Mendelian Randomization Study in CVD

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Epidemiolgical studies in CVD

- Identified most major risk factors.
- Effectiveness of screening, diagnosis and treatment modalities
- Discovered a huge number of biomarkers

- Biomarkers for CVD
  - Causally related with disease
  - Causally **NOT** related with disease

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- Identified most major risk factors.
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- Biomarkers for CVD
  - Causally related with disease: Potential prevention & treatment target
  - Causally **NOT** related with disease: Diagnostic or prognostic values

Causal relationship between biomarker & disease

- Extremely difficult to determine
- Randomized controlled trial (RCT) is the best solution
- RCT usually not feasible
  because, we cannot randomly assign biomarker levels
- Mendelian randomization study is a new alternative

Ex 1) Alcohol intake -> Depression

International Journal of Epidemiology, 2015, 526–539
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Original article

Mendelian Randomization Causal Analysis

Increased alcohol consumption as a cause of alcoholism, without similar evidence for depression: a Mendelian randomization study

Marie Kim Wium-Andersen,[1,2,3] David Dynnes Ørsted,[1,2,3] Janne Schurmann Tolstrup[4] and Børge Grønne Nordestgaard[1,2,3,5]*

Int J Epidemiol. 2015;44(2):526-39.

Drinking - Depression

Alcohol causes depression?

Depression makes people drinking?

Third factor?

Study designs

Study population

- Copenhagen General Population Study (n = 67,650)
- Copenhagen City Heart Study (n = 10,504)

Outcome

- Depression
- Alcoholism

Covariates

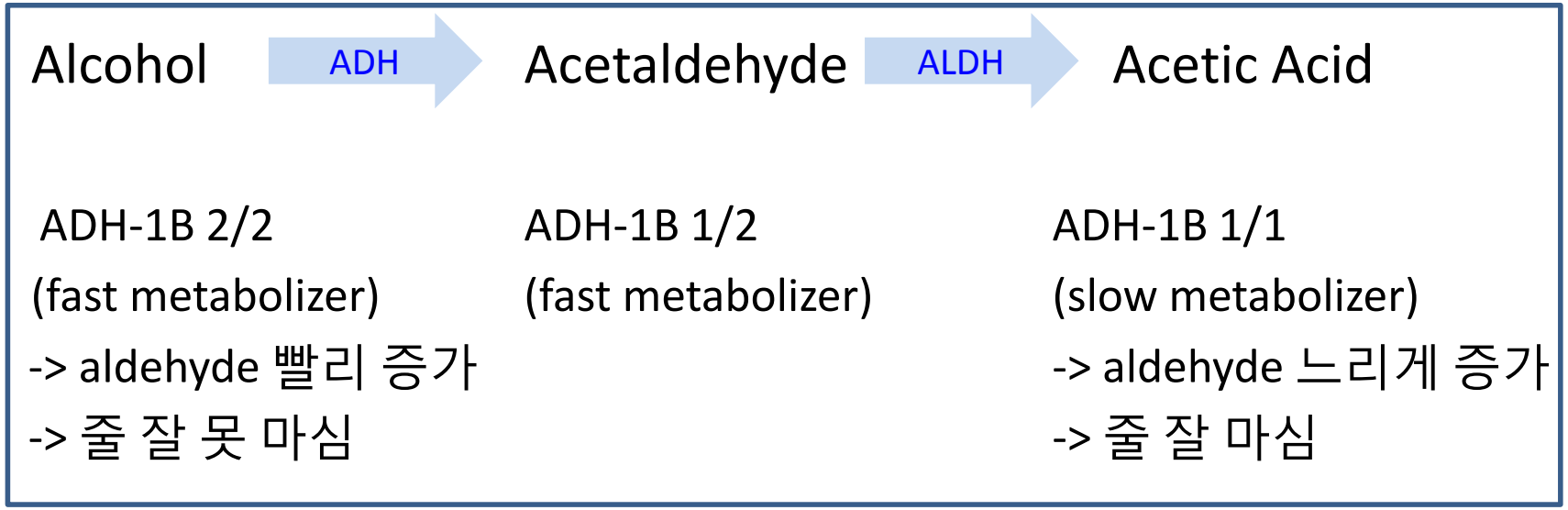
- BMI, CRP, Smoking, Physical activity, Education, …

Int J Epidemiol. 2015;44(2):526-39.

