C-reactive protein and Coronary Heart Disease

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Structure of the lecture

Cholesterol and CHD - illustrative example

Inflammation [CRP] and CHD

Integration of genetics and blood-markers for aetiology and drug-target validation

Uses of biomarkers in coronary heart disease

1. Aetiology
2. Drug-target validation
3. Risk prediction

Uses of biomarkers in coronary heart disease

1. Aetiology
2. Drug-target validation
3. Risk prediction

From aetiology to risk modification:
Simplified steps

Distal exposure

Identify a biomarker

Search for a drug-target that affect the biomarker

Randomised trial to evaluate effect on outcome

Structure of the lecture

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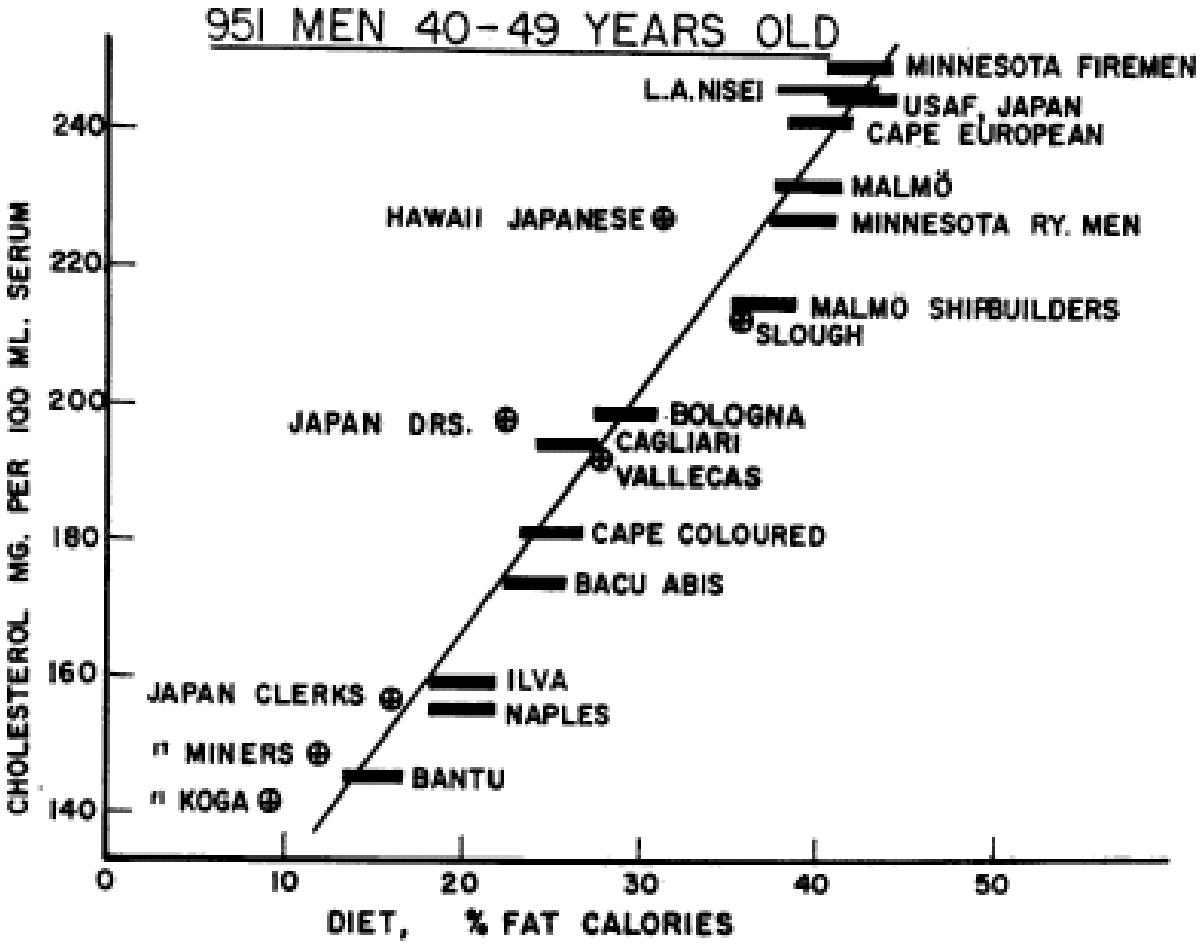
Integration of genetics and blood-markers for aetiology and drug-target validation


TWENTY-FIVE CENTS
JANUARY 12, 1961
Diet & Health
TIME
THE WEEKLY NEWSMAGAZINE
PHYSIOLOGIST
ANCEL KEYS
$7.00 A YEAR
VOL. LXXVII NO. 2

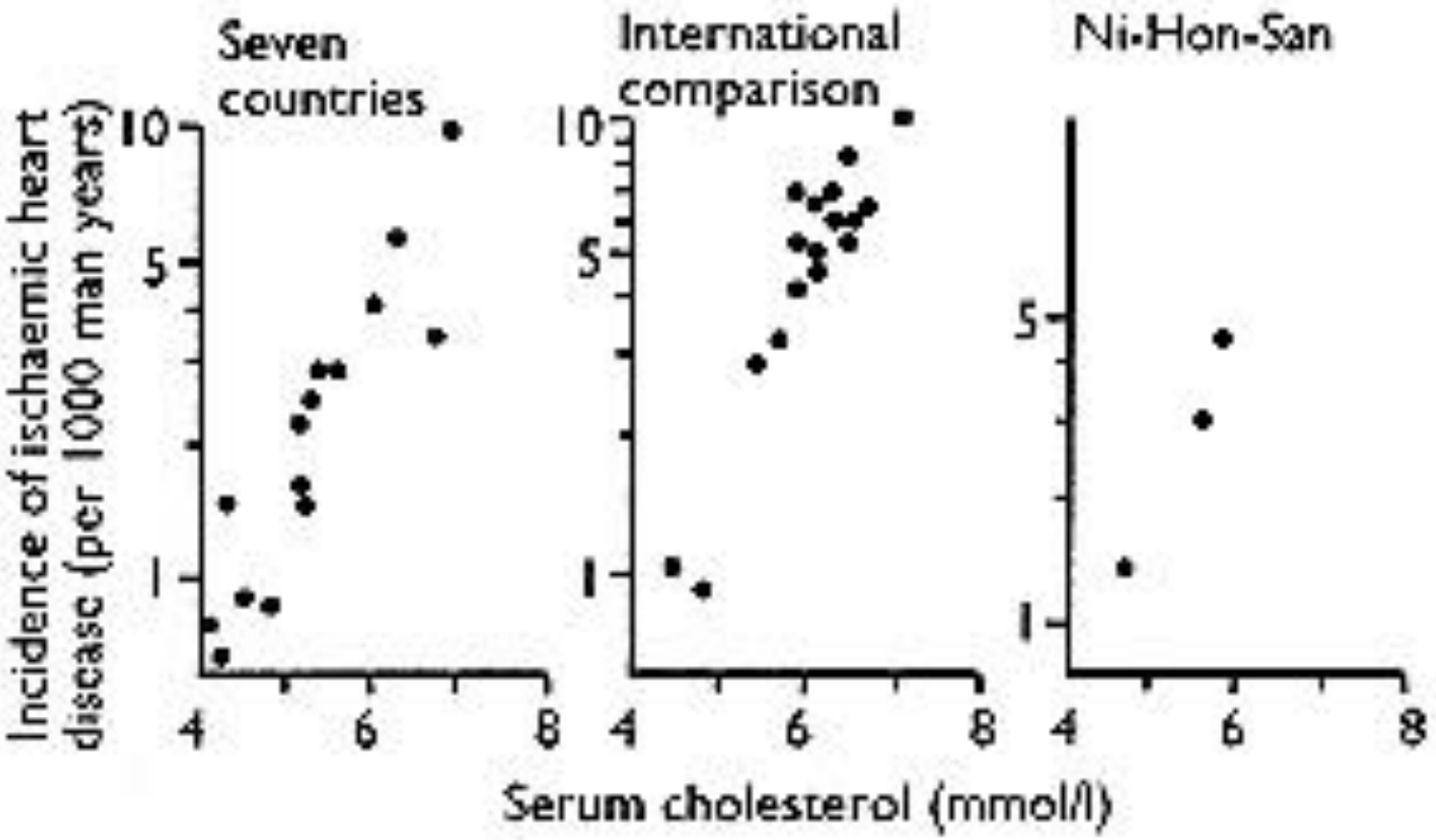
Distal exposure and biomarker

Average diet and serum total cholesterol concentration in clinically healthy men selected from 21 population groups



Ancel keys Am J Pub health 1957

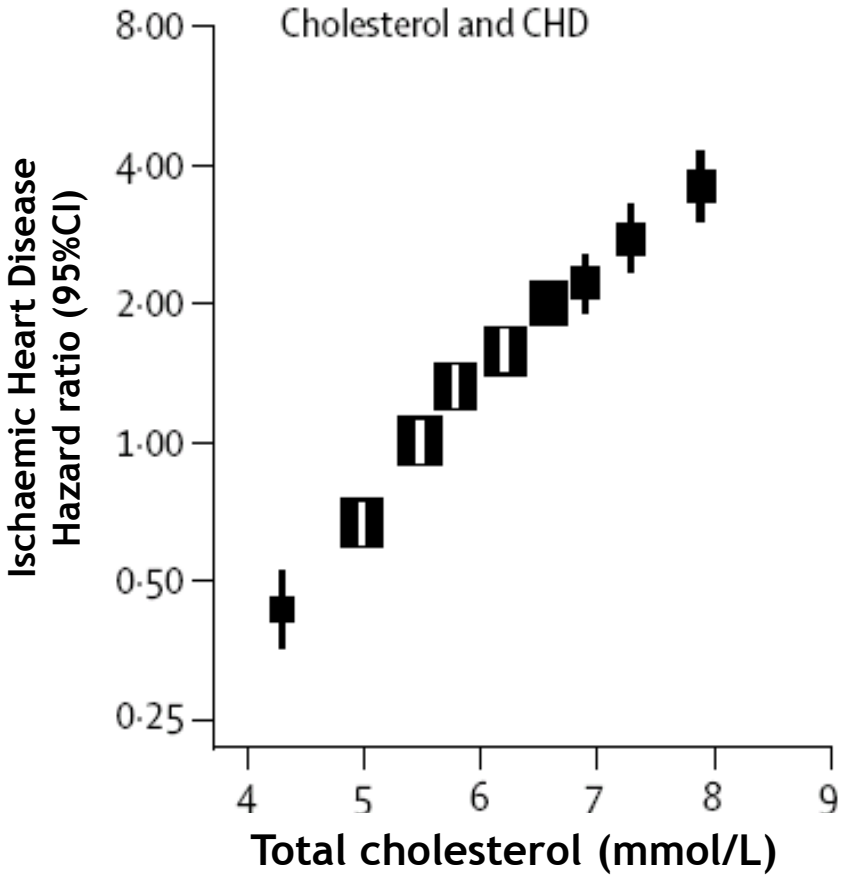
International studies:
comparing rates of ischaemic heart disease between communities with varying mean cholesterol concentrations



