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 tipple 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 tipple 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

(B) Alcohol decreases risk of heart disease

(C) No causal relationship

(D) Don't know

“Bad” LDL Cholesterol and Heart Disease

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'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

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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.

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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

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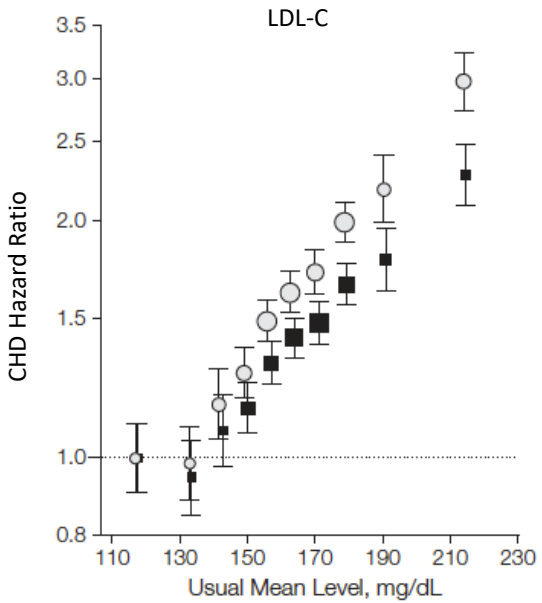
For years doctors have prescribed statins to reduce the risk of heart attacks and strokes caused by 'bad' cholesterol in the blood.

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

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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

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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

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

- 'Good' cholesteral 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

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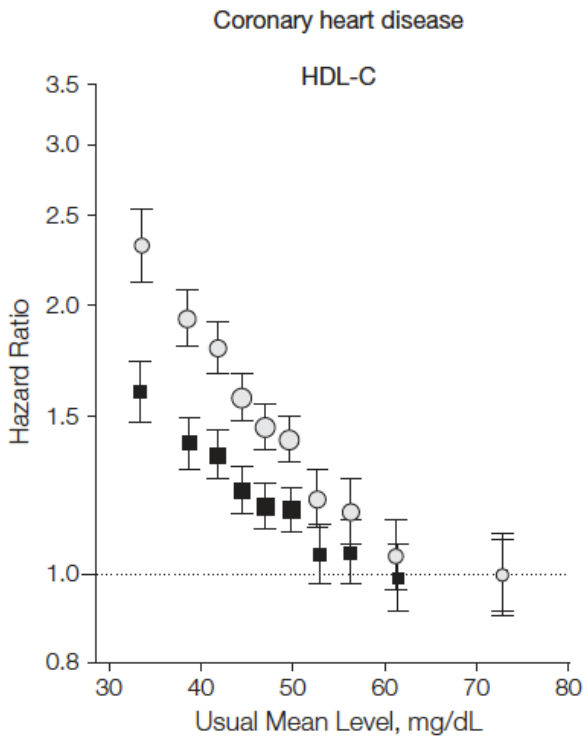
There may be no such thing as 'good' cholesterol after all, a federally-funded study suggests.

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.

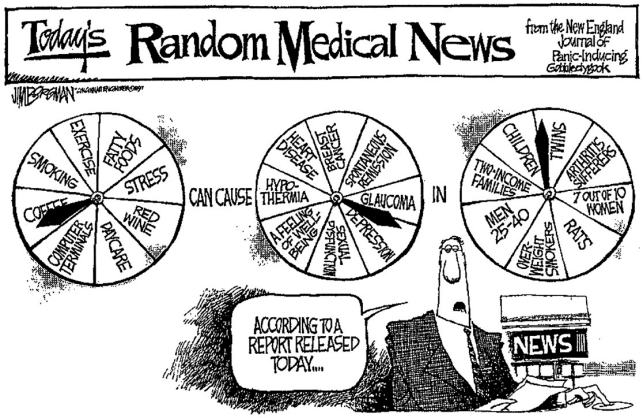


(A) High HDL decreases risk of heart disease

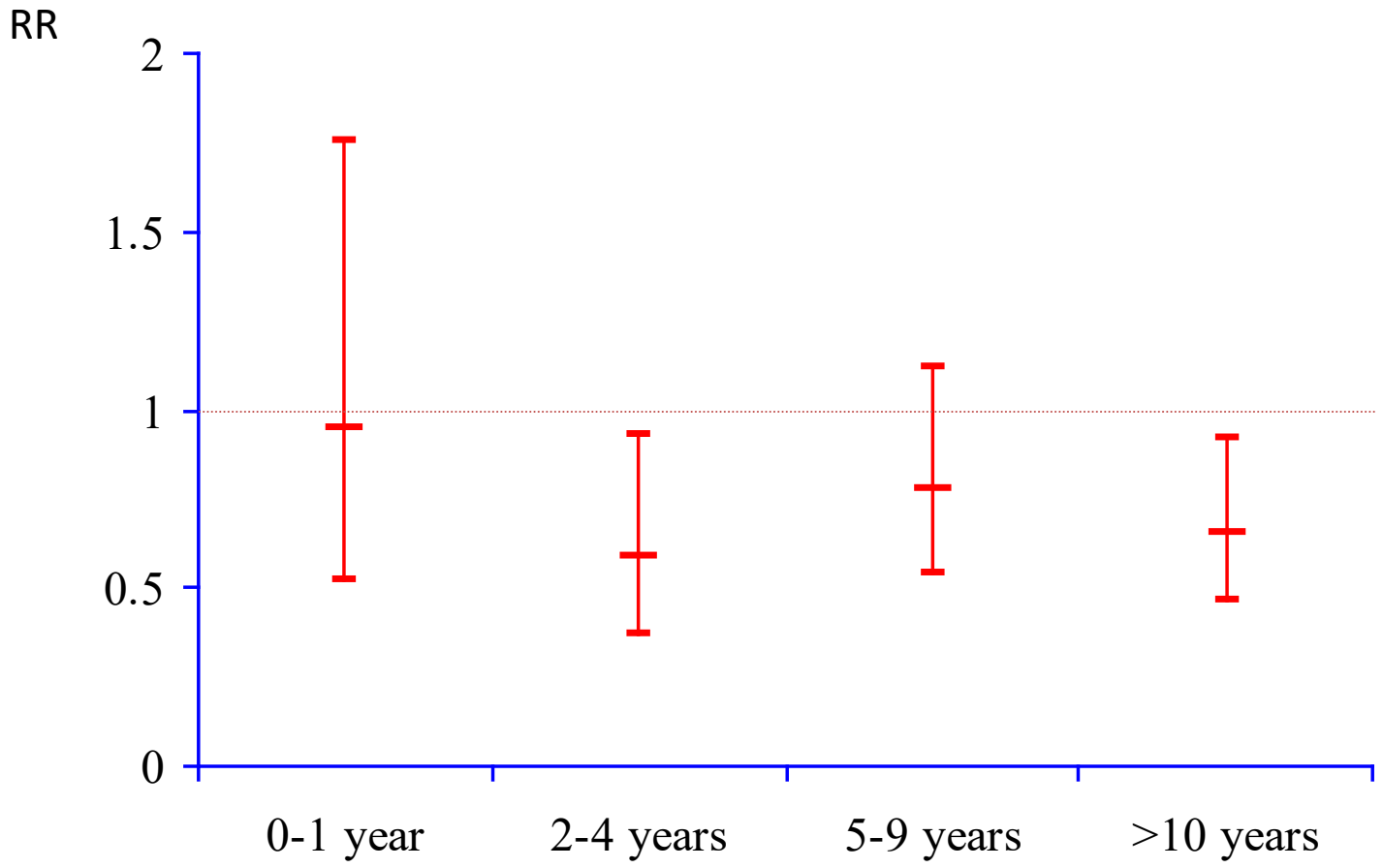
(B) High HDL increases risk of heart disease