Study designs

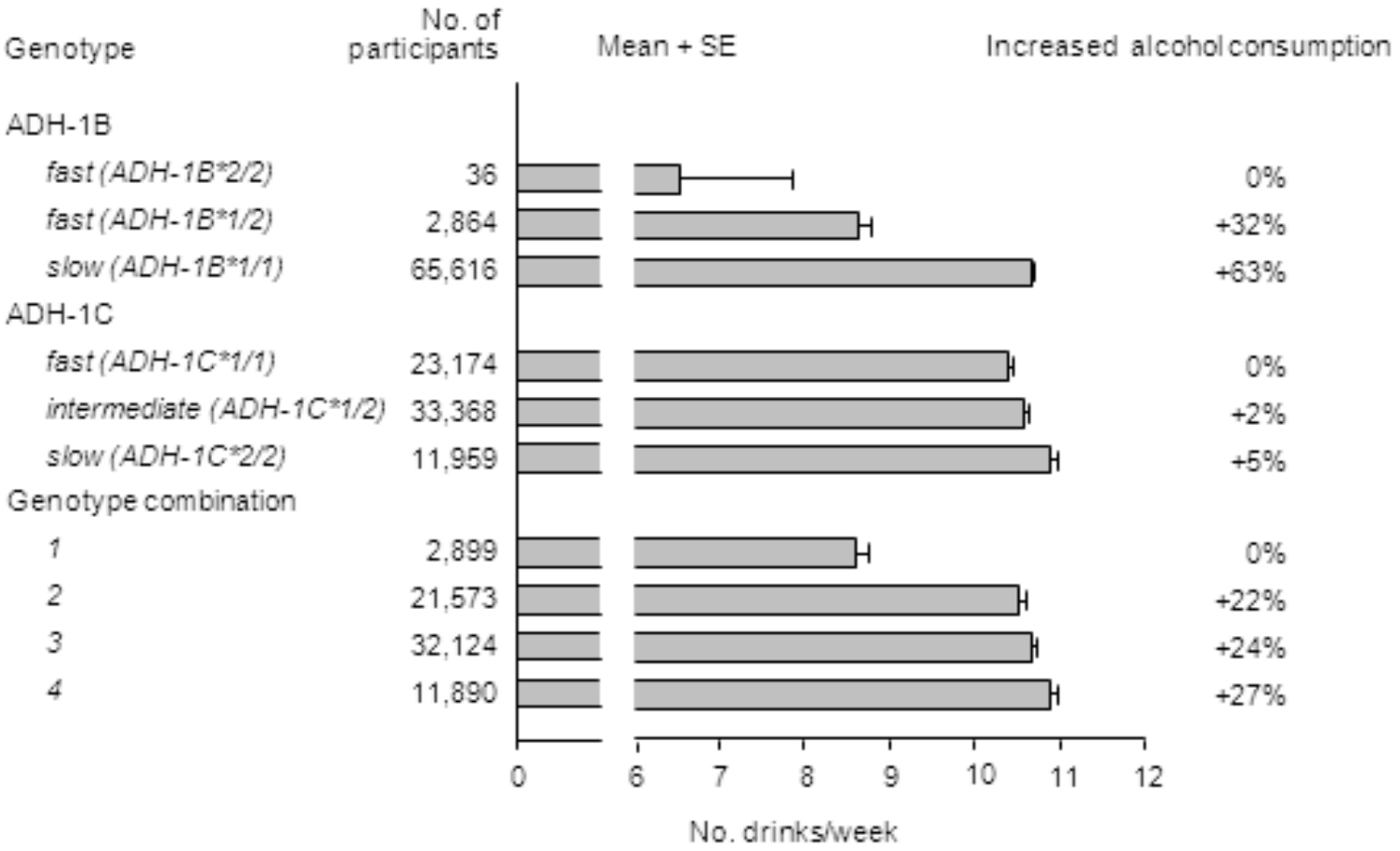
Exposure

- Alcohol intake by questionnaire