Law M R et al. BMJ 1994;308:367-372

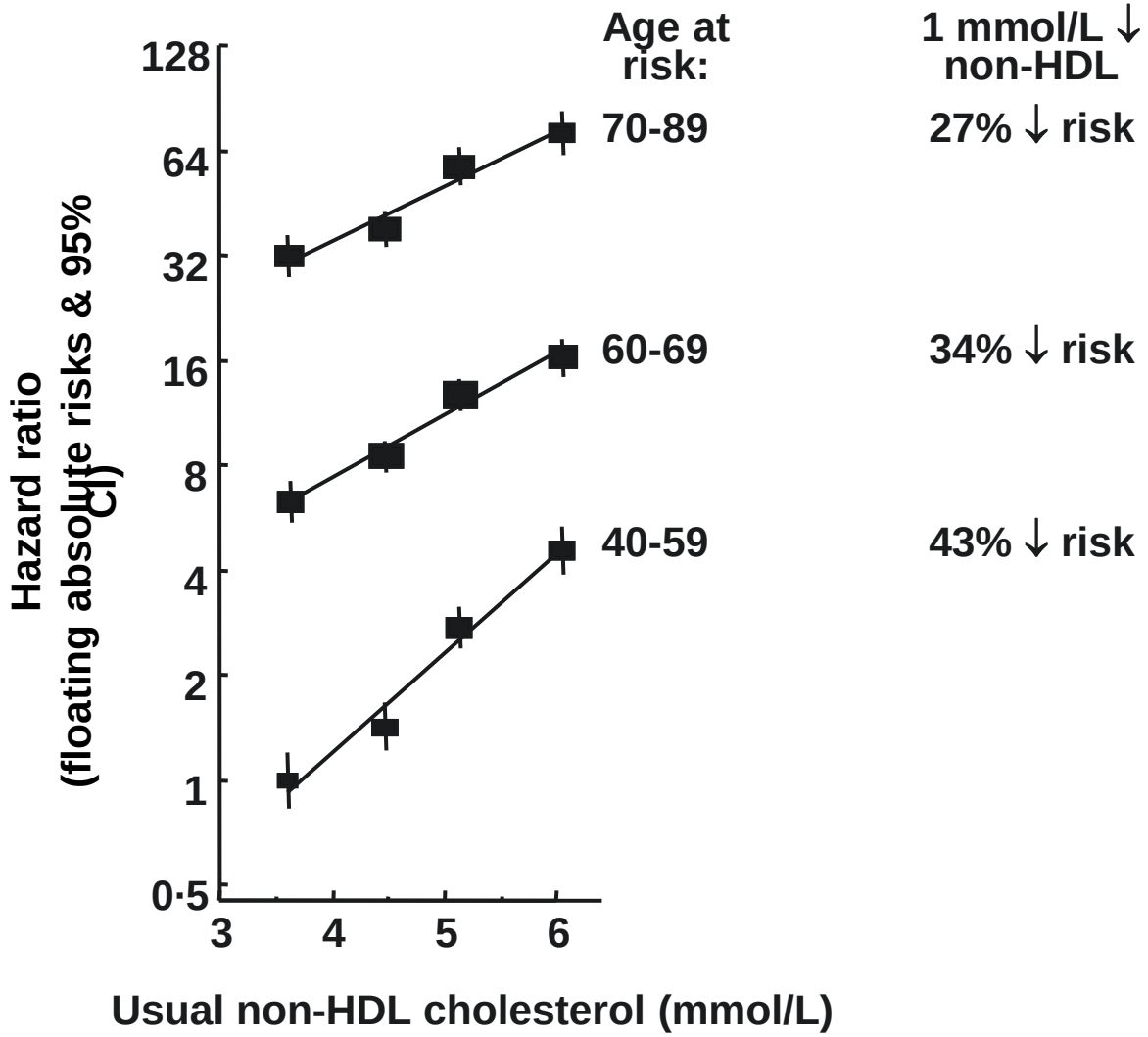
Biomarkers and clinical event

Meta-analysis of prospective cohort studies



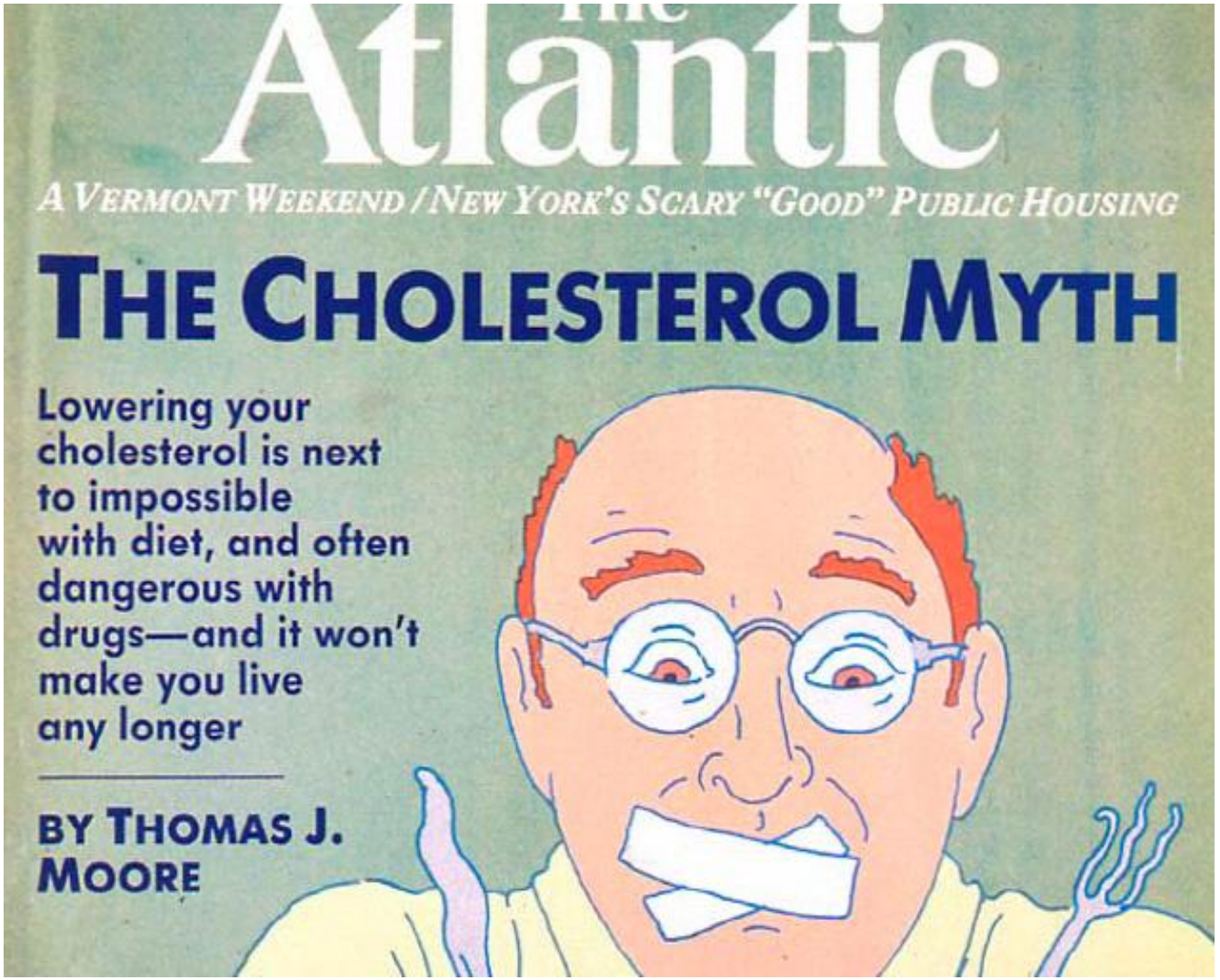
Lancet 2005

IHD mortality (3020 deaths) versus usual non-HDL cholesterol



Lancet 2007; 370:1829-39

"The cholesterol myth"



Identification of a “drug-target”
(e.g. HMG-CoA reductase)

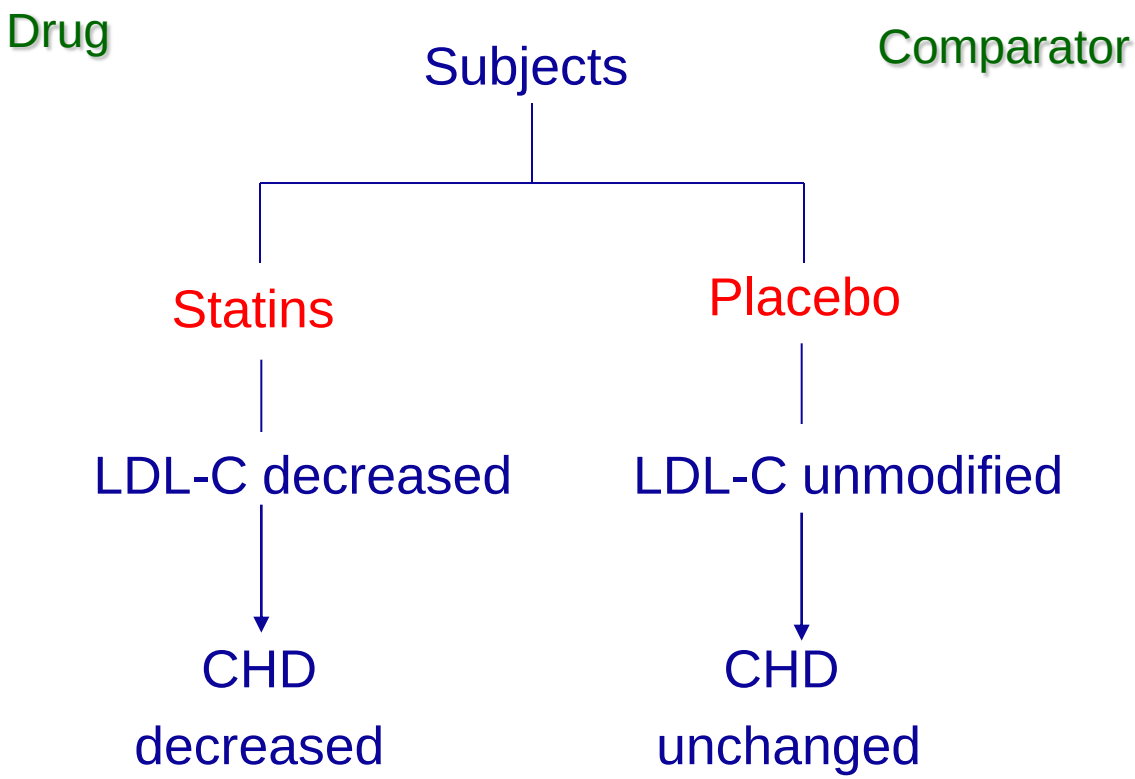
Drug-target discovery

Endo A, Kuroda M, Tanzawa K.

Competitive inhibition of 3-hydroxy-3-methylglutaryl coenzyme A reductase by ML-236A and ML-236B fungal metabolites, having hypocholesterolemic activity.