(C) HDL is not causally related to heart disease

Problems with inferring causality in observational studies

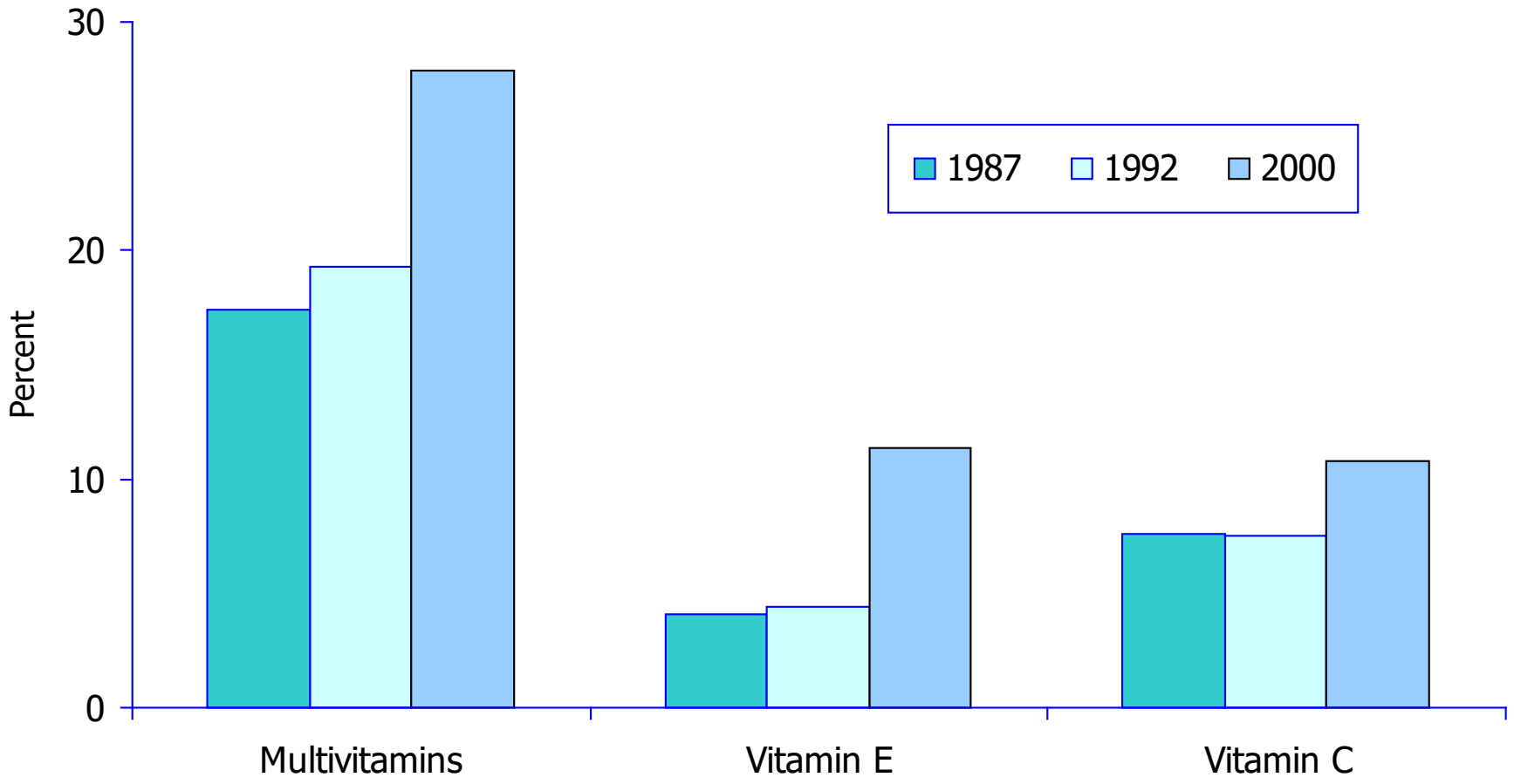


CHD risk according to duration of current Vitamin E supplement use compared to no use



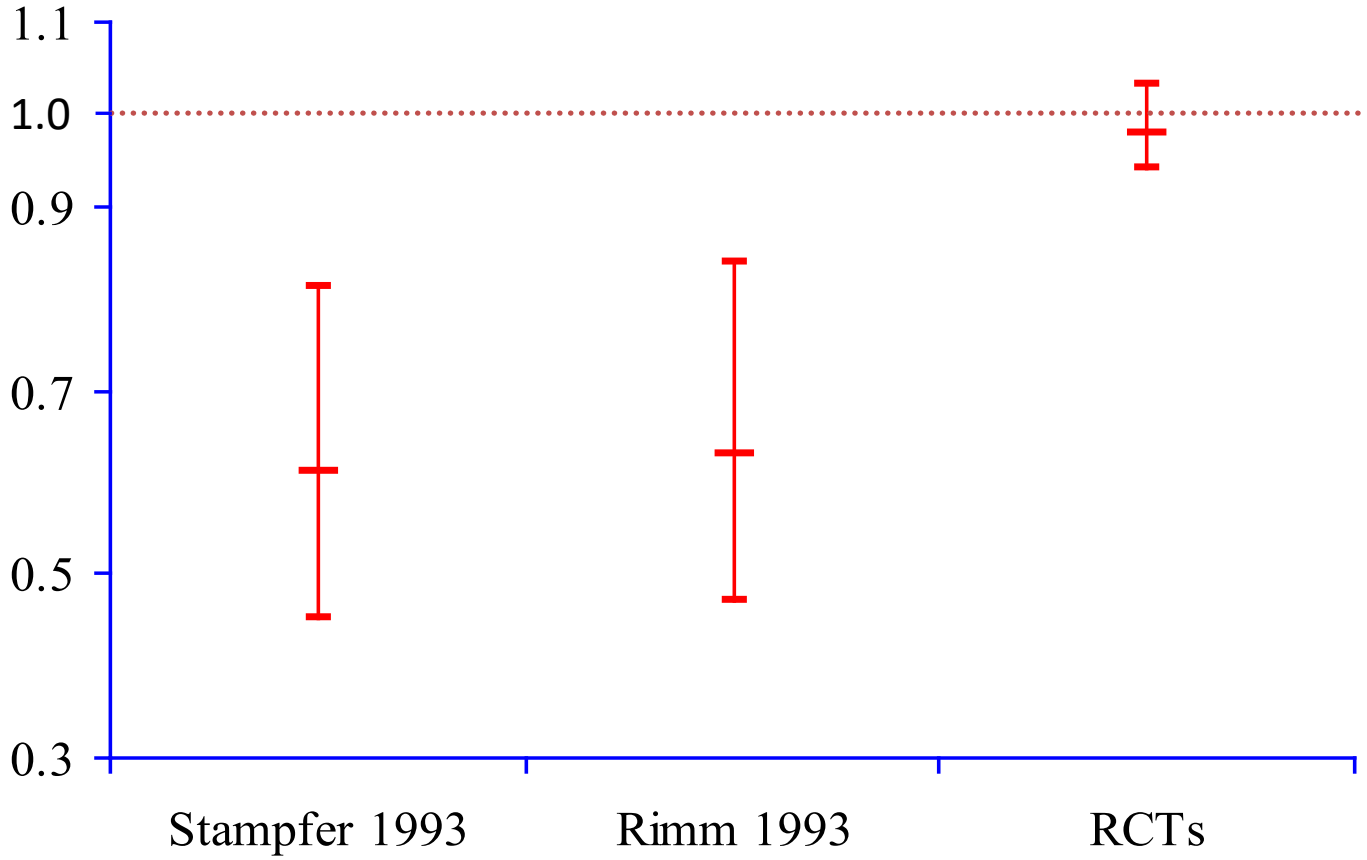
Rimm et al NEJM 1993; 328: 1450-6

Use of vitamin supplements by US adults, 1987-2000



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

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 ↑

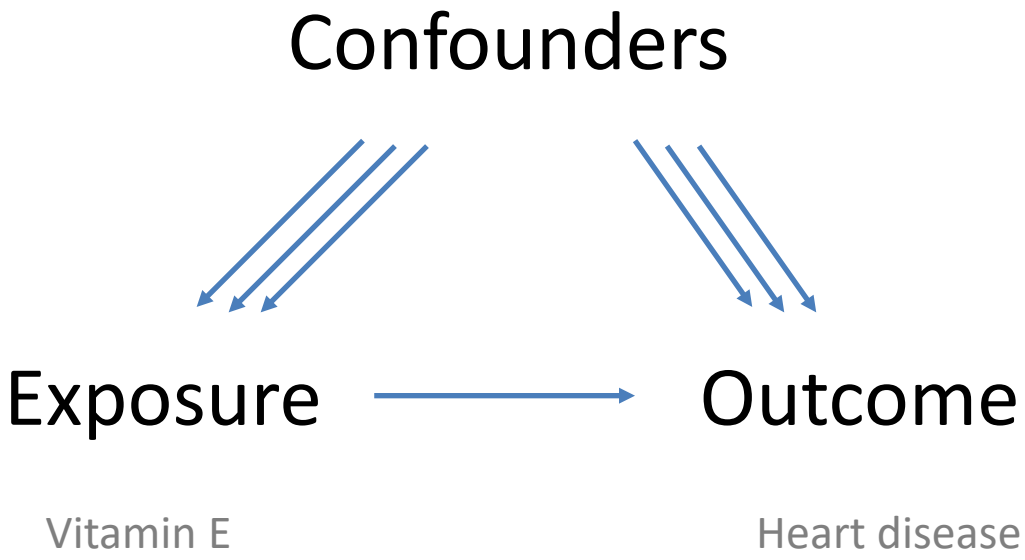
Height ↑

Leg length ↑

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

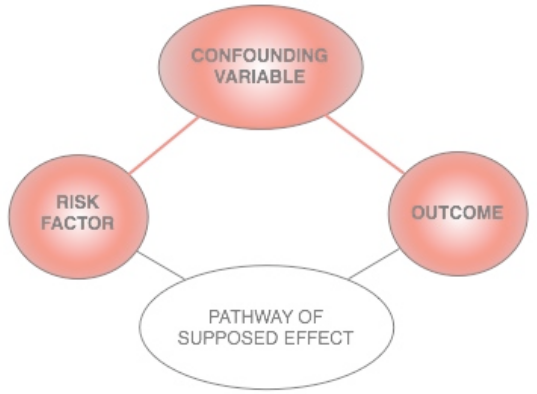
Confounding

Smoking, diet, alcohol, socioeconomic position….



