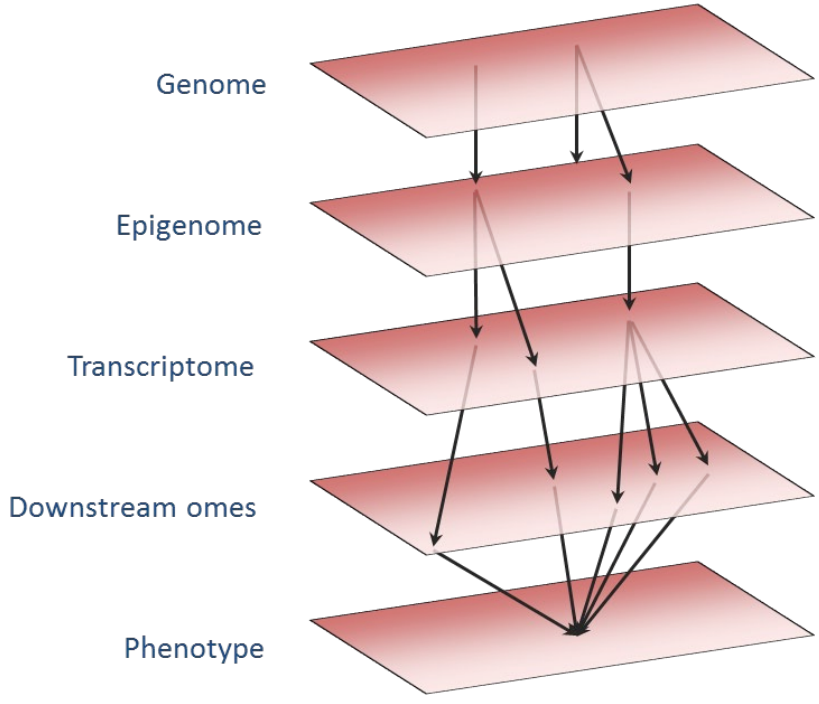
Analyzing multiple omics levels

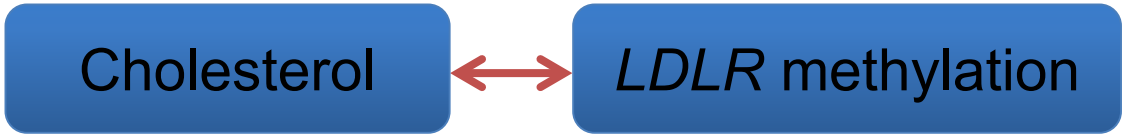
Bas Heijmans
Molecular Epidemiology
Leiden University Medical Center
The Netherlands
bas.heijmans@lumc.nl

FOS course Molecular Data Science – 29 October 2018.

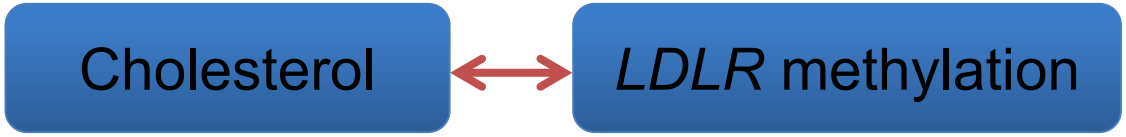

Genome
Epigenome
Transcriptome
Downstream omes
Phenotype

Epigenome-wide Association Study

1. Data: methylation at 450 thousand CpGs + lipids levels in 2000 individuals
2. Test per CpG: DNAm ~ cholesterol + gender + age + cell counts + batches

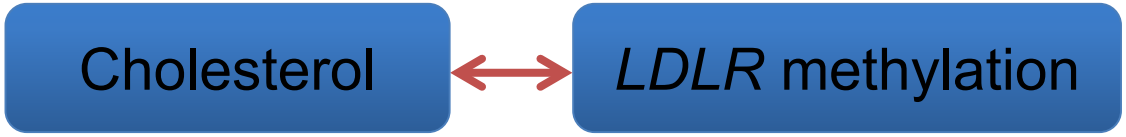


What's next?



- Can we make conclusions stronger?
- What are the main limitations in observational epidemiology?

What's next?