- Genotypes affecting alcohol intake



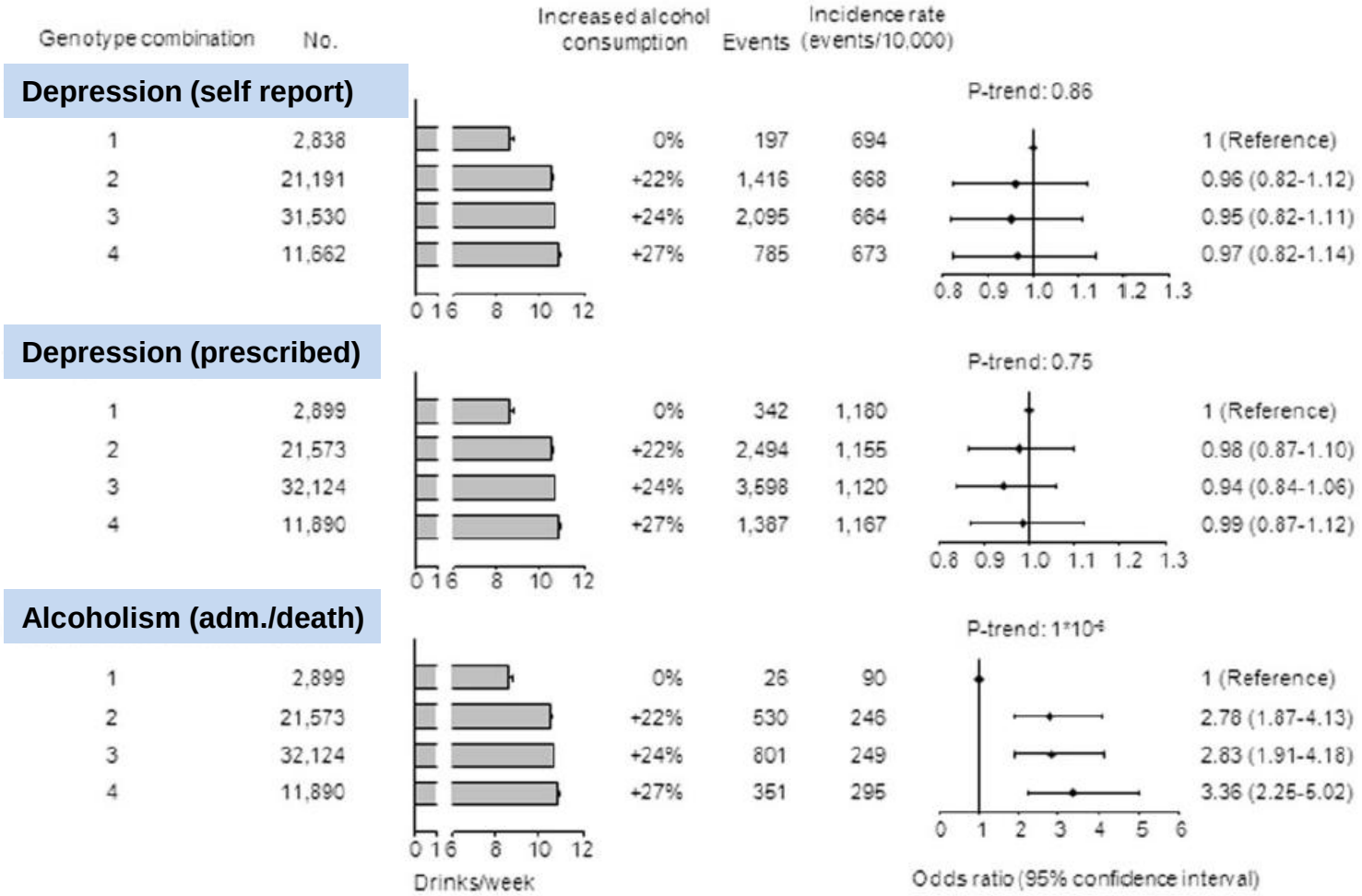
Int J Epidemiol. 2015;44(2):526-39.