Classic limitations to "observational" science

- **Confounding**

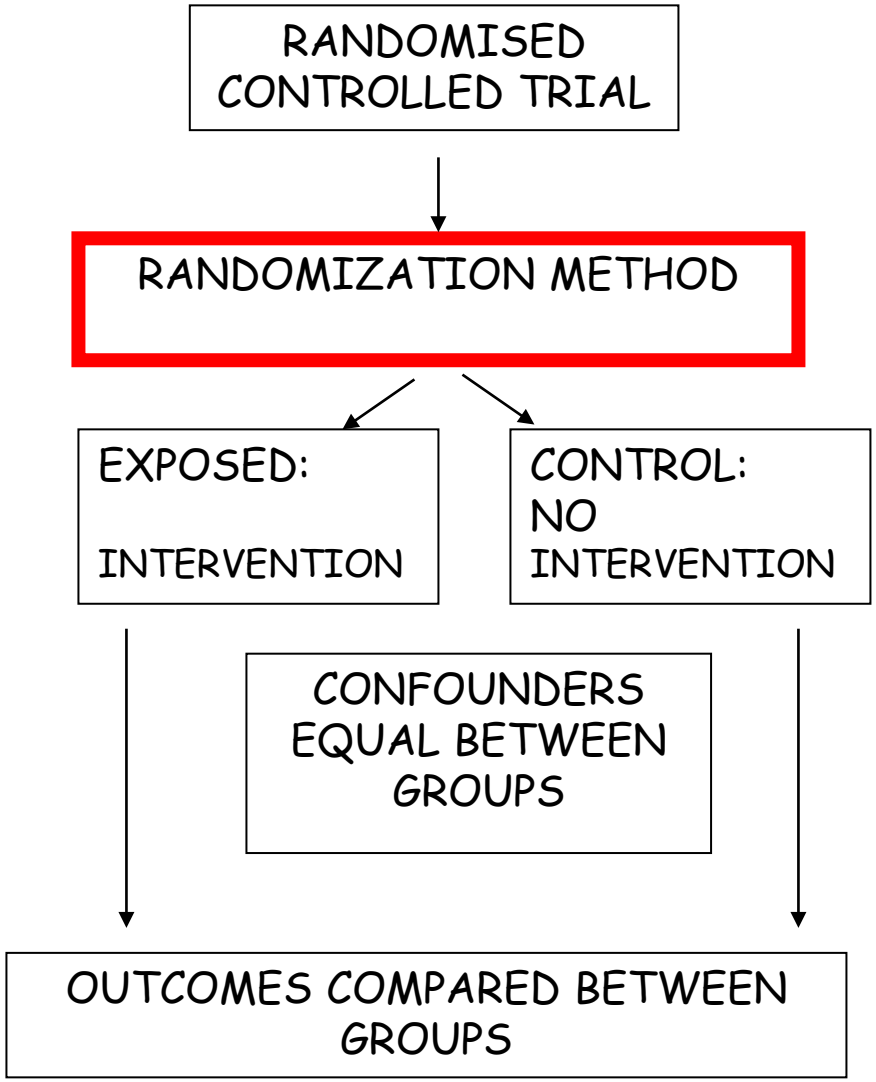


- **Reverse Causation**

- 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

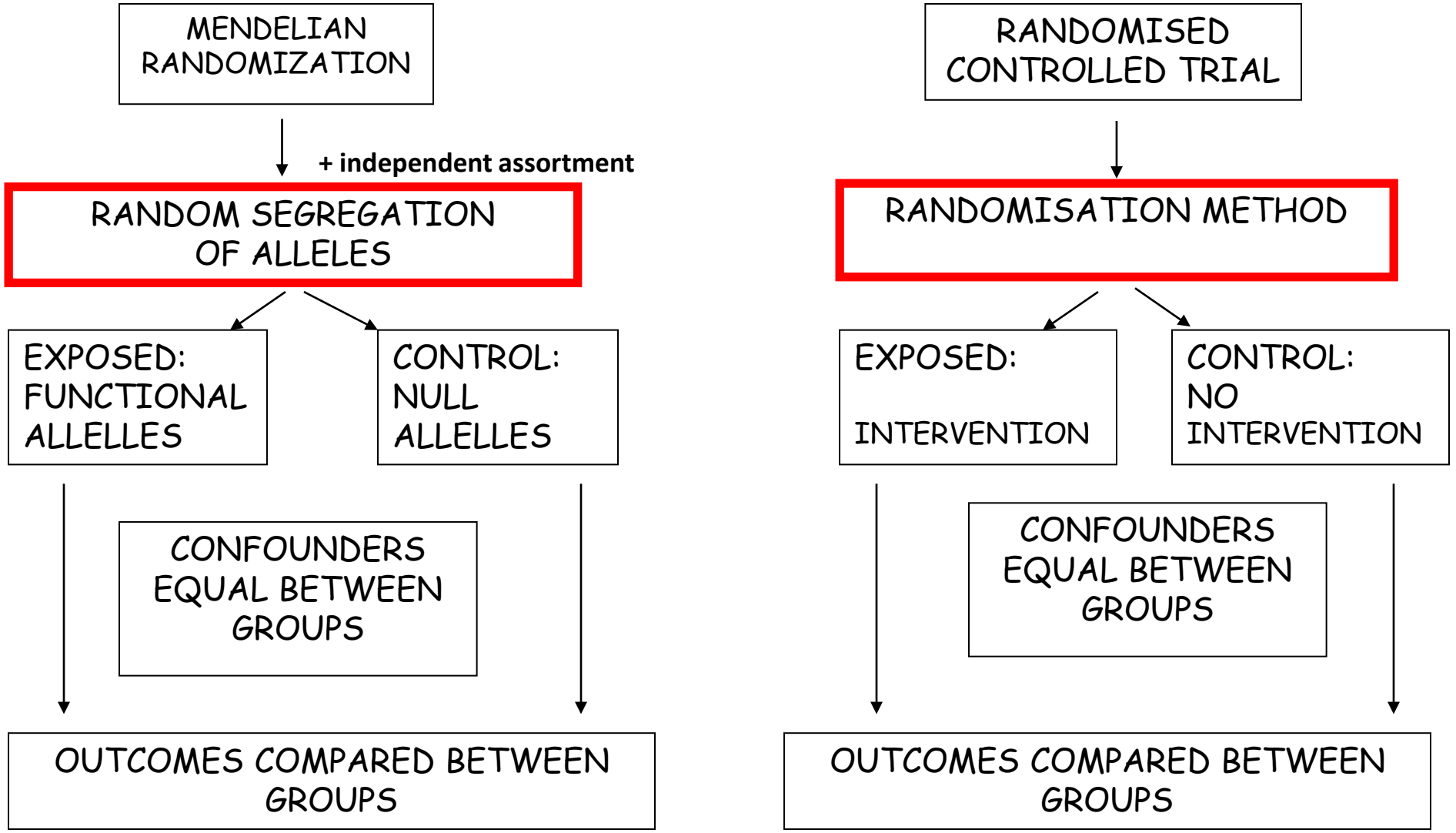
Mendel's Laws of Inheritance

Mendel in 1862

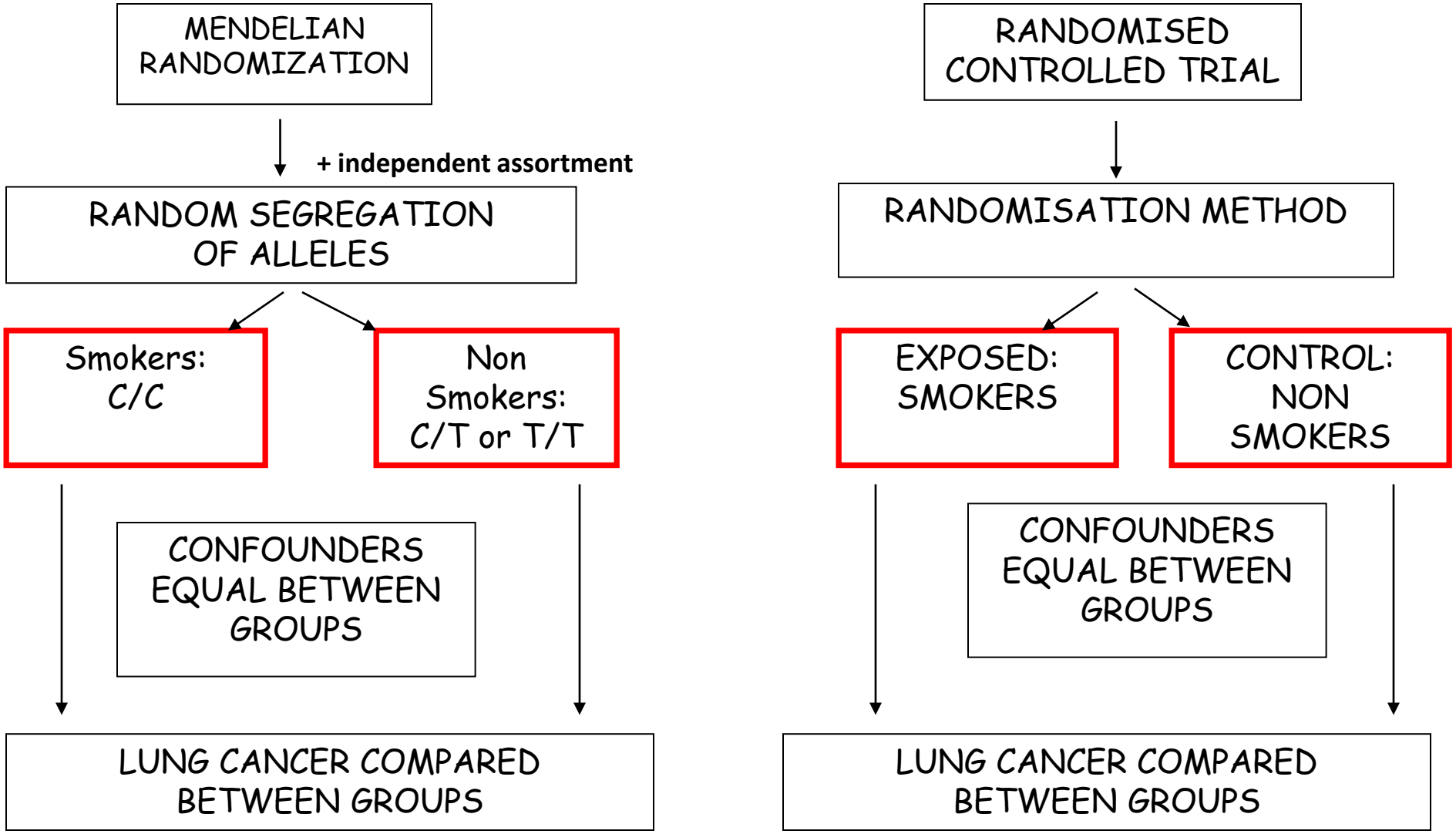
1. **Segregation:** alleles separate at meiosis and a randomly selected allele is transmitted to offspring

2. **Independent assortment:** alleles for separate traits are transmitted independently of one another