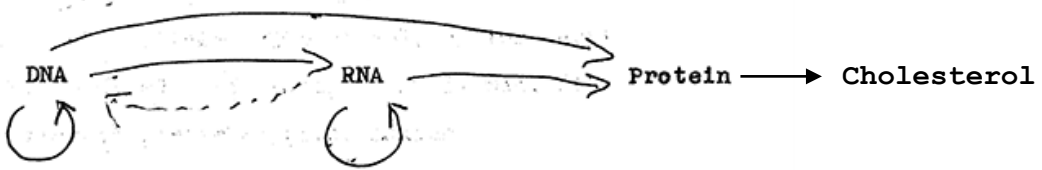


- Causality
- Confounding

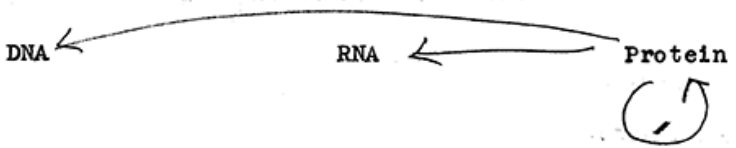
Alternative for experiment

Cholesterol ↔ *LDLR* methylation

The Central Dogma: "Once information has got into a protein it can't get out again". Information here means the sequence of the amino acid residues, or other sequences related to it. That is, we may be able to have



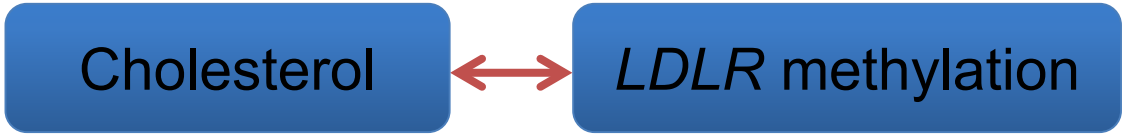
but never



where the arrows show the transfer of information.

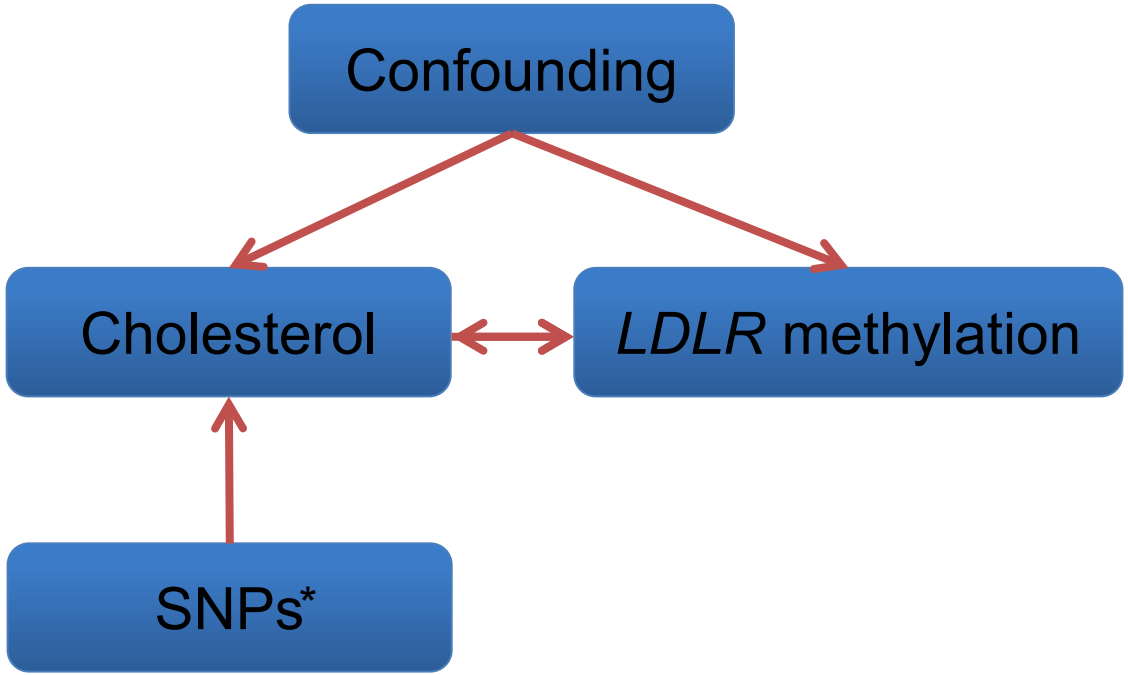
Crick, 1956

Alternative for experiment



- An experiment of nature using genetic variation as causal anchor
- ‘Mendelian randomization’: a natural trial with exposures to genetic variations randomized according to Mendel’s law and with the exposed blinded towards exposure.
- Uses genetic variant(s) as ‘instrumental variable’ instead of measured variable itself.