FEBS Lett. 1976

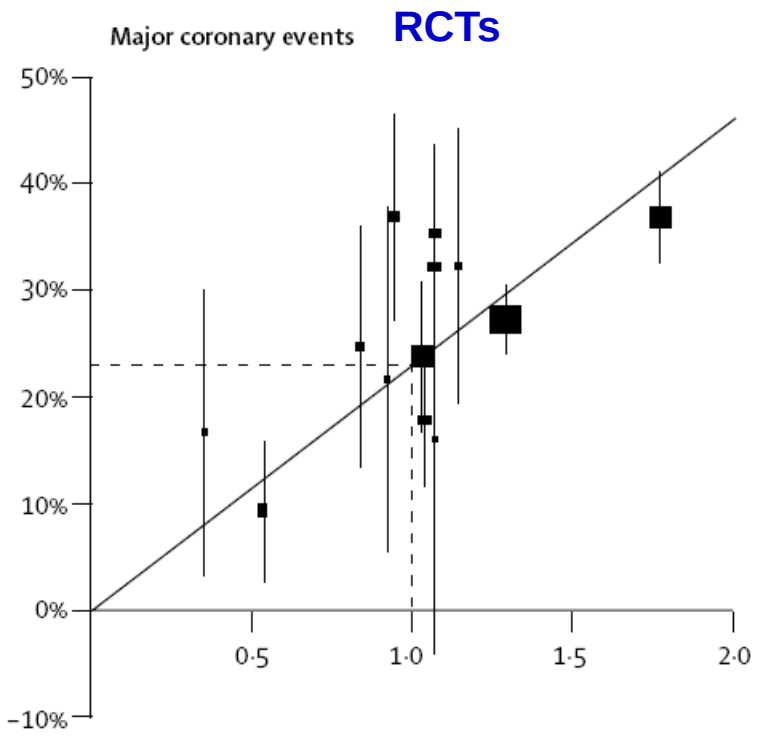
The final arbiter of the validity of the therapeutic target is the RCT in humans



Use randomisation to balance confounders

Validation of a “drug-target”
(e.g. HMG-CoA reductase)

Drug-target validation



Cholesterol Treatment Trialists’ collaborators
Lancet 2005.

Cholesterol, HMG-CoA reductase and CHD: A successful story

Dietary cholesterol

LDL-cholesterol

HMG-CoA reductase inhibitors

Randomised trials to evaluate effect on CHD

Structure of the lecture

Cholesterol and CHD illustrative example

Inflammation [CRP] and CHD

Integration of genetics and blood-markers for aetiology and drug-target validation

INTERHEART study: 9 risk factors explain ~90% of CHD

Smoking

Blood pressure

Cholesterol

Diabetes

Obesity

Fruit & vegetables

Physical activity

Alcohol consumption

Psychosocial factors

Risk factors with effective known interventions that reverse risk of CHD

Smoking

Blood pressure

Cholesterol

Diabetes

Obesity

Fruit & vegetables

Physical activity

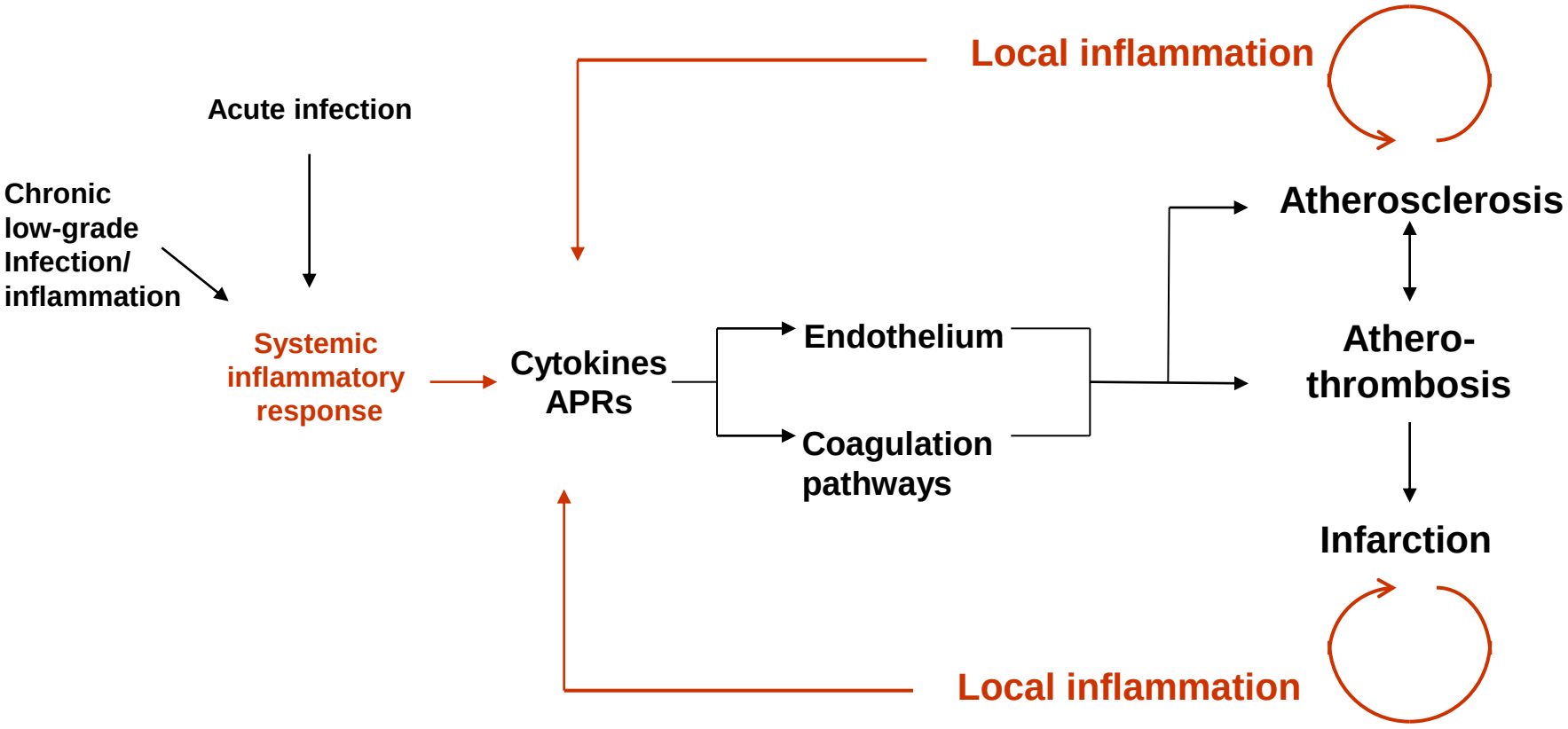
Alcohol consumption

Psychosocial factors

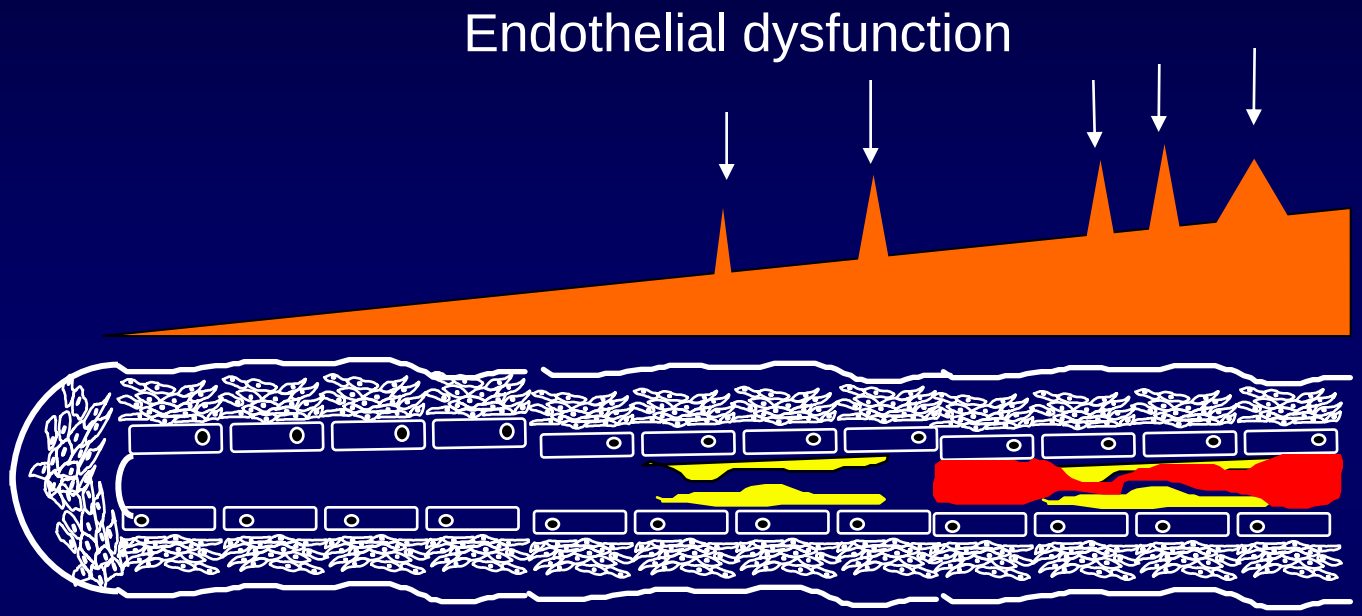
Evidence of a role of Inflammation in CHD

- Experiments *in vitro* and *in vivo* in animals
- Associations between infections and CVD
- Associations between inflammatory diseases and CVD
- Associations of CV risk factors and the inflammatory response
- Involvement of inflammatory cells and products in atherosclerotic plaques
- Associations between circulating agents/markers of the inflammatory response and CVD

A model linking infection and inflammation with atherosclerosis and its acute complications



Atherosclerosis timeline



Ischaemia and infarction

Genetic predisposition
Risk factor exposure

Early lesion

Complex lesion
Clinical events

Atherosclerosis → Atherothrombosis

Biology of C-reactive protein

Tissue injury
Infection
Inflammation
Adverse non-physiological “stress”

Regulators
IL-1
IL-6
TNF-alpha

Liver

CRP
phosphocholine

Bacterial cell wall
Fungi, parasites
Apoptotic cells
Modified lipids

Opsonisation

Complement fixation

Clearance
(constant
half-life 19h)

Hirschfield and Pepys, JCI 2003

CRP as a useful biomarker to evaluate the role of inflammation on Coronary Heart Disease