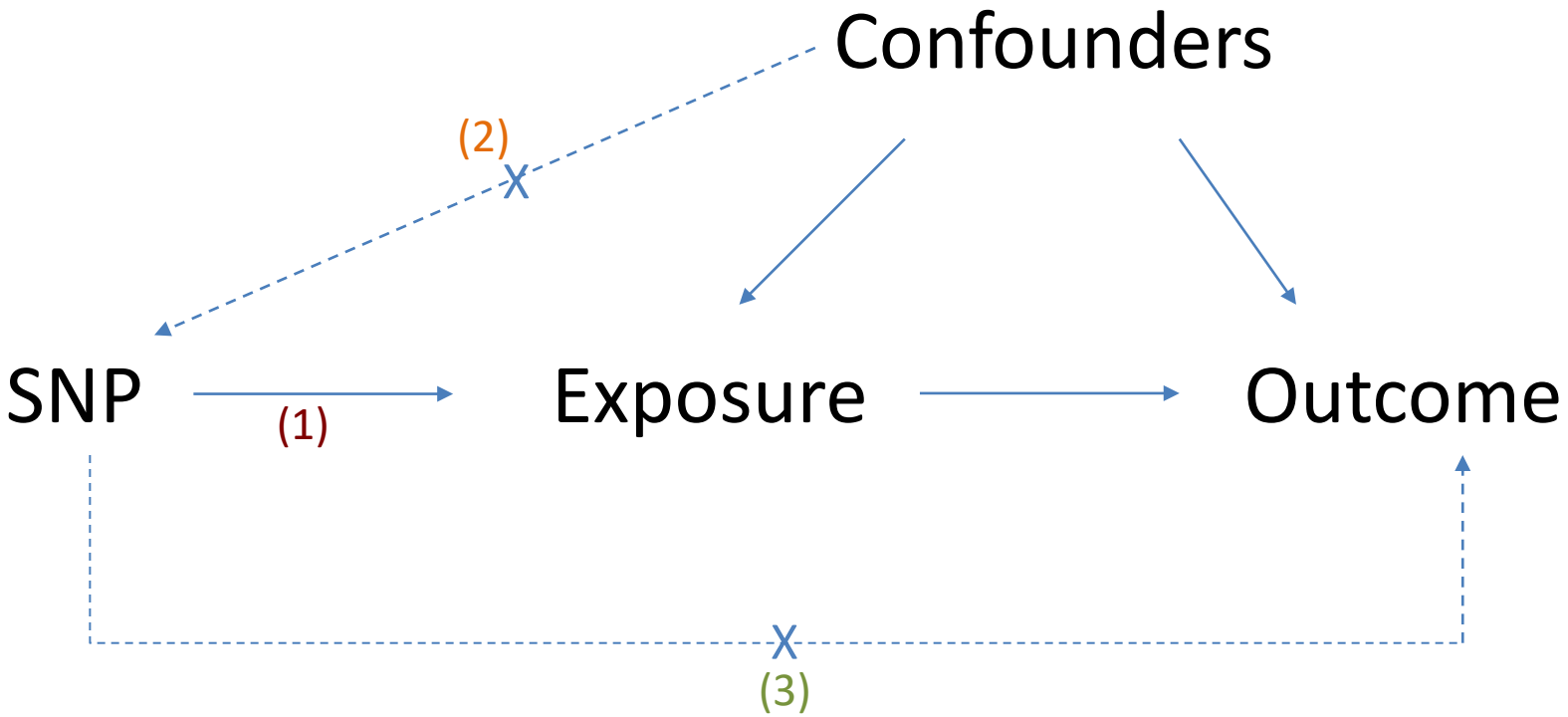
Mendelian randomization and RCTs



Mendelian randomization: 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

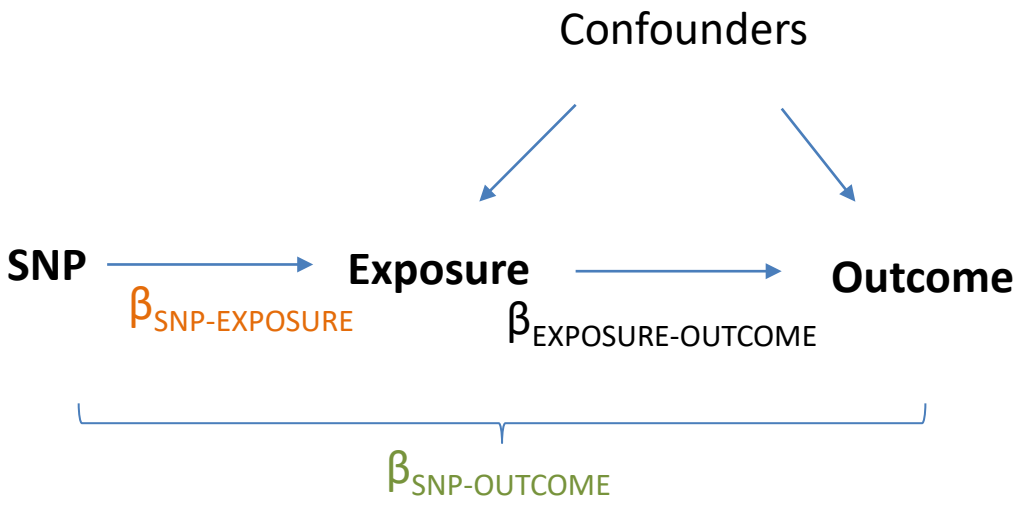
Why are genetic associations special?

- 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

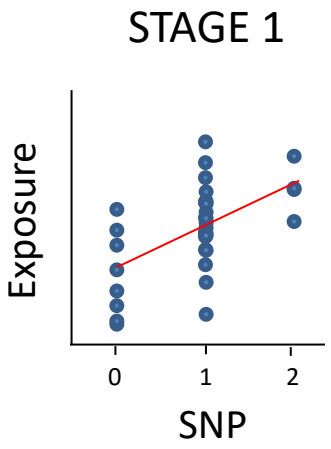
Calculating Causal Effect Estimates

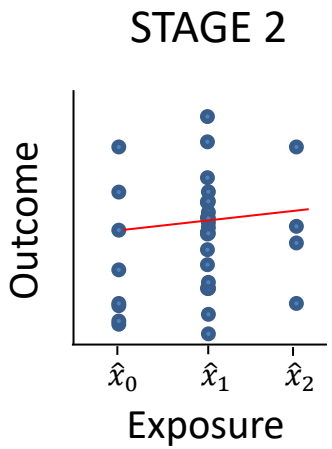


After SNP identified robustly associated with exposure of interest:

- 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)

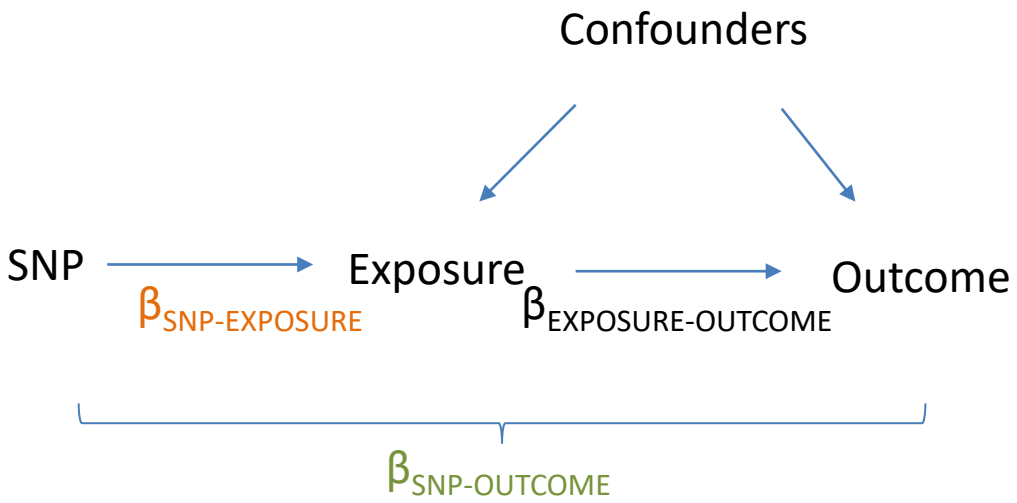
(2) Regress outcome on predicted values of the exposure (STAGE 2)

(3) Adjust standard errors

(4) Slope of 2nd 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* :

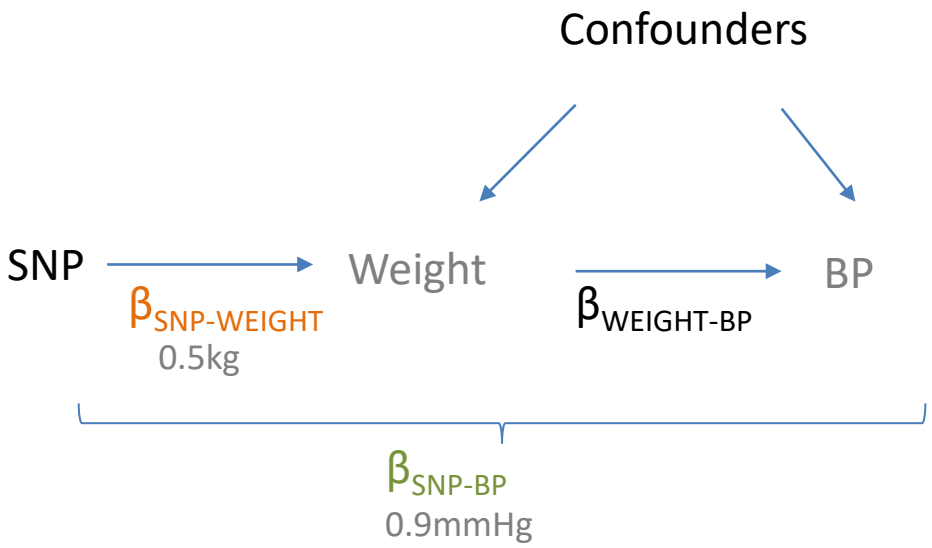
$$\frac{\hat{\beta}_{SNP\text{-}OUTCOME}}{\hat{\beta}_{SNP\text{-}EXPOSURE}}$$