Genotype -> Alcohol intake



Int J Epidemiol. 2015;44(2):526-39.

Gene-related alcohol intake -> Depression



Int J Epidemiol. 2015;44(2):526-39.

Conclusion

Findings support that

- Increased alcohol intake may cause alcoholism.
- Increased alcohol intake does not cause depression.

Int J Epidemiol. 2015;44(2):526-39.

Mendelian Randomization (MR) Study

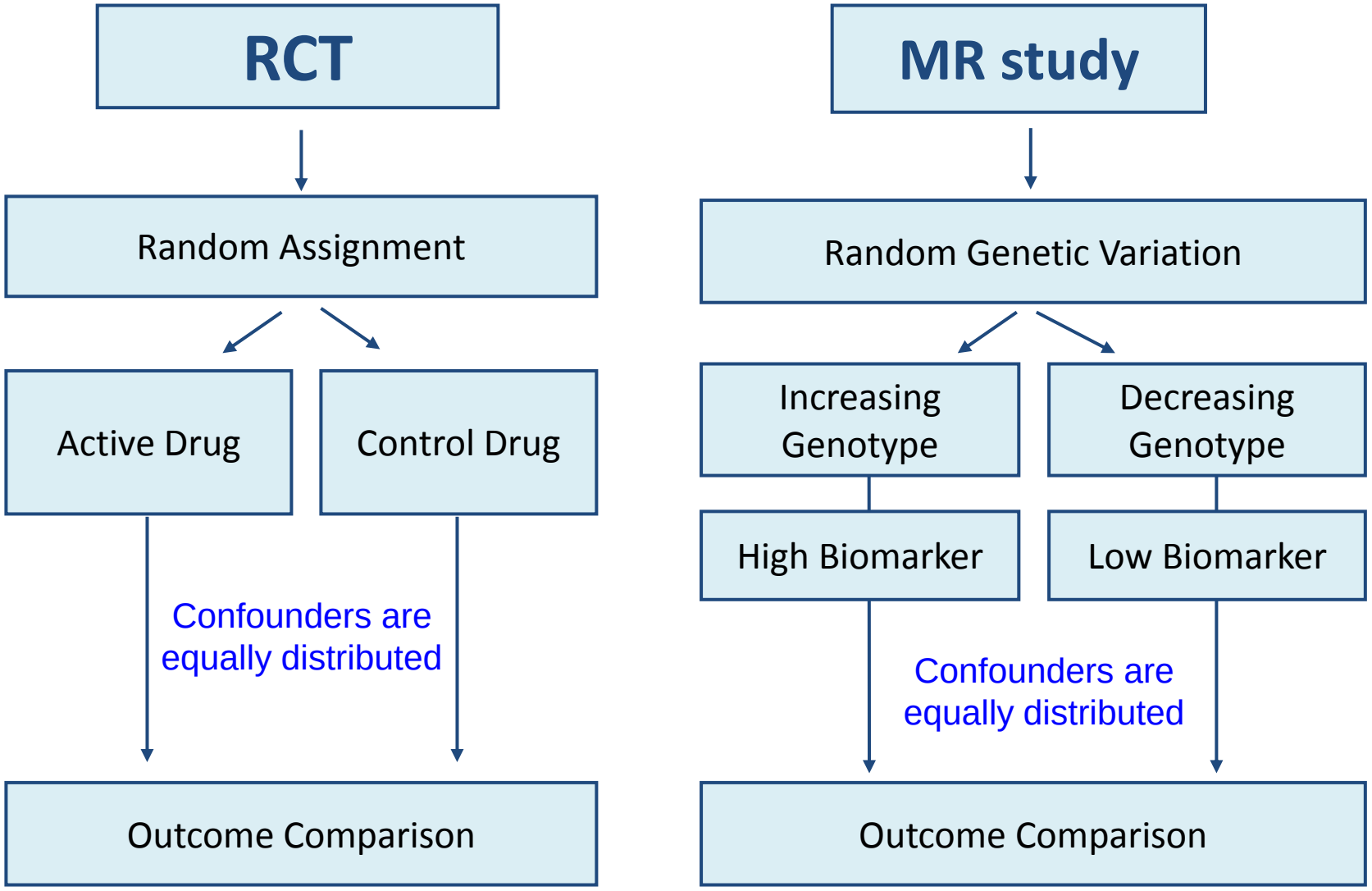
- **MR studies** evaluate the relationship between **genetically-determined biomarker levels** and the risk of **target disease**.

