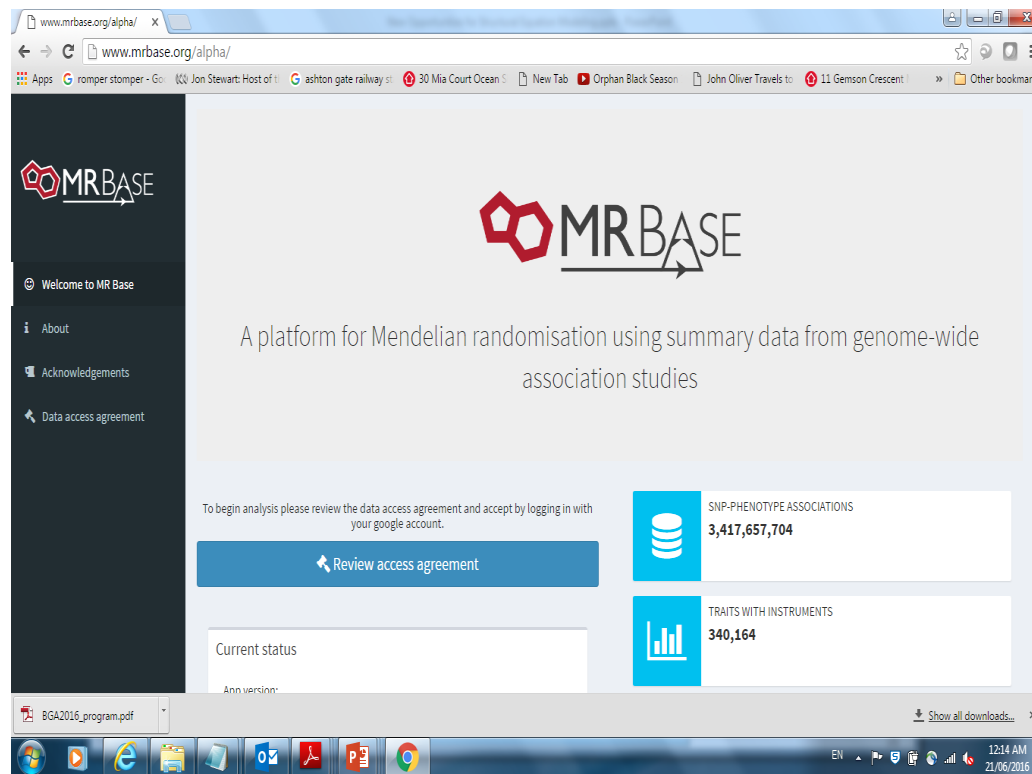
<http://www.mrbase.org/>



Gib Hemani



Phil Haycock



<https://mrcieu.github.io/TwoSampleMR/articles/introduction.html>

# Alcohol and Heart Disease



BMJ 2014;349:g4164 doi: 10.1136/bmj.g4164 (Published 10 July 2014)

Page 1 of 16

## RESEARCH

### Association between alcohol and cardiovascular disease: Mendelian randomisation analysis based on individual participant data

OPEN ACCESS

#### Abstract

**Objective** To use the rs1229984 variant in the alcohol dehydrogenase 1B gene (*ADH1B*) as an instrument to investigate the causal role of alcohol in cardiovascular disease.

**Design** Mendelian randomisation meta-analysis of 56 epidemiological studies.

**Participants** 261 991 individuals of European descent, including 20 259 coronary heart disease cases and 10 164 stroke events. Data were available on *ADH1B* rs1229984 variant, alcohol phenotypes, and cardiovascular biomarkers.

**Main outcome measures** Odds ratio for coronary heart disease and stroke associated with the *ADH1B* variant in all individuals and by categories of alcohol consumption.

**Results** Carriers of the A-allele of *ADH1B* rs1229984 consumed 17.2% fewer units of alcohol per week (95% confidence interval 15.6% to 18.9%), had a lower prevalence of binge drinking (odds ratio 0.78 (95% CI 0.73 to 0.84)), and had higher abstinence (odds ratio 1.27 (1.21 to 1.34)) than non-carriers. Rs1229984 A-allele carriers had lower systolic blood pressure (−0.88 (−1.19 to −0.56) mm Hg), interleukin-6 levels (−5.2% (−7.8 to −2.4%)), waist circumference (−0.3 (−0.6 to −0.1) cm), and body mass index (−0.17 (−0.24 to −0.10) kg/m<sup>2</sup>). Rs1229984 A-allele carriers had lower odds of coronary heart disease (odds ratio 0.90 (0.84 to 0.96)). The protective association of the *ADH1B* rs1229984 A-allele variant remained the same across all categories of alcohol consumption ( $P=0.83$  for heterogeneity). Although no association of rs1229984 was identified with the combined subtypes of stroke, carriers of the A-allele had lower odds of ischaemic stroke (odds ratio 0.83 (0.72 to 0.95)).