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

*Can be used in different samples ("Two sample MR")

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

Calculating Causal Effect Estimates



Causal effect by Wald Estimator* :

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

= change in outcome per unit change in exposure

BP and weight:

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

=1.8 mmHg/kg

*Can be used in different samples ("Two sample MR")

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

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

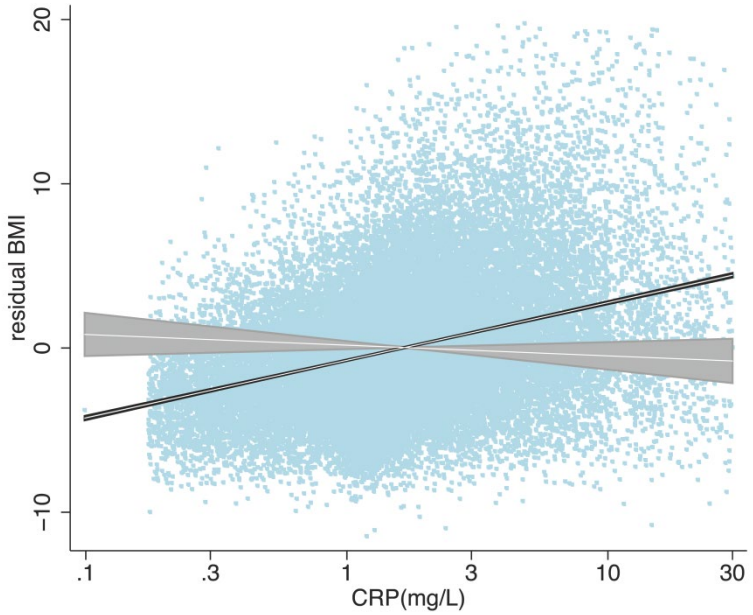
MR Example using CRP

- 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



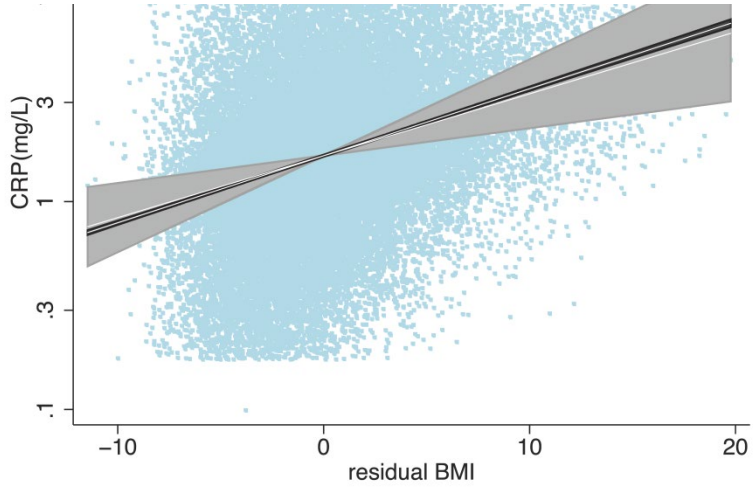
P_{IV}- Test of whether MR causal effect estimate different from zero

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

2- Canalisation ("Developmental compensation")

3- The existence of instruments

4- Power and "weak instrument bias"

5- Pleiotropy

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

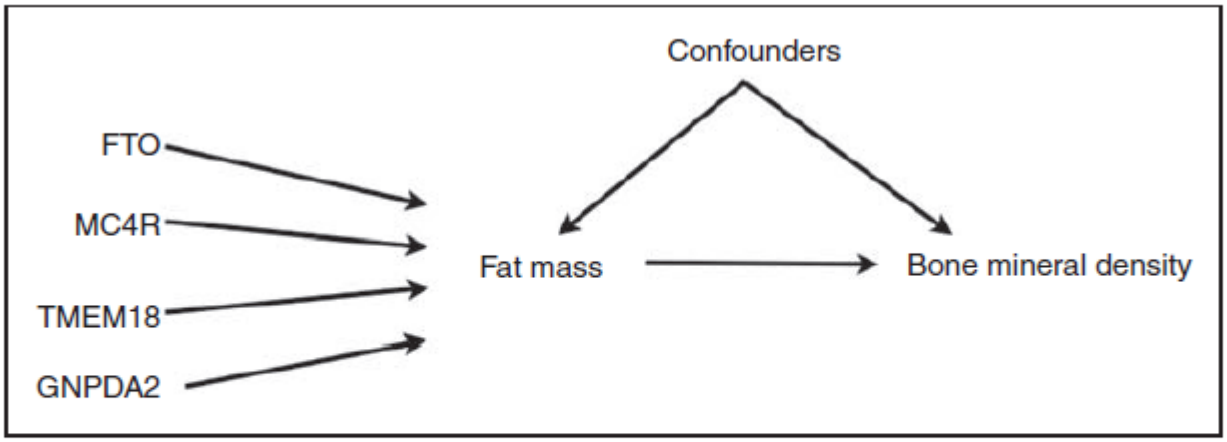
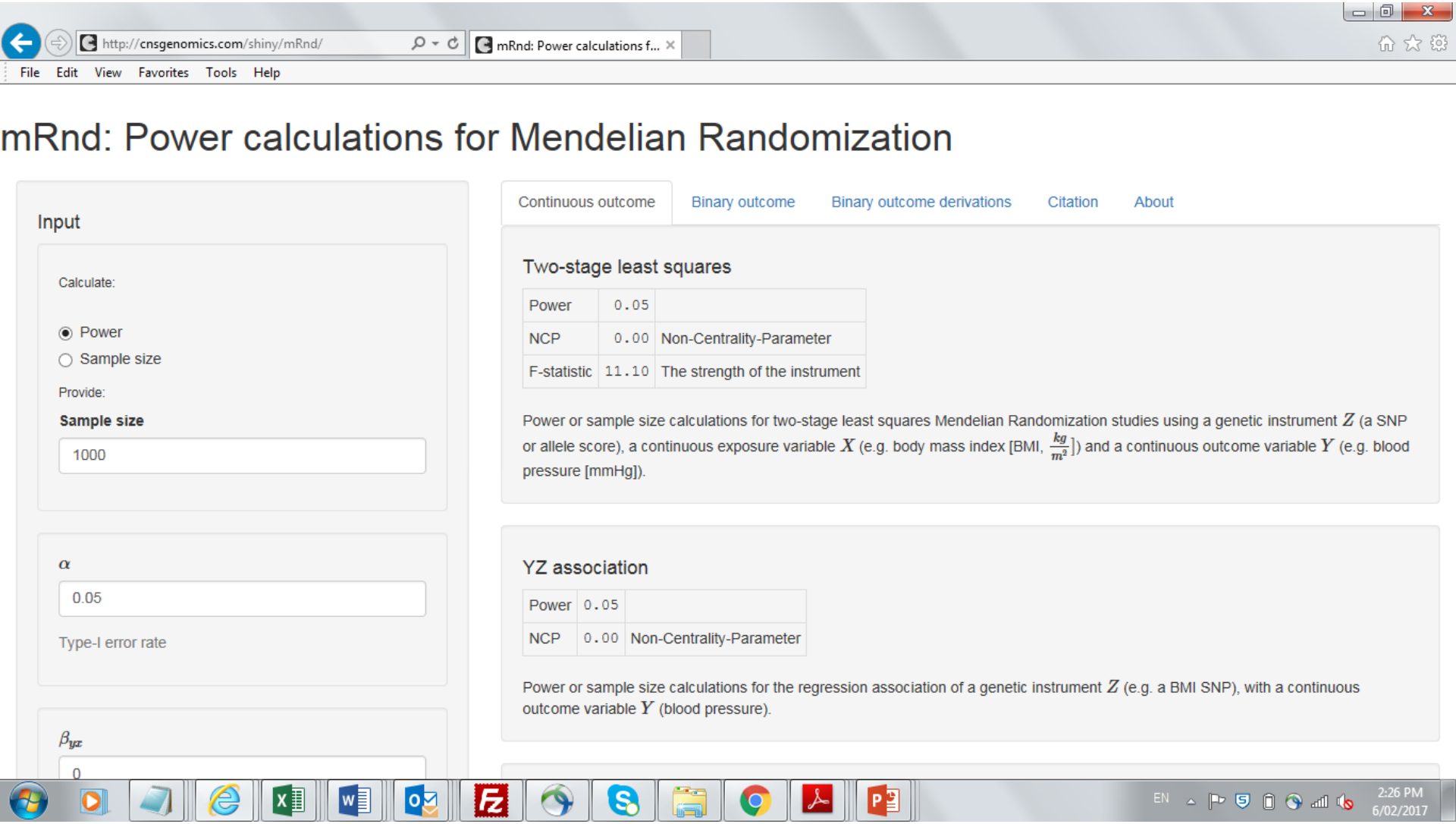


Figure 1. DAG for a Mendelian randomisation analysis using four genetic variants as instrumental variables for the effect of fat mass on bone mineral density.