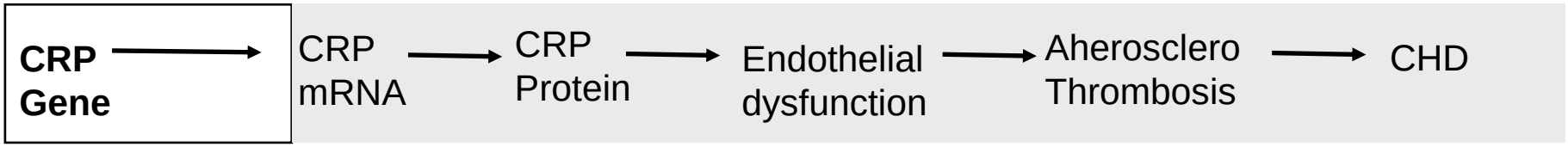
CRP was discovered in 1930

Technology: ~ mid-1990s Immunoassays methods available

CRP levels were associated with endothelial dysfunction

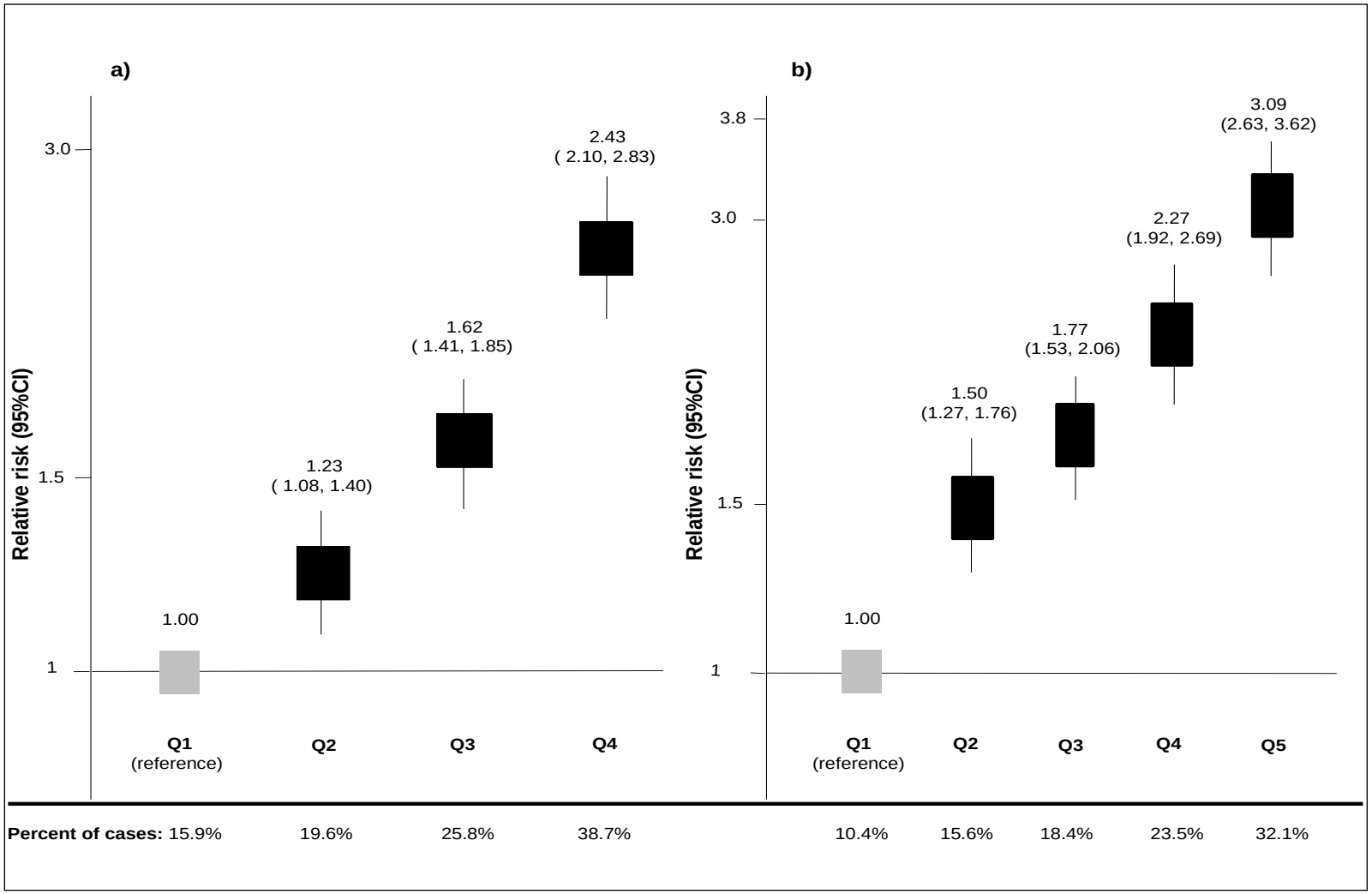
CRP levels were correlated with higher levels of atherosclerosis (C-IMT)

CRP levels were associated with incident CHD in several prospective studies



Observation: CRP is associated with risk CHD

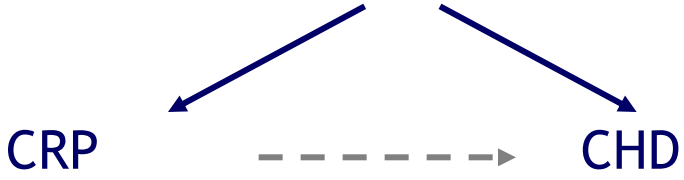
Systematic Review of 31 prospective studies



Shah T, et al. Int J Epidemiol 2008

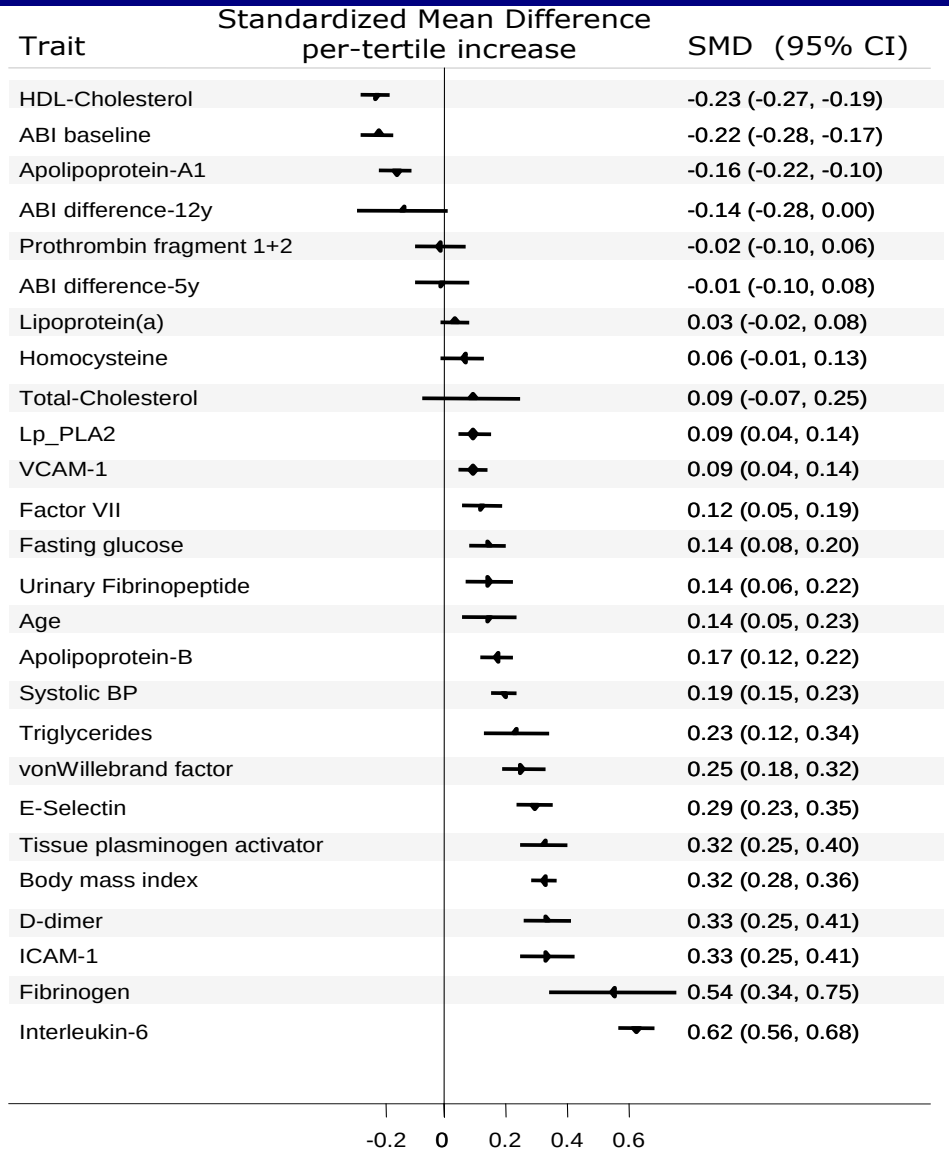
C-reactive protein and CHD: cause, consequence or confounding

Smoking, Alcohol, physical inactivity, LDL, excess of adiposity ……..