**Conclusions** Individuals with a genetic variant associated with non-drinking and lower alcohol consumption had a more favourable cardiovascular profile and a reduced risk of coronary heart disease than those without the genetic variant. This suggests that reduction of alcohol consumption, even for light to moderate drinkers, is beneficial for cardiovascular health.

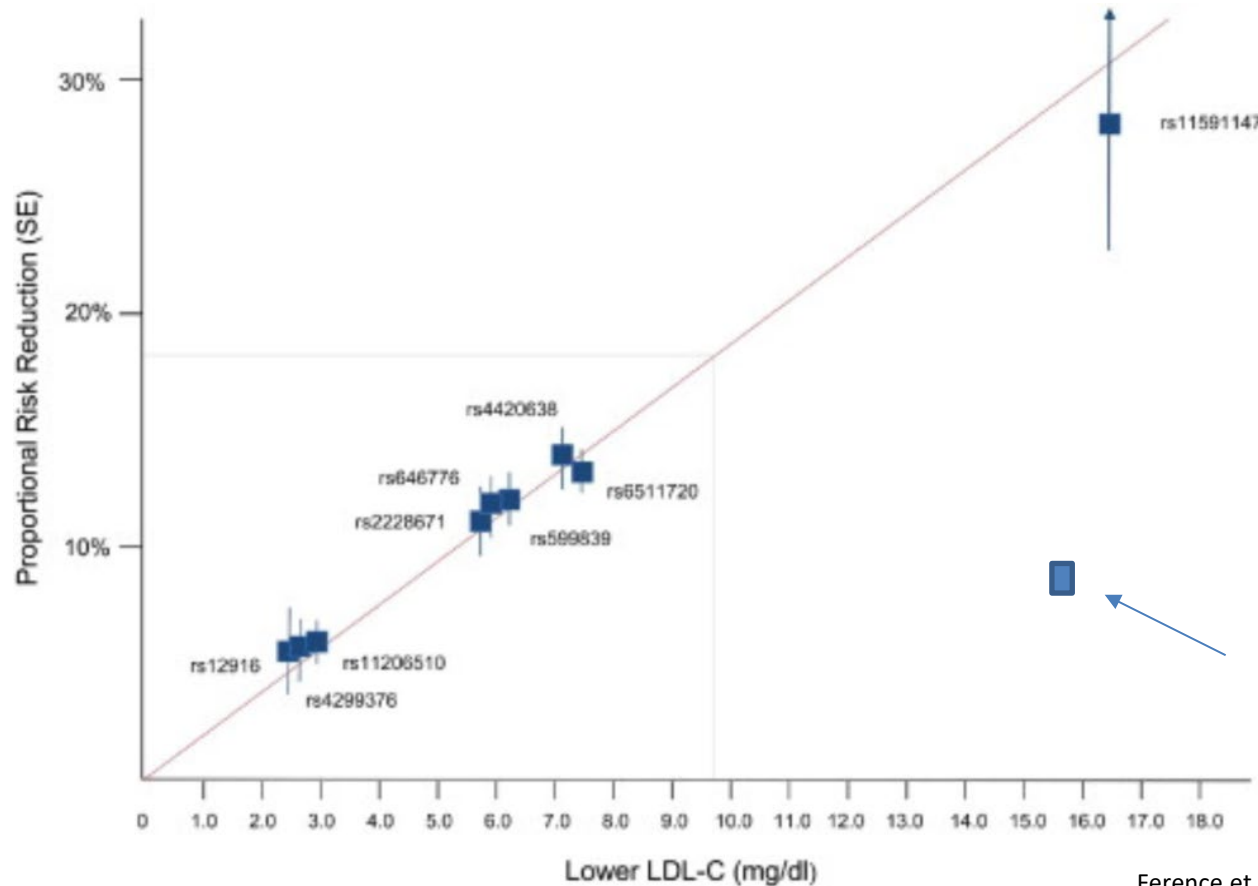
(A) Alcohol increases risk of heart disease