Palmer et al (2011) Stat Method Res

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

Calculating Power in Mendelian Randomization Studies



Limitations to Mendelian Randomization

1- Population stratification

2- Canalisation (“Developmental compensation”)

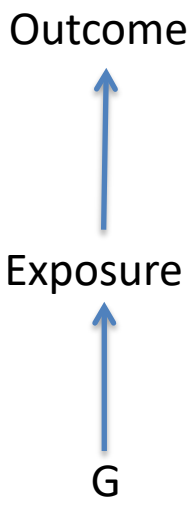
3- The existence of instruments

4- Power (also “weak instrument bias”)

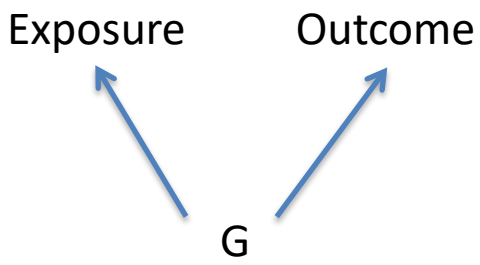
5- Pleiotropy

Pleiotropy

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



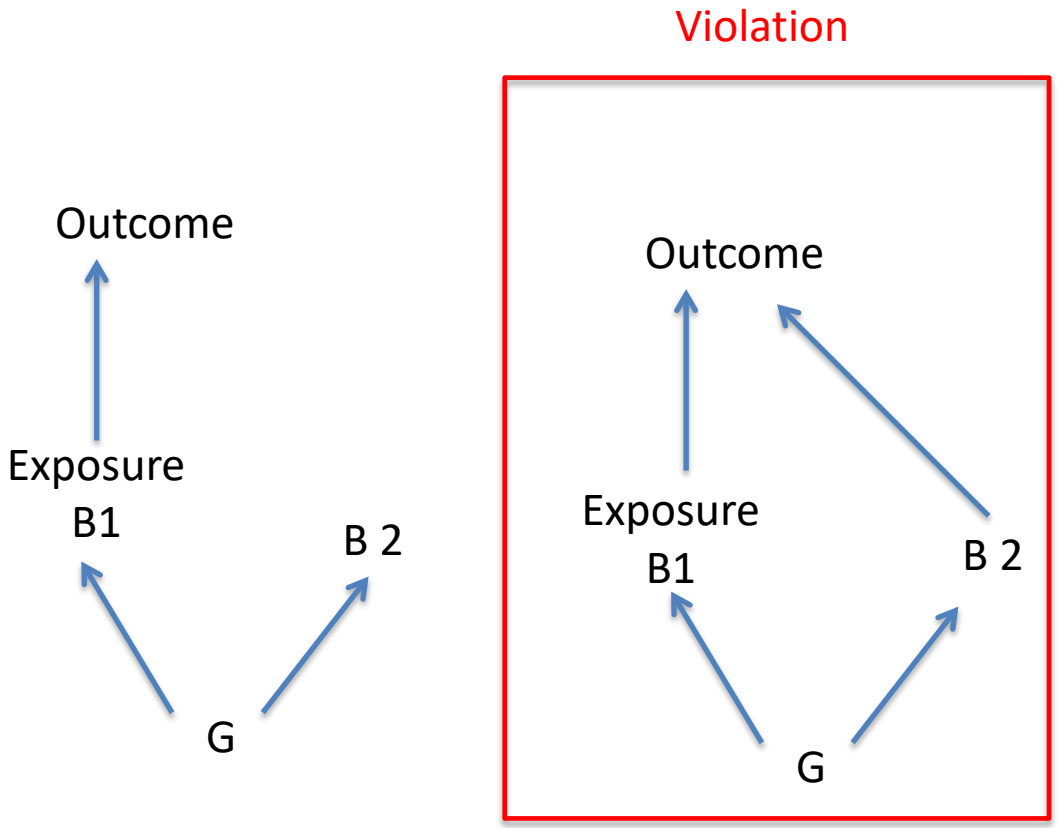
Vertical Pleiotropy



Horizontal 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 <u>affects your outcome</u>



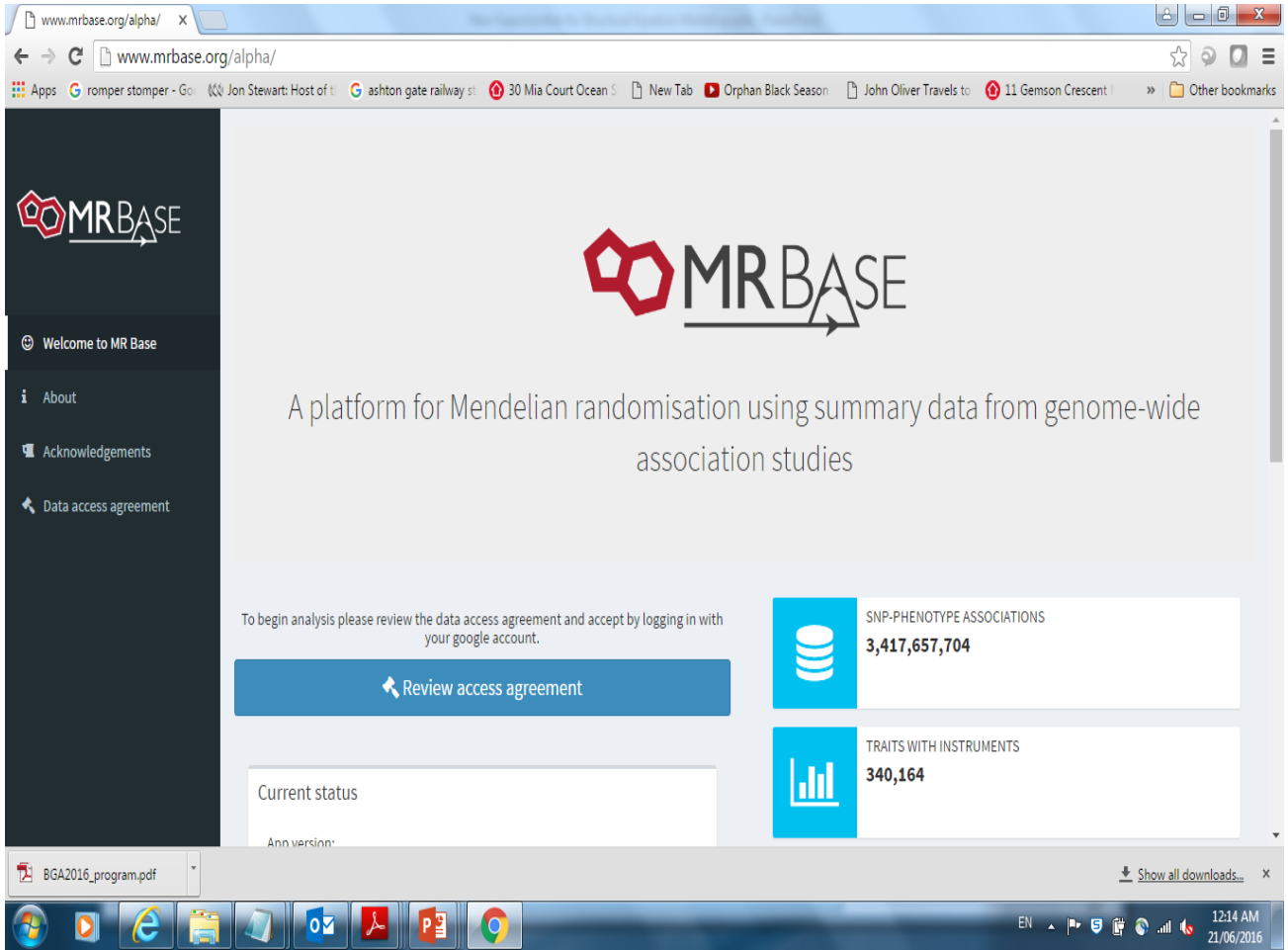
MR Base

Jie “Chris” Zheng

http://www.mrbase.org/

Gib Hemani

Phil Haycock



MR BASE

- Welcome to MR Base
- About
- Acknowledgements
- Data access agreement

Logged in as
David Evans
epxde@bristol.ac.uk

- **Perform MR analysis**
  - **Choose exposures**
  - Choose outcomes
  - Run MR
- Quick SNP lookup

Choosing instruments for the exposure

To use two sample MR to estimate the causal effect of an exposure on an outcome, the first step is to identify SNPs that are robustly associated with the exposure. These summary statistics for these SNPs can be taken from a sample from which there is no data on the outcome.

Please provide instruments by choosing from one of the data sources below, or by uploading your own data. You can choose multiple exposures to be analysed, and multiple instruments per exposure.

Choose instruments

Select exposure source

- (•) Manual file upload
- ( ) NHGRI-EBI GWAS catalog
- ( ) MR Base GWAS catalog
- ( ) Gene expression QTLs
- ( ) Protein level QTLs
- ( ) Metabolite level QTLs
- ( ) Methylation level QTLs

Manual file upload

The file must be a plain text file.

To do simple SNP look ups it must have at least one column with the header **SNP** .

To do an MR analysis it must have the following column headers:

- **SNP** - rs IDs of the instruments for the exposure
- **beta** - effect sizes for each SNP
- **se** - standard errors
- **effect_allele** - Effect allele