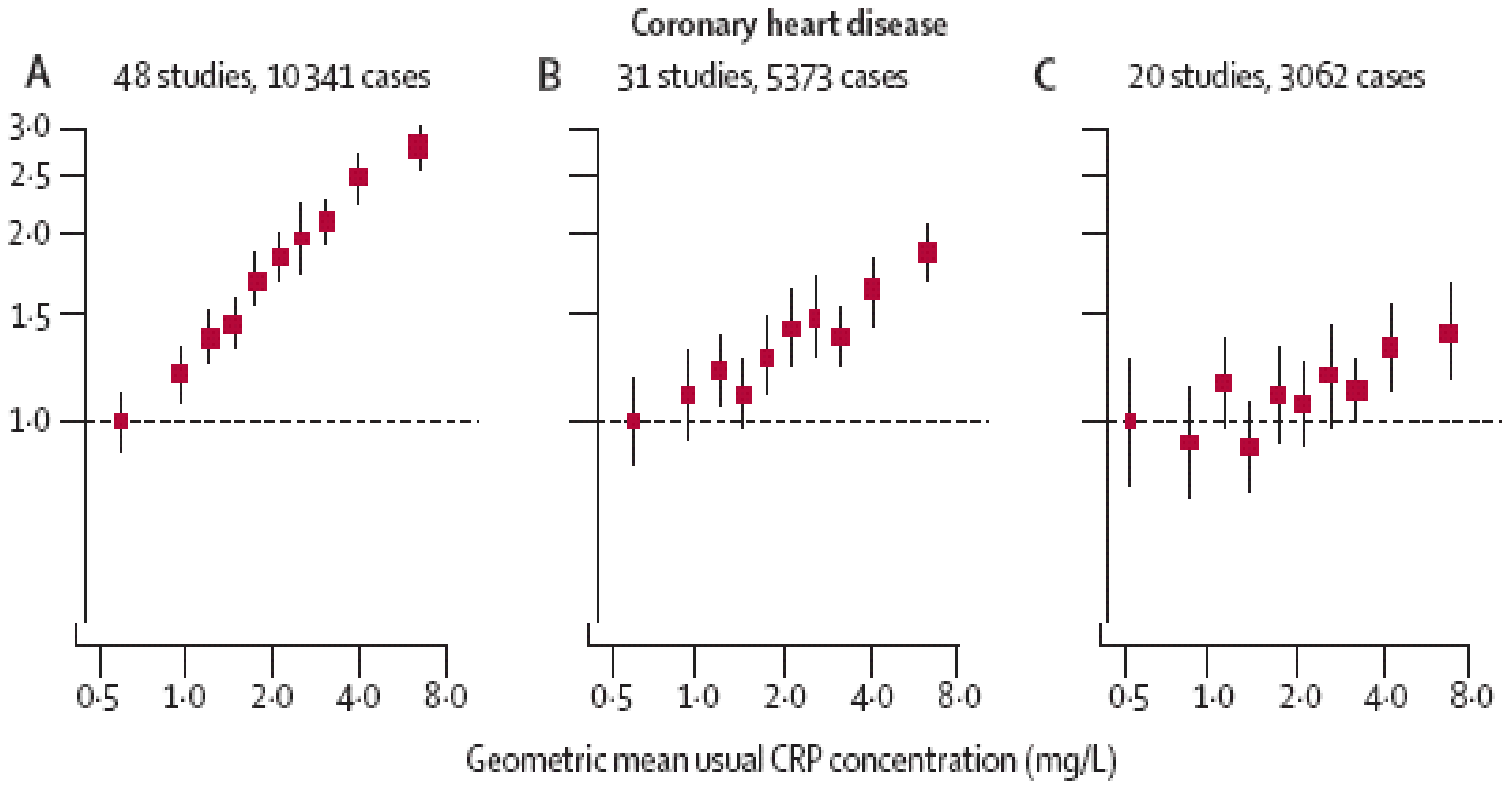


C-reactive protein and CHD: *confounding*

Effect of plasma CRP on 26 CV traits



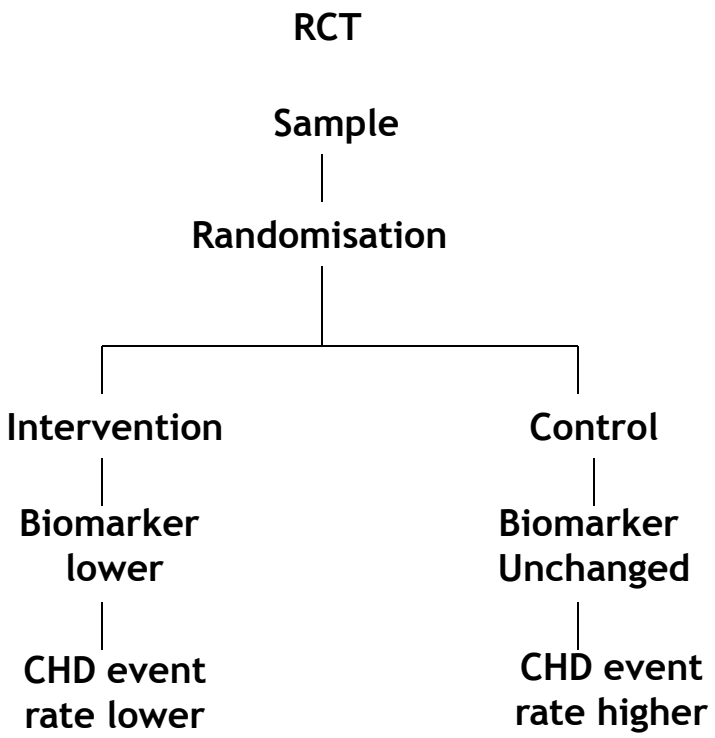
C-reactive protein and risk of CHD disease

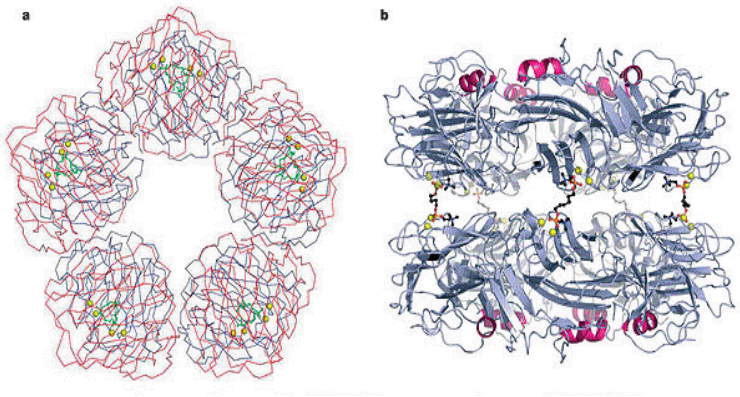


ERFC Lancet 2009

Randomisation to judge causality

Drug intervention





Pepys MB et al.
Nature 2006; 440: 1217-1221

Structure of the lecture

Cholesterol and CHD illustrative example

Inflammation [CRP] and CHD

Integration of genetics and blood-markers for aetiology and drug-target validation

Can genetics help us to obtain randomised - unbiased - evidence about environmental factors ?

Mendel's second law
– the law of independent assortment –

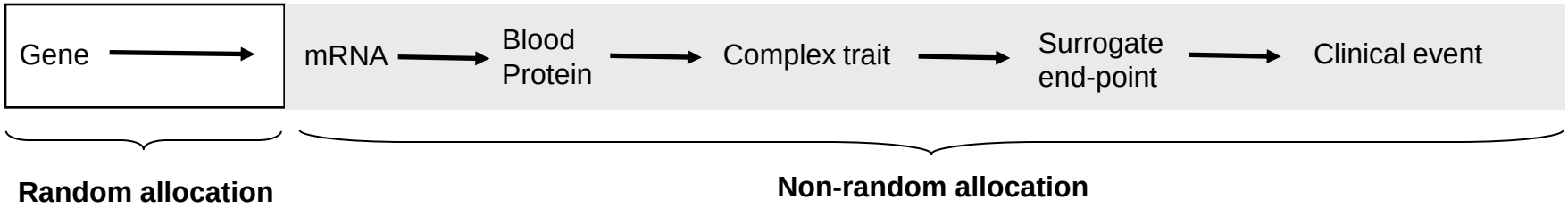
Mendel in 1862

"the behaviour of each pair of differentiating characteristics in hybrid union is *independent* of the other differences between the two original plants, and, further, the hybrid produces just so many kinds of egg and pollen cells as there are possible constant combination forms"

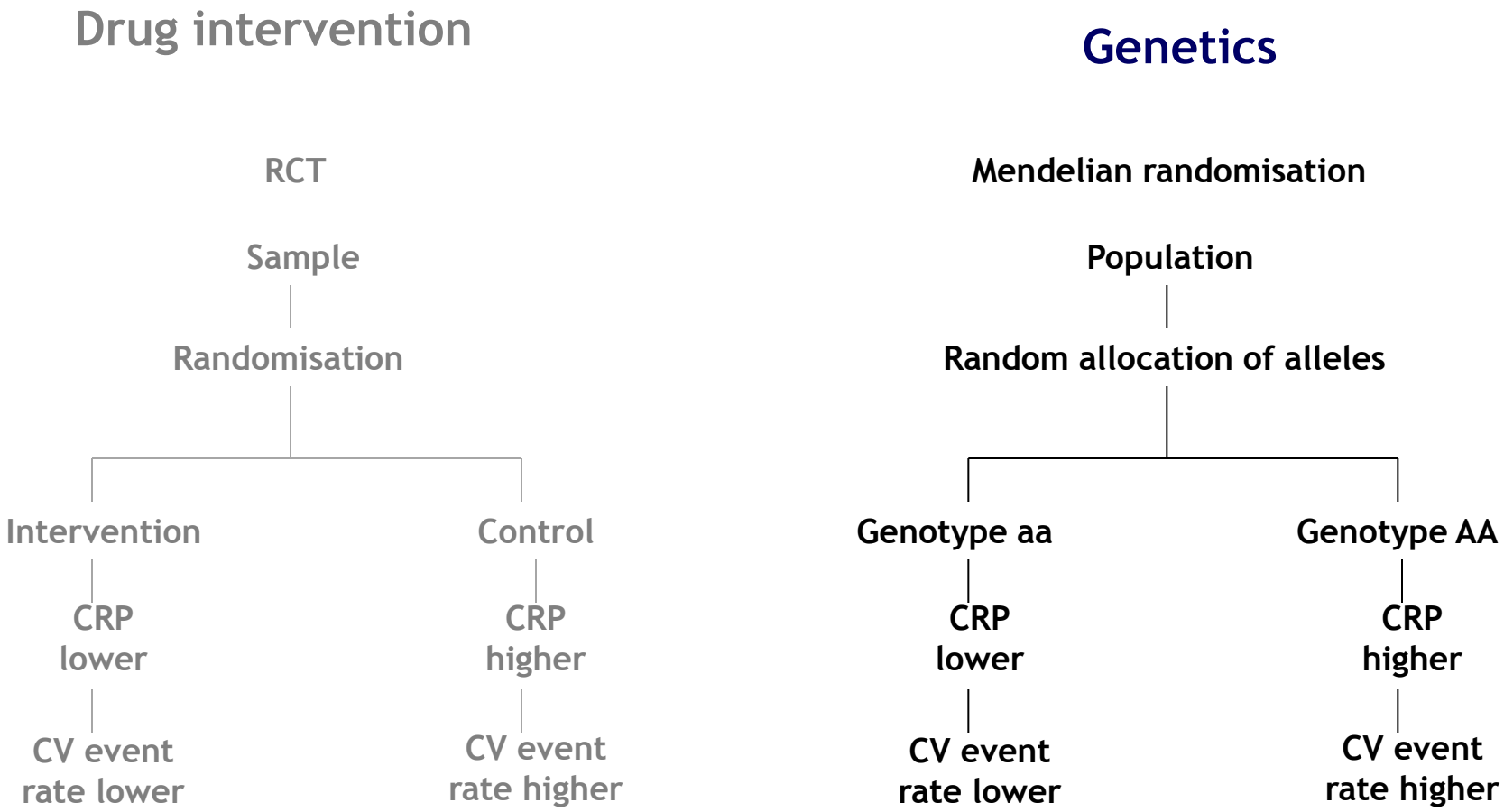
Gregor Mendel, 1865.

How can we capitalise on the Mendel second law for the search of causes ?

- Minimise substantially confounding
- Abolish reverse causality
- Minimise / abolish regression dilution bias