- If the **genetic determination** of biomarker level is **random** and **independent** of non-genetic confounders,
- We can assume that the observed biomarker-disease relationship is **similar to** the relationship between **randomly assigned** biomarker levels and the disease risk.

Mendelian Randomization (MR) Study

- **MR studies require following conditions:**

1. The genetic variant is associated with the exposure;
2. The genetic variant affects the outcome only through the exposure;
3. The genetic variant is not related to other factors that affect the outcome.


RCT
Random Assignment
Active Drug
Control Drug
Confounders are equally distributed
Outcome Comparison
MR study
Random Genetic Variation
Increasing Genotype
Decreasing Genotype
High Biomarker
Low Biomarker
Confounders are equally distributed
Outcome Comparison

C-reactive protein -> CHD

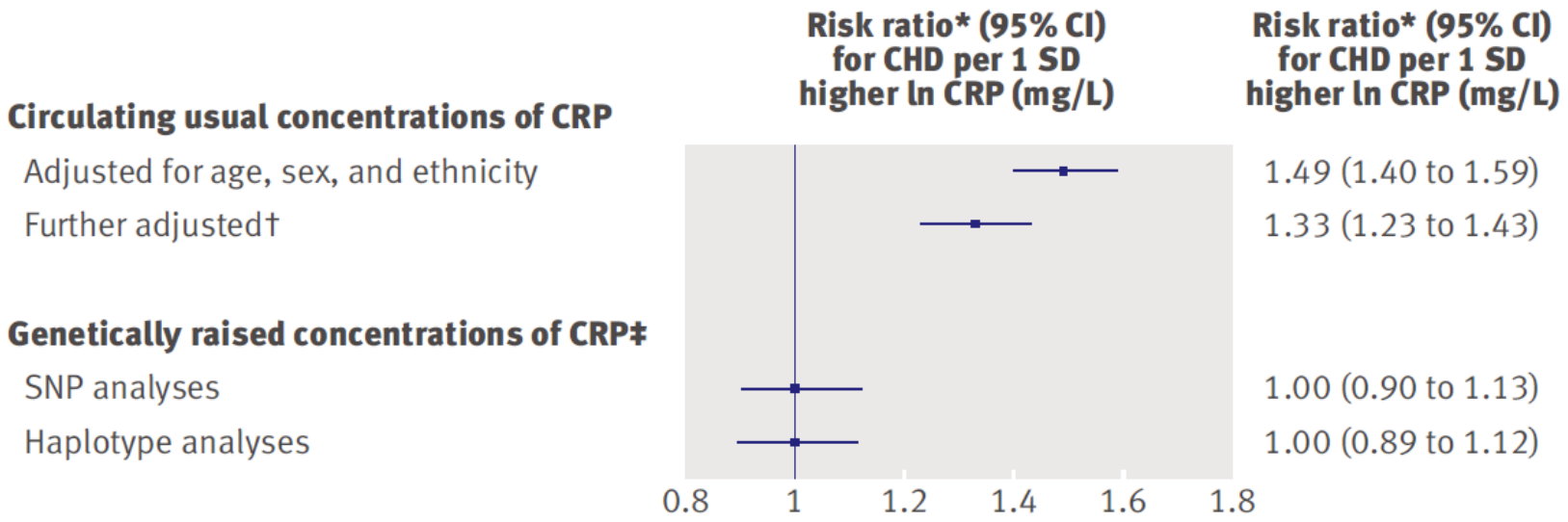
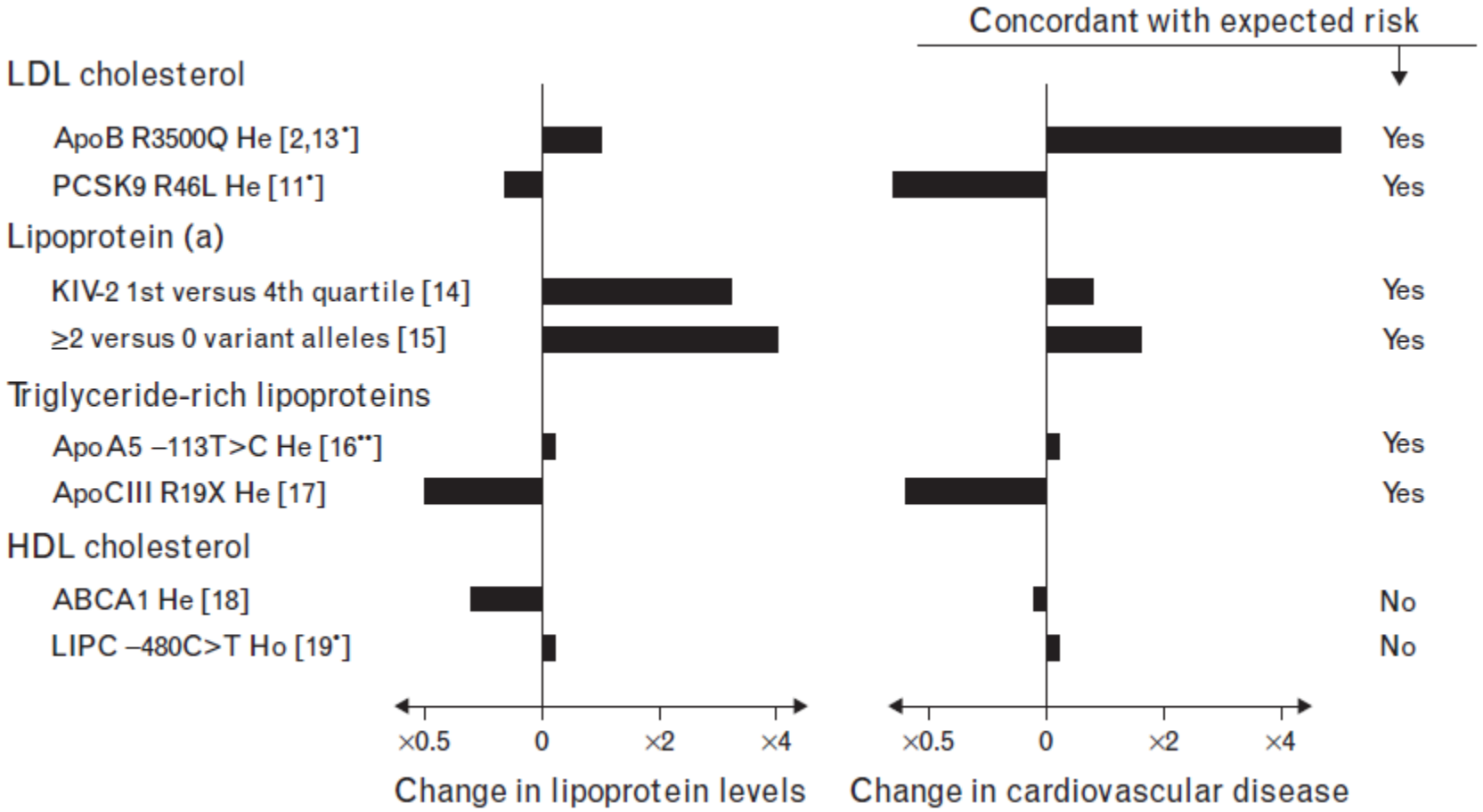