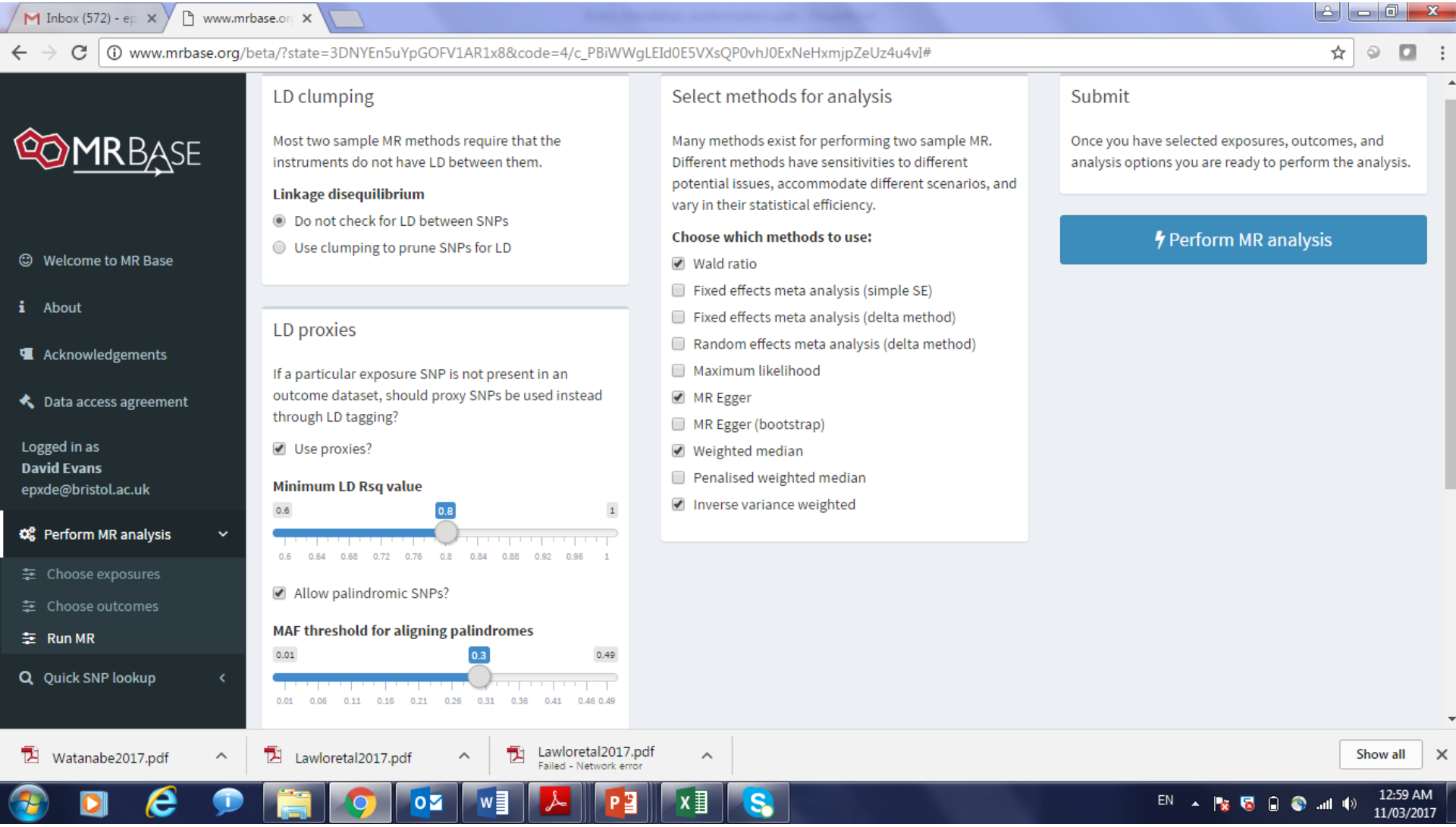
It's useful to have these columns too:

- **other_allele** - Other allele
- **eaf** - Effect allele frequency

You can see an example file here: telomere_length.txt

Upload plain text file *Preview of uploaded table*

Browse... No file s...


Inbox (572) - ep
www.mrbase.org
www.mrbase.org/beta/?state=3DNYEn5uYpGOFV1AR1x8&code=4/c_PBiWWgLEId0E5VXsQP0vhJ0ExNeHxmjpZeUz4u4vI#
MR BASE
Welcome to MR Base
About
Acknowledgements
Data access agreement
Logged in as
David Evans
epxde@bristol.ac.uk
Perform MR analysis
Choose exposures
Choose outcomes
Run MR
Quick SNP lookup
LD clumping
Most two sample MR methods require that the instruments do not have LD between them.
Linkage disequilibrium
Do not check for LD between SNPs
Use clumping to prune SNPs for LD
LD proxies
If a particular exposure SNP is not present in an outcome dataset, should proxy SNPs be used instead through LD tagging?
Use proxies?
Minimum LD Rsq value
0.6 0.8 1
0.6 0.64 0.68 0.72 0.76 0.8 0.84 0.88 0.92 0.96 1
Allow palindromic SNPs?
MAF threshold for aligning palindromes
0.01 0.3 0.49
0.01 0.06 0.11 0.16 0.21 0.26 0.31 0.36 0.41 0.46 0.49
Select methods for analysis
Many methods exist for performing two sample MR. Different methods have sensitivities to different potential issues, accommodate different scenarios, and vary in their statistical efficiency.
Choose which methods to use:
Wald ratio
Fixed effects meta analysis (simple SE)
Fixed effects meta analysis (delta method)
Random effects meta analysis (delta method)
Maximum likelihood
MR Egger
MR Egger (bootstrap)
Weighted median
Penalised weighted median
Inverse variance weighted
Submit
Once you have selected exposures, outcomes, and analysis options you are ready to perform the analysis.
Perform MR analysis
Watanabe2017.pdf
Lawloretal2017.pdf
Lawloretal2017.pdf
Failed - Network error
Show all
EN
12:59 AM
11/03/2017


Inbox (572) - epxde@bris
www.mrbase.org/beta/?s
www.mrbase.org/beta/?state=3DNYEn5uYpGOFV1AR1x8&code=4/c_PBiWWgLEId0E5VXsQP0vhJ0ExNeHxmjpZeUz4u4vI#
Run MR
MR Results
Quick SNP lookup
5e-08
Perform clumping
Display columns
ID
Trait
Note
First author
Consortium
Number of cases
Number of controls
Sample size
Number of variants
Year
PubmedID
Access
Category
Population
Priority
Sd
Sex
Subcategory
Unit
Search: ldl
ID Trait Note First author Consortium Number of cases Number of controls Sample size Number of variants Year PubmedID Access Category Po
300 300 LDL cholesterol Willer CJ GLGC 173082 2437752 2013 24097068 public Risk factor
781 781 LDL cholesterol Metabo-chip Willer CJ GLGC 83198 120251 2013 24097068 public Risk factor
880 880 Total cholesterol in large LDL L.LDL.C Kettunen 21552 11871461 2016 27005778 public Metabolites
881 881 Cholesterol esters in large VLDL L.LDL.CE Kettunen 19273 11820655 2016 27005778 public Metabolites
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Lawloretal2017.pdf
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Display columns

- [ ] ID
- [x] Trait
- [x] Note
- [x] First author
- [x] Consortium
- [x] Number of cases
- [x] Number of controls
- [x] Sample size
- [x] Number of variants
- [x] Year
- [ ] PubmedID
- [ ] Access
- [ ] Category
- [ ] Population
- [ ] Priority
- [ ] Sd
- [ ] Sex
- [x] Subcategory
- [ ] Unit

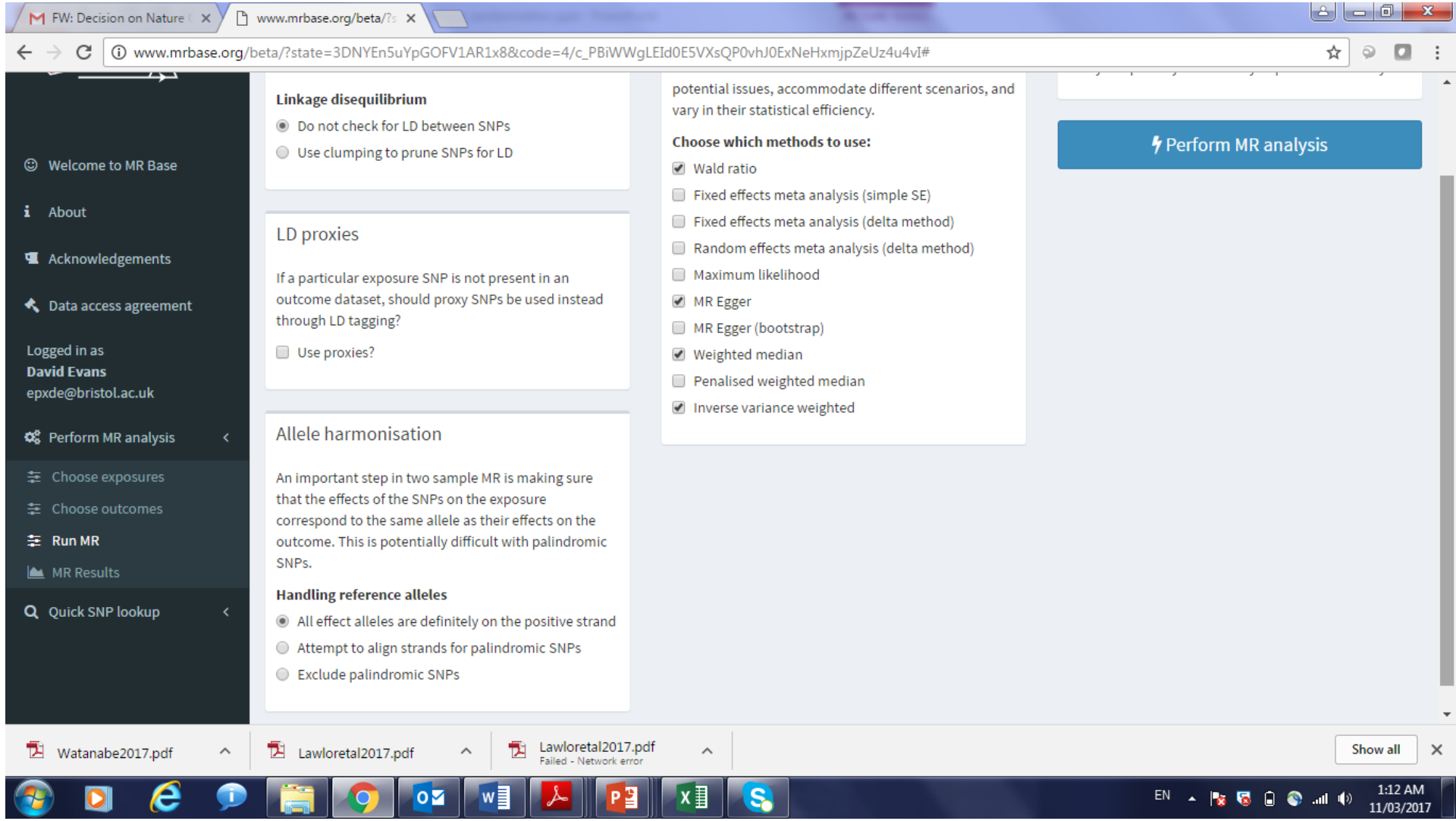
Show 10 entries

Search: coro

	Trait	Note	First author	Consortium	Number of cases	Number of controls	Sample size	Number of variants	Year	Subcategory
6	Coronary heart disease		Peden	C4D	15420	15062	30482	540233	2011	Cardiovascular
7	**Coronary heart disease**		**Nikpay**	**CARDIoGRAMplusC4D**	**60801**	**123504**	**184305**	**9455779**	**2015**	**Cardiovascular**
8	Coronary heart disease		Schunkert H	CARDIoGRAM	22233	64762	86995	2420361	2011	Cardiovascular
9	Coronary heart disease		Deloukas	CARDIoGRAMplusC4D	63746	130681	194427	79129	2013	Cardiovascular
	All	All	All	All	All	All	All	All	All	All