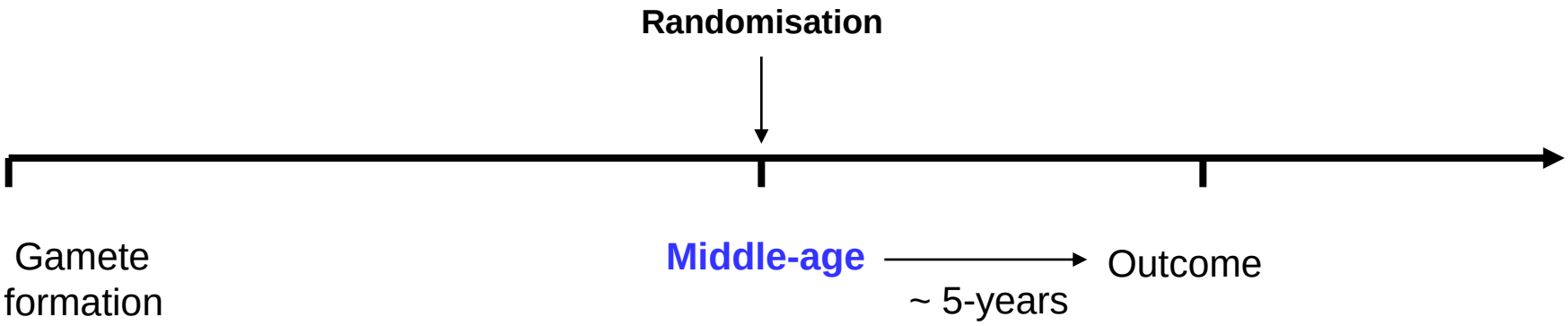


Randomisation to judge CRP causality in CHD

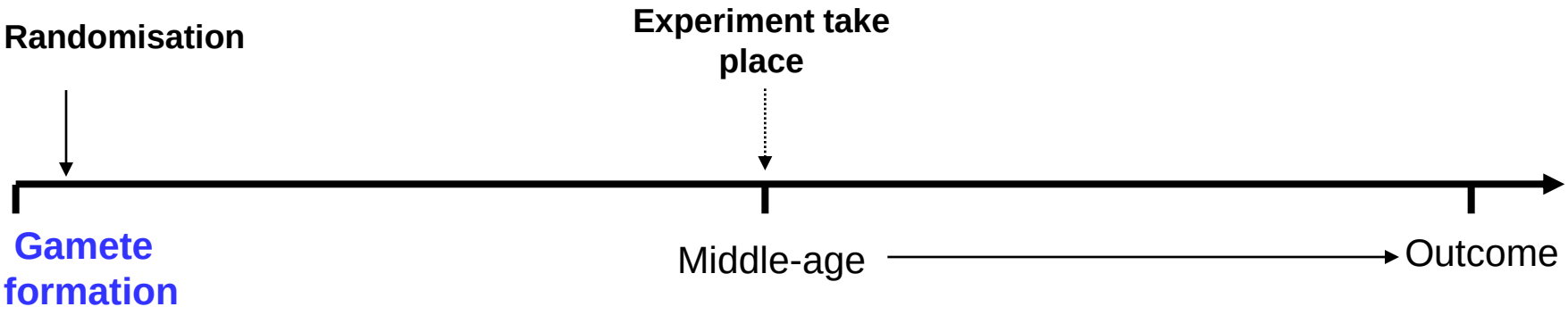


Nature's *Life-time* randomised trials
vs.
Fixed-duration randomised trials

Drug intervention

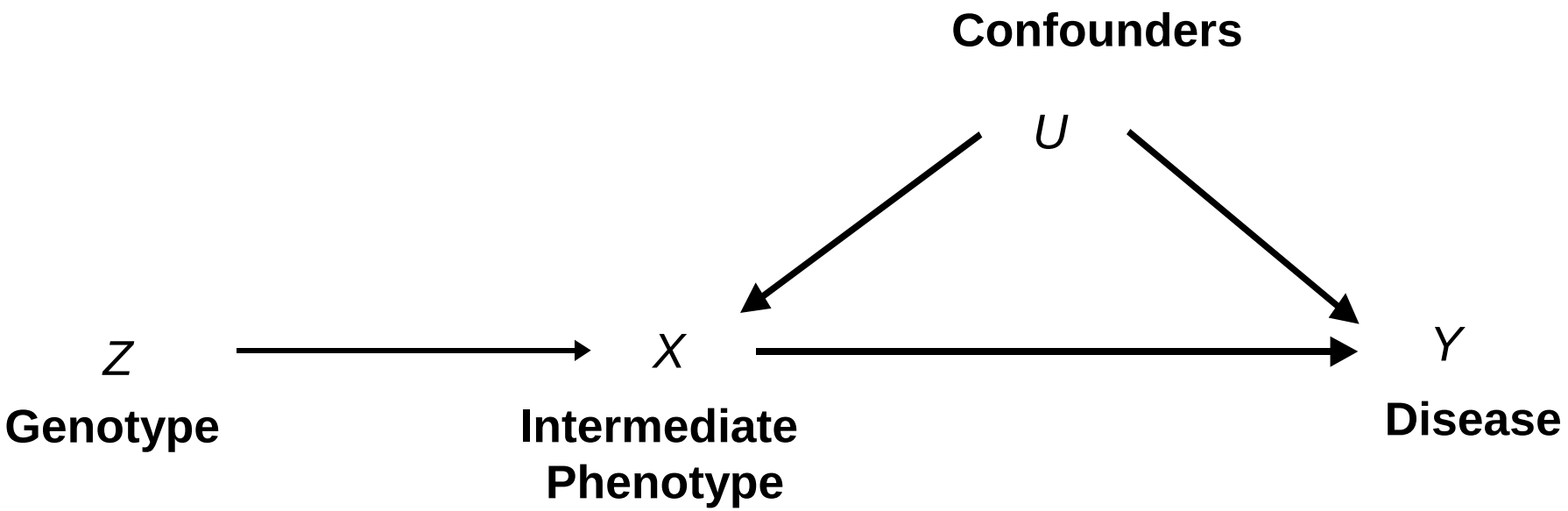


Genetics



Mendelian randomisation analysis

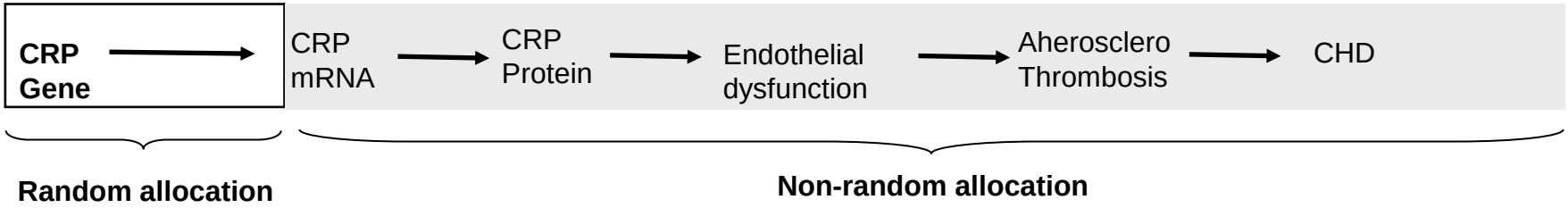
"Instrumental variable" technique



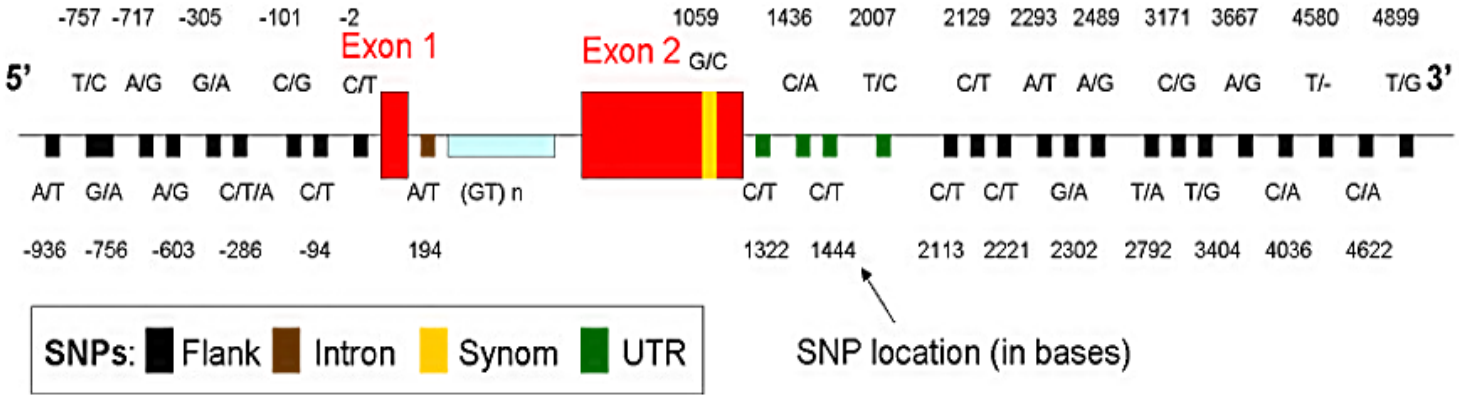
Assumptions of IV technique for Mendelian randomisation:

1. The Instrumental variable (IV) *Z* is associated with exposure of interest *X*
2. Z is independent of the confounding factors *U* (that confound X-*Y* association)
3. **Genotype is related to the outcome only *via* its association with the modifiable exposure**

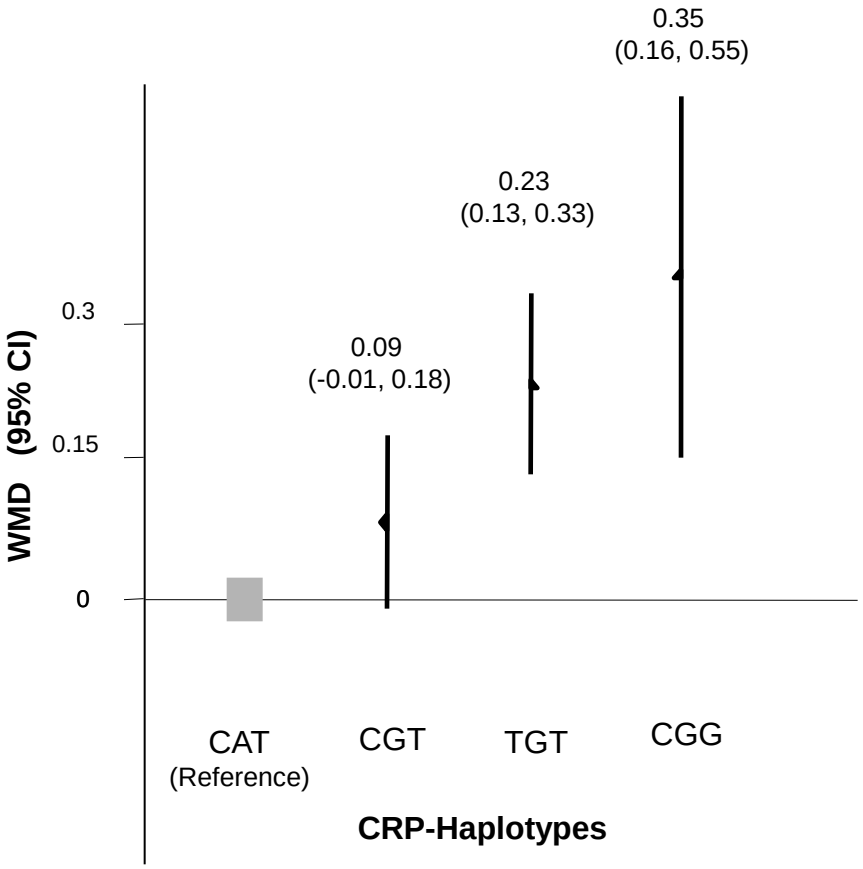
First step: Adequate selection of the most suitable “tools” to conduct a Mendelian randomisation experiment



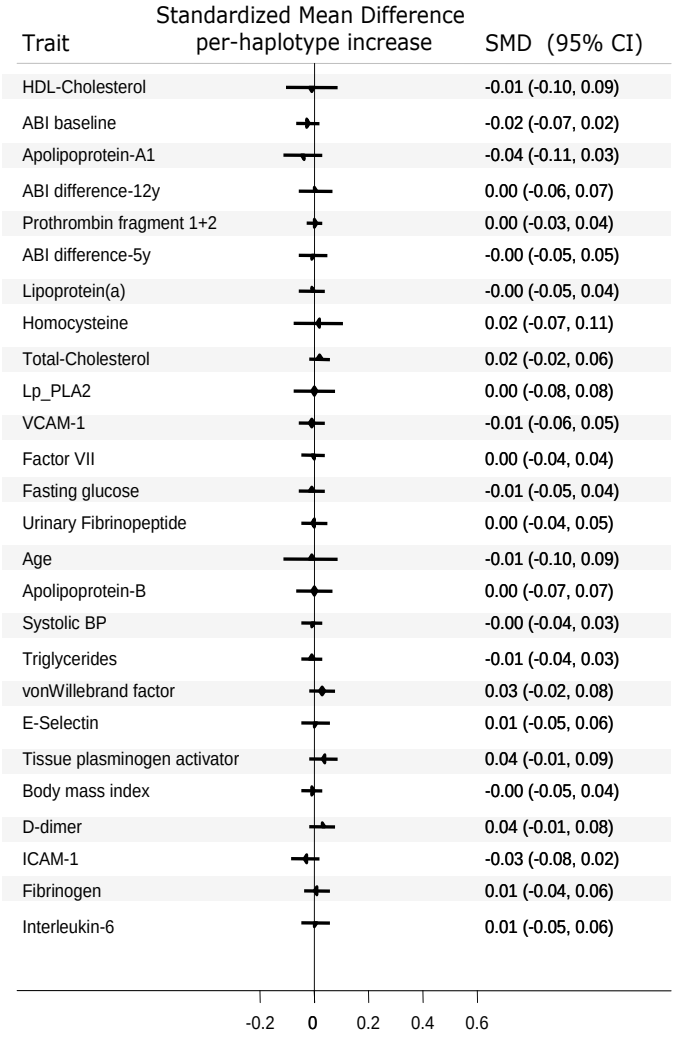
15 SNPs in the CRP gene in individuals of European ancestors