(C) No causal relationship

(B) Alcohol decreases risk of heart disease

(D) Don't know

# “Bad” LDL Cholesterol and Heart Disease



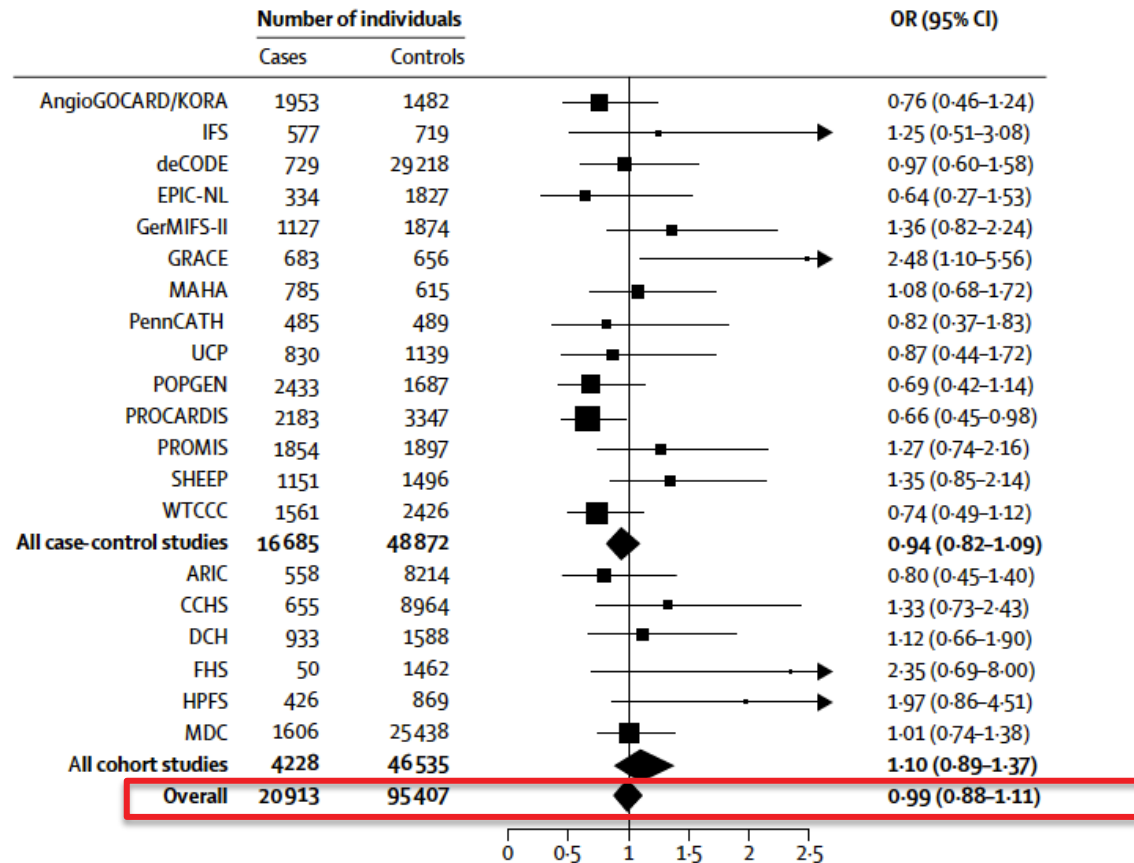
Ference et al, JACC 2012

(A) High LDL decreases risk of heart disease

(B) High LDL increases risk of heart disease

(C) LDL is not causally related to heart disease

# “Good” HDL Cholesterol and Heart Disease



(A) High HDL decreases risk of heart disease

(B) High HDL increases risk of heart disease

(C) HDL is not causally related to heart disease

# Triangulation in Science



## Repeating experiments is not enough

Verifying results requires disparate lines of evidence — a technique called triangulation. **Marcus R. Munafò** and **George Davey Smith** explain.

*Nature* (2018)



# Useful References

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- ▶ [Davies et al \(2018\). Reading Mendelian randomization studies: a guide, glossary, and checklist for clinicians. BMJ, Jul 12, 362:k601.](#)
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- ▶ [Evans & Davey-Smith \(2015\). Mendelian randomization: New applications in the coming age of hypothesis free causality. Annu Rev Genomics Hum Genet, 16, 327-50.](#)
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- ▶ [Munafo & Davey Smith \(2018\). Robust research needs many lines of evidence. Nature, 553\(7689\), 399-401.](#)
- ▶ [Sanderson et al. \(2022\). Mendelian randomization. Nat Rev Methods Primers, 2\(6\), 10.1038/s43586-021-00092-5.](#)
- ▶ [Zheng et al. \(2017\). Recent developments in Mendelian randomization studies. Curr Epidemiol Rep, 4\(4\), 330-345.](#)

# MR Practical