Showing 1 to 4 of 4 entries (filtered from 1,033 total entries)

Previous 1 Next


FW: Decision on Nature
www.mrbase.org/beta/?s
www.mrbase.org/beta/?state=3DNYEn5uYpGOFV1AR1x8&code=4/c_PBiWWgLEId0E5VXsQP0vhJ0ExNeHxmjpZeUz4u4vI#
Welcome to MR Base
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Data access agreement
Logged in as
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epxde@bristol.ac.uk
Perform MR analysis
Choose exposures
Choose outcomes
Run MR
MR Results
Quick SNP lookup
Linkage disequilibrium
Do not check for LD between SNPs
Use clumping to prune SNPs for LD
LD proxies
If a particular exposure SNP is not present in an outcome dataset, should proxy SNPs be used instead through LD tagging?
Use proxies?
Allele harmonisation
An important step in two sample MR is making sure that the effects of the SNPs on the exposure correspond to the same allele as their effects on the outcome. This is potentially difficult with palindromic SNPs.
Handling reference alleles
All effect alleles are definitely on the positive strand
Attempt to align strands for palindromic SNPs
Exclude palindromic SNPs
potential issues, accommodate different scenarios, and vary in their statistical efficiency.
Choose which methods to use:
Wald ratio
Fixed effects meta analysis (simple SE)
Fixed effects meta analysis (delta method)
Random effects meta analysis (delta method)
Maximum likelihood
MR Egger
MR Egger (bootstrap)
Weighted median
Penalised weighted median
Inverse variance weighted
Perform MR analysis
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Alcohol and Heart Disease

thebmj

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

RESEARCH

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

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 abstention (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^2). 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.

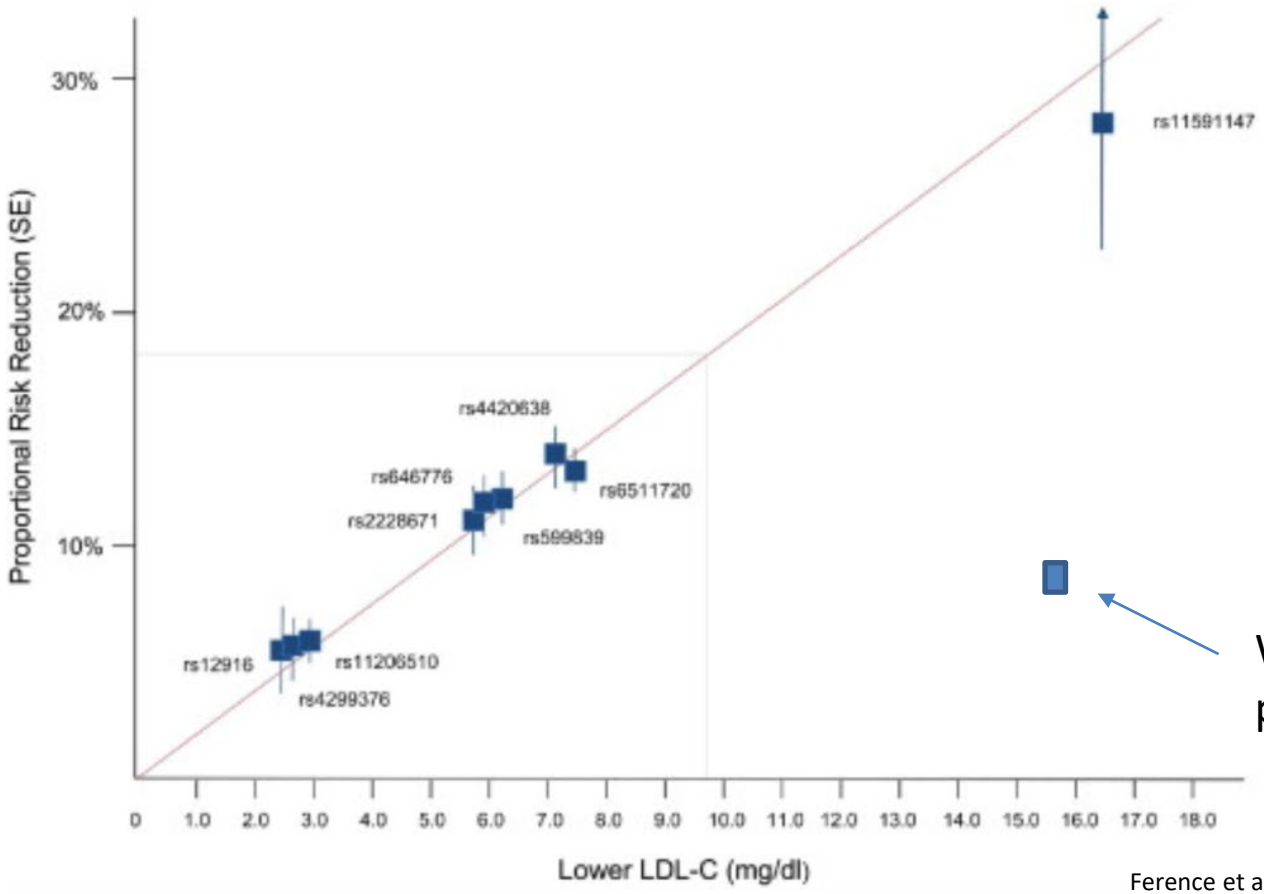
(A) Alcohol increases risk of heart disease

(B) Alcohol decreases risk of heart disease

(C) No causal relationship

(D) Don't know

“Bad” LDL Cholesterol and Heart Disease



What would a data point here indicate?

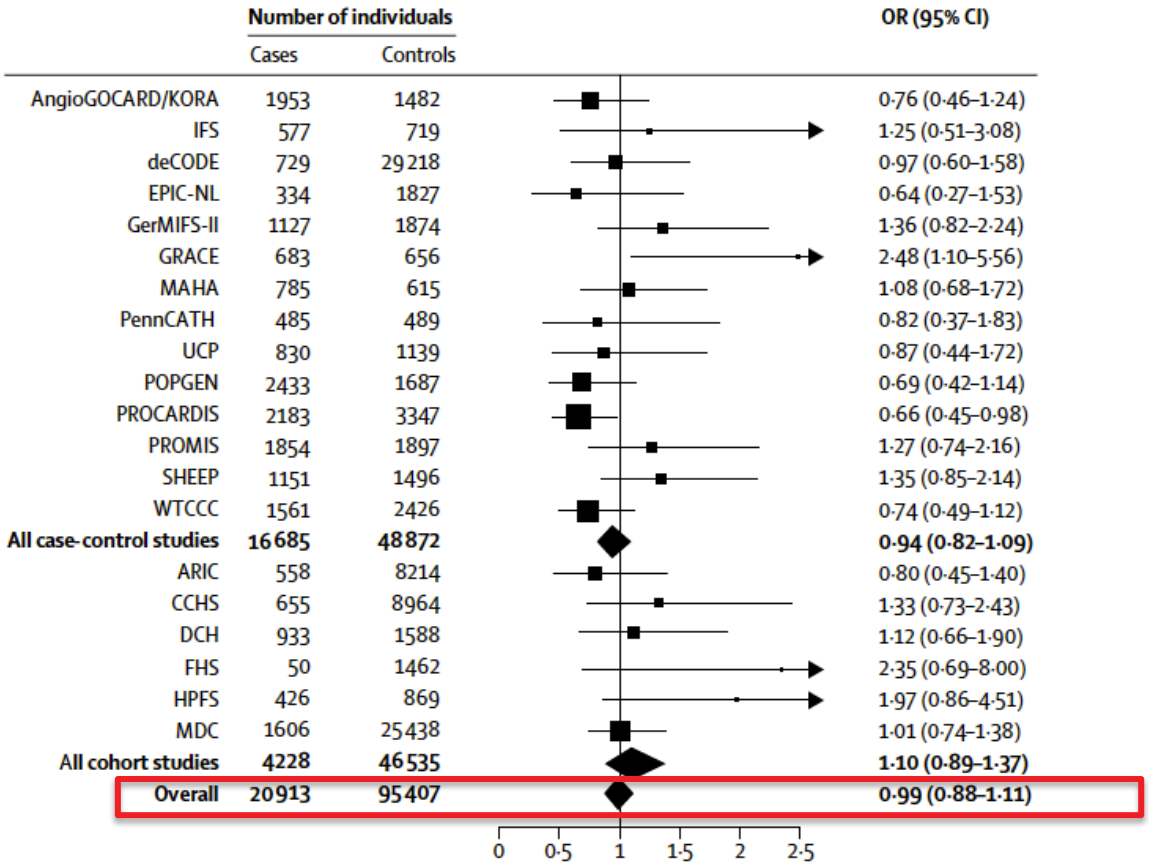
Ference et al, JACC 2012

(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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- Davey-Smith & Hemani (2014). Mendelian randomization: genetic anchors for causal inference in epidemiological studies. *Hum Mol Genet*, 23(1), R89-98.
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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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MR Practical