Maintenance of the random allocation of potential confounders among most common CRP haplotypes



ii) CRP-haplotype & cardiovascular traits



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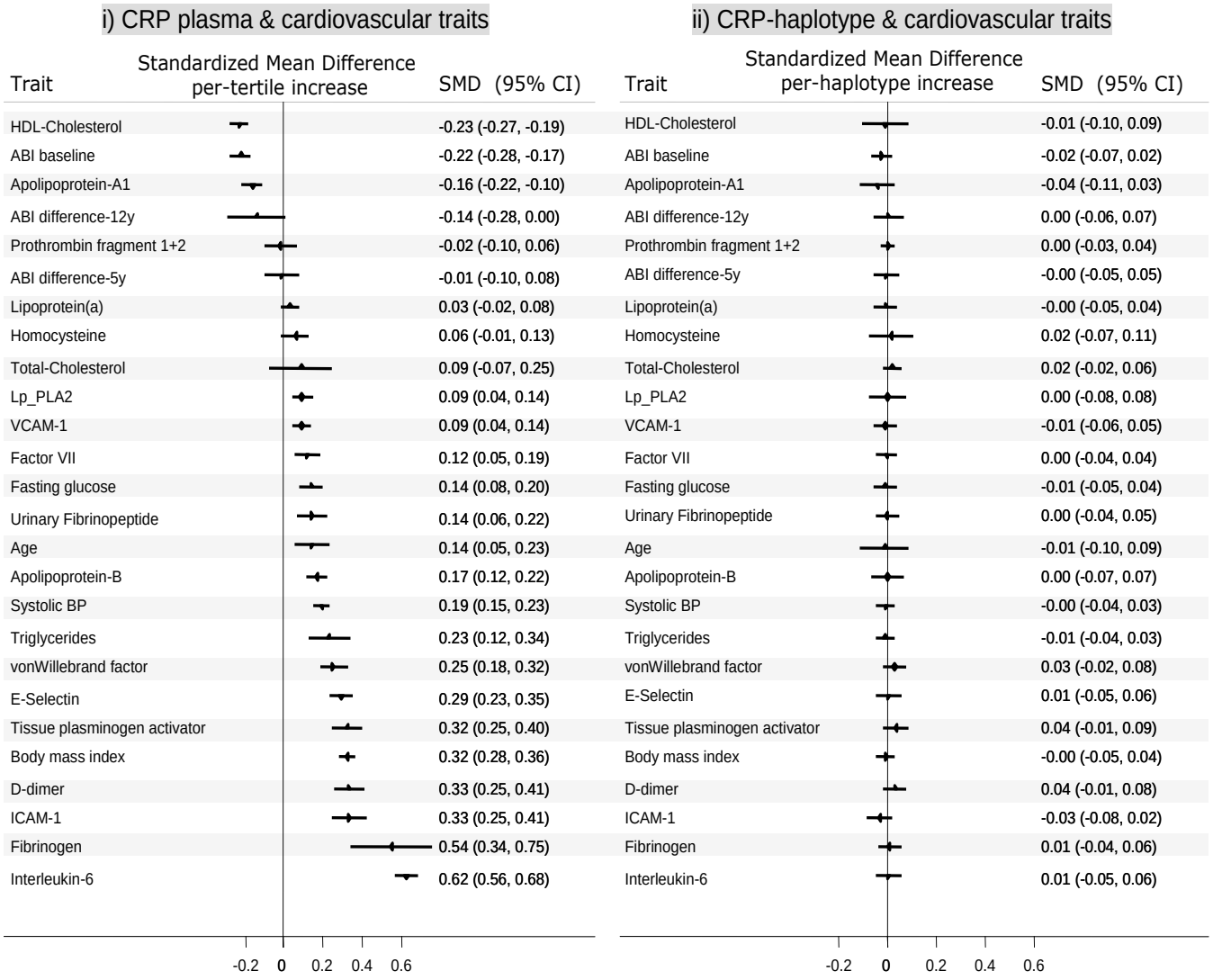
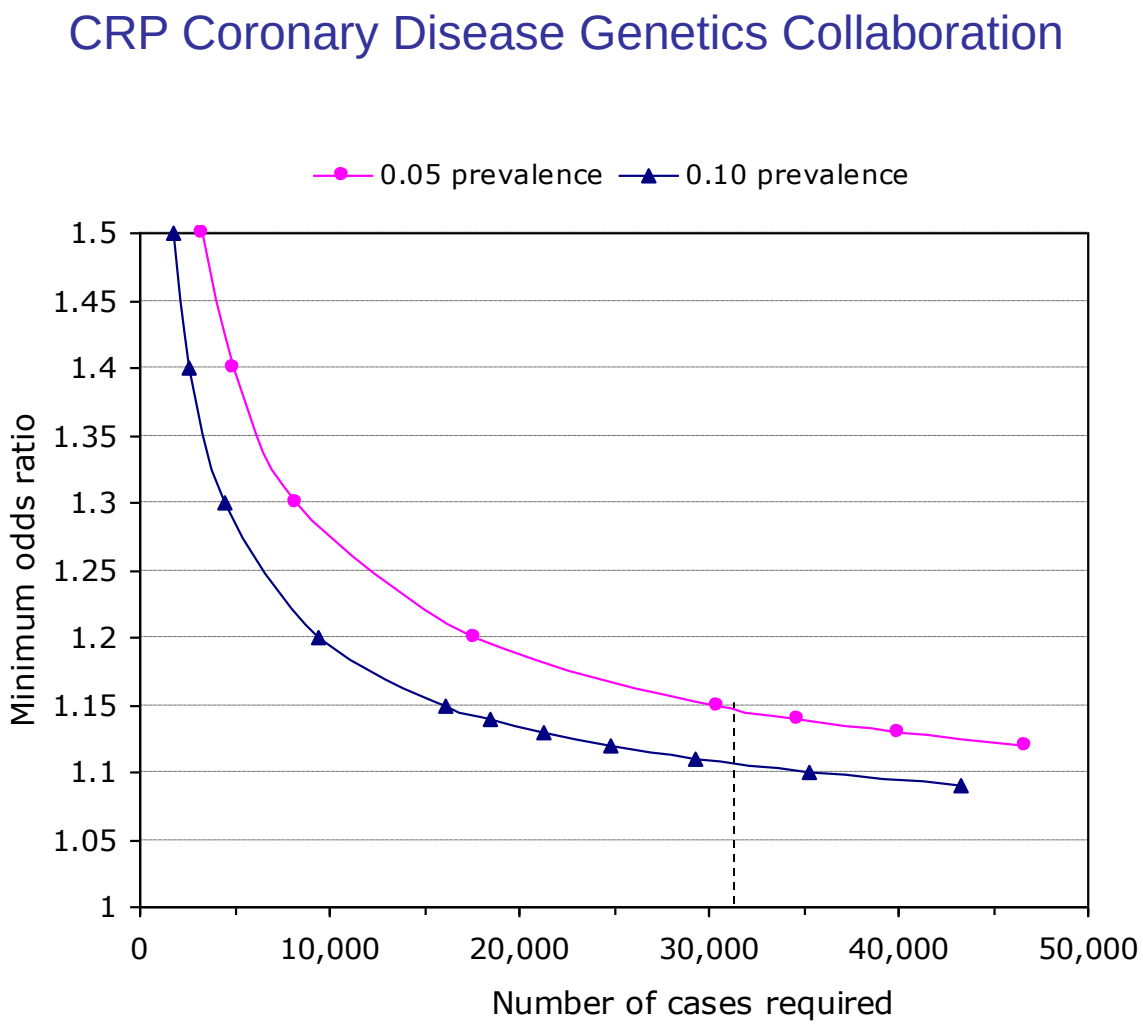
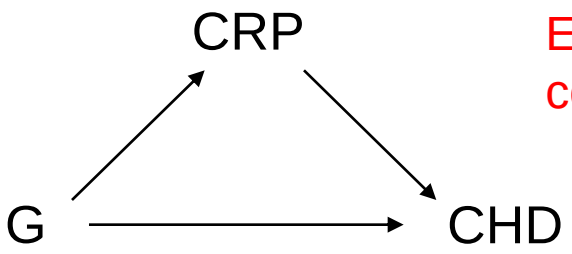


Second step: Get the adequate sample size



Mendelian randomisation experiment to assess the causal relevance of CRP for coronary disease