Fig 4 |Estimates of association of circulating concentrations and genetically raised concentrations of C reactive protein (CRP) with risk of coronary heart disease (CHD). *Corrected for regression dilution in C reactive protein and potential confounding factors.

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

LDL, Lp(a), TG, HDL -> CVD



Curr Opin Lipidol. 2011;22:113-22.

HDL cholesterol -> Myocardial Infarction

	Odds ratio (95% CI) per SD increase in plasma lipid based on observational epidemiology*	Odds ratio (95% CI) per SD increase in plasma lipid conferred by genetic score†
LDL cholesterol	1·54 (1·45–1·63)	2·13 (1·69–2·69), $p=2\times10^{-10}$
HDL cholesterol	0·62 (0·58–0·66)	0·93 (0·68–1·26), p=0·63

*Observational epidemiology estimates derived from more than 25 000 individuals from prospective cohort studies as shown in the appendix p 22. †LDL genetic score consisting of 13 single nucleotide polymorphisms (SNPs) as shown in the appendix p 27; HDL genetic score consisting of 14 SNPs as shown in the appendix p 28.

Table 4: Estimate of the association of genetically raised LDL cholesterol or HDL cholesterol and risk of myocardial infarction using multiple genetic variants as instruments

Analysis of 19,139 cases and 50,812 controls 30 observational studies. Lancet. 2012;380:572-80

Biomarker	Epidemiologic study	MR study
LDL-cholesterol	++	LDL receptor gene → CAD (+) PCSK9 gene → LDLC → MI (+)
HDL-cholesterol	++	LCAT gene → HDLC → MI (-) Endothelial lipase gene → HDLC → CAD (-)
Lipoprotein(a)	+	LP(a) genes → MI (+)
Triglycerides	+	APOA5 gene → TG → MI (+) 44 SNPs affecting TG but not LDLC → CAD (+)
Lp-PLA2	+	PLASG7 gene → Lp-PLA2 → CAD, CHD (-)
C-reactive Protein	+	Several large MR studies (-)
IL-6 receptor	+/-	IL-6R gene → inflammation → CAD (+)
Pentraxin 3	+	PTX3 gene → PTX3 → MI (-)
Fibrinogen	+/-	Meta-analysis of GWAS studies for CAD (-)
Body mass index	++	FTO, MC4R, TMEM 18 → CAD (+)
Blood pressure	++	**CARDIoGRAM-CAD-GWAS** 30 variants affecting BP → CAD (++) > Epi. Findings
Diabetes mellitus	++	**CARDIoGRAM-CAD-GWAS** 40 variants affecting DM → CAD (+) < Epi. Findings
Telomere length	+	**CARDIoGRAM-CAD-GWAS** 7 variants affecting LTL → CAD (+)

Mendelian randomization studies in coronary artery disease. Eur Heart J. 2014;35:1917-24

Conclusions

- MR is a method that allows one to test for a **causal effect** from **observational data** in the presence of confounding factors.

- MR studies also have several **inherent limitations** and need to be carefully designed and interpreted. MR studies **cannot replace** the RCTs and other epidemiological studies.

- But, MR studies will **improve our understanding** of the **roles of biomarkers** in the development of cardiovascular disease. They will also help us identifying **potential therapeutic/preventive targets** among the increasingly reported biomarkers.