Cross-sectional or prospective studies



Emerging risk factors collaboration

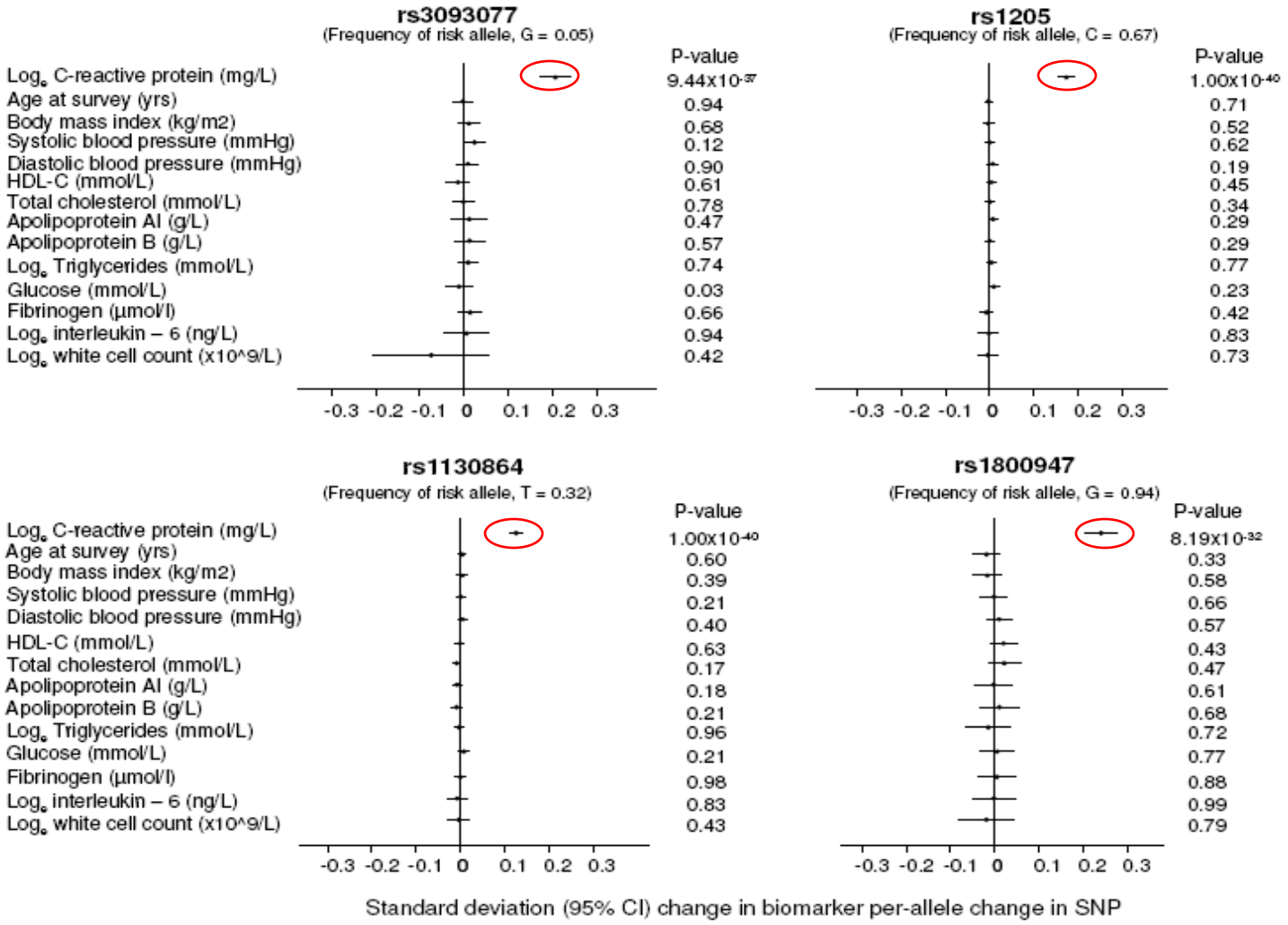
Case-control or Prospective studies

CRP Coronary Disease Genetic Collaboration (CCGC)
31 studies, 30,000 cases, 100,000 controls

Coordinators Centres: Cambridge, UCL and LSHTM

CRP Coronary Disease Genetics Collaboration

194,418 participants and 46,557 coronary heart disease events



BMJ 2011

CRP Coronary Disease Genetics Collaboration

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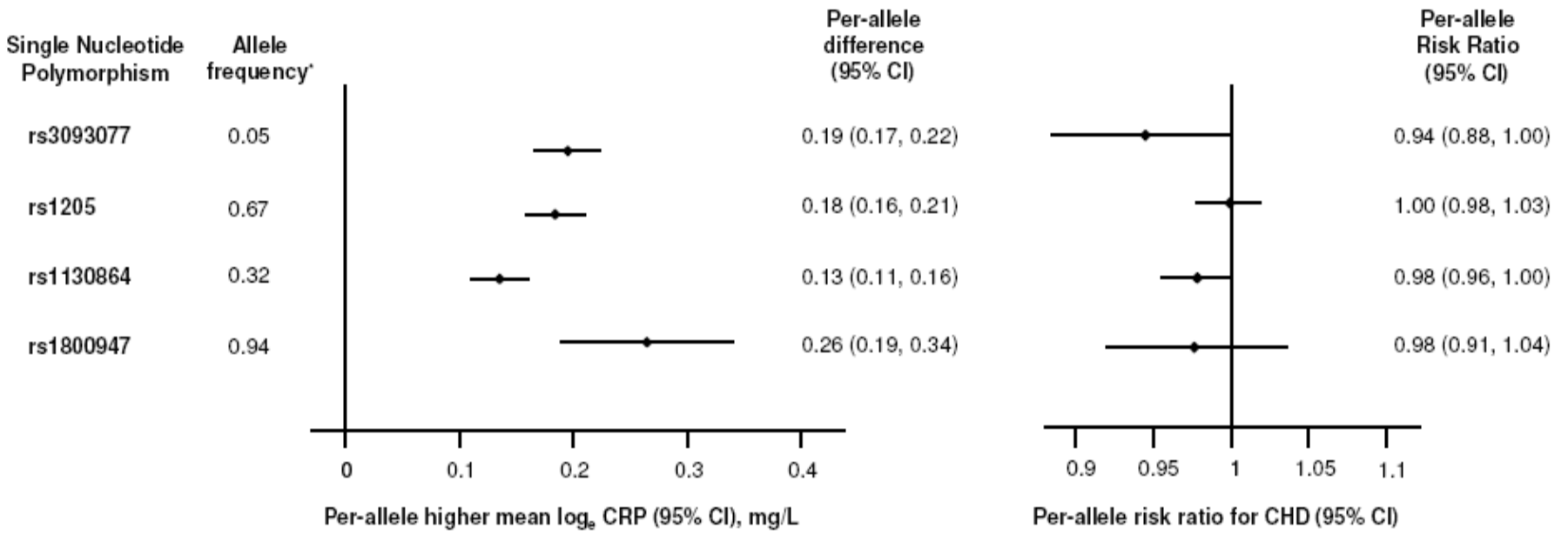


Biomarkers and Coronary Heart Disease

- Excessive number of drug-targets (e.g. CVD)

Inflammation
C-reactive protein
SAA
Interleukins
Soluble adhesion molecules
sCD40 ligand

Haemostasis/ thrombosis
Fibrinogen
vWF
tPA
D-dimer
PAI-1

Oxidative stress/lipids
Homocysteine
Lipoprotein associated phospholipase A2
Myeloperoxidase

…….and around 200 others….

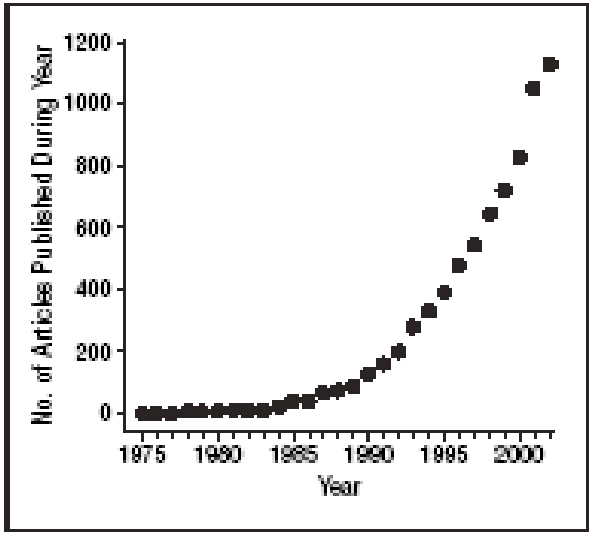
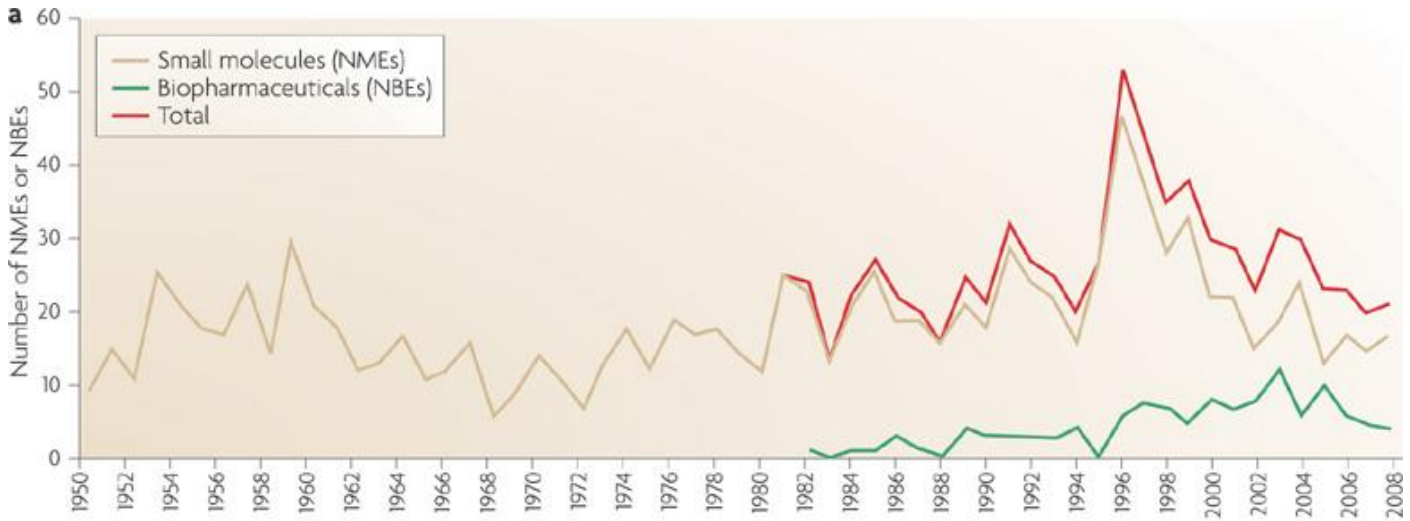


Figure 1. Increase in the number of articles per year that contain the terms *independent risk factor* or *independent predictor* in their title or abstract.

Causal link?
Drug targets?

Output of new molecular entities (NMEs) since 1950

Munos B. Nature Rev Drug Discovery 2009



Conclusions

1. Use of biomarkers in epidemiology provides new option in aetiology – drug-developement and risk prediction

2. The sharp increase in technology and the low-cost of these techniques will provide access to an increasingly large numbers of biomarkers

3. Old known biases in epidemiology remain as the main challenges to translate findings from molecular epidemiology into risk prevention

4. Integration of different layers of biological factors, each of them exposed to a different set of biases seems to be a promising approach to accelerate the translation of biomarkers research into clinical care

Suggested readings

C-reactive protein and coronary heart disease: a critical review.
Casas JP, Shah T, Hingorani AD, Danesh J, Pepys MB.
J Intern Med. 2008 Oct;264(4):295-314.

Association between C reactive protein and coronary heart disease: mendelian randomisation analysis based on individual participant data.
C Reactive Protein Coronary Heart Disease Genetics Collaboration (CCGC), Wensley F, Gao P, Burgess S, Kaptoge S, Di Angelantonio E, Shah T, Engert JC, Clarke R, Davey-Smith G, Nordestgaard BG, Saleheen D, Samani NJ, Sandhu M, Anand S, Pepys MB, Smeeth L, Whittaker J, Casas JP, Thompson SG, Hingorani AD, Danesh J.
BMJ. 2011 Feb 15;342:d548

Critical appraisal of CRP measurement for the prediction of coronary heart disease events: new data and systematic review of 31 prospective cohorts.
Shah T, Casas JP, Cooper JA, Tzoulaki I, Sofat R, McCormack V, Smeeth L, Deanfield JE, Lowe GD, Rumley A, Fowkes FG, Humphries SE, Hingorani AD.
Int J Epidemiol. 2009 Feb;38(1):217-31.

C-reactive protein concentration and risk of coronary heart disease, stroke, and mortality: an individual participant meta-analysis.
Emerging Risk Factors Collaboration, Kaptoge S, Di Angelantonio E, Lowe G, Pepys MB, Thompson SG, Collins R, Danesh J.
Lancet. 2010 Jan 9;375(9709):132-40. Epub 2009 Dec 22.