Alternative for experiment



**Which we know from GWASs*

Mendelian randomization

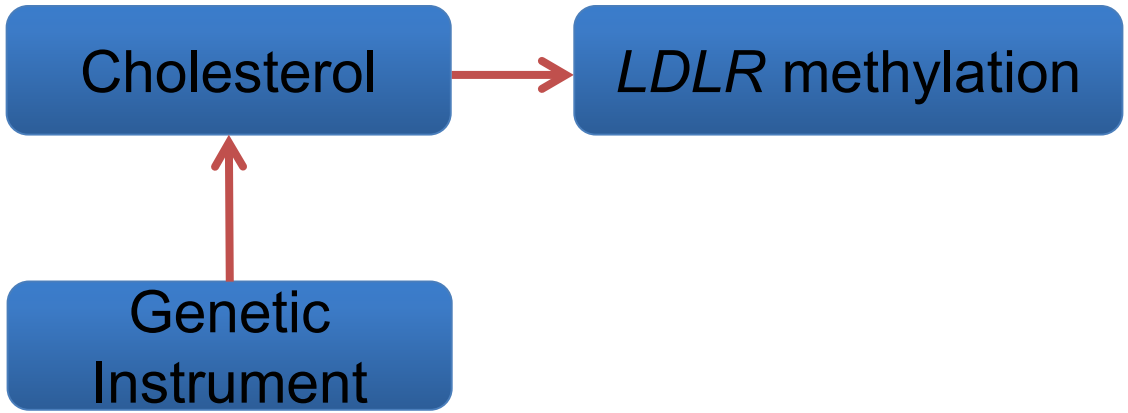
1. Identify (sufficiently strong) genetic instrument.
   Here: SNP associated with cholesterol from GWAS (see Wednesday practical)
2. Predict cholesterol level for every individual on basis of one's genotype.
   Will explain only small proportion of variation
3. Test whether predicted (genetic) level is associated with methylation.
   No confounding (unbiased effect estimate) & only one possible direction of causality

LUMC

Two-stage least squares model

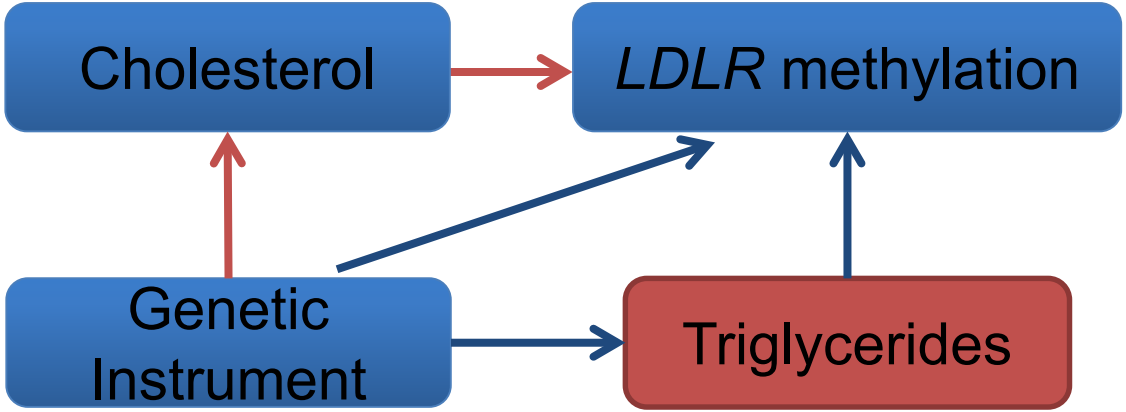
1. Pred(Chol) = $\gamma_0 + \gamma_1$ x genotype + γ_2 x age + γ_3 x batch + ε_i (i=1,…, n)

2. DNAm = $\beta_0 + \beta_1$ x pred(Chol) + β_2 x age + β_3 x batch + ε_i (i=1,…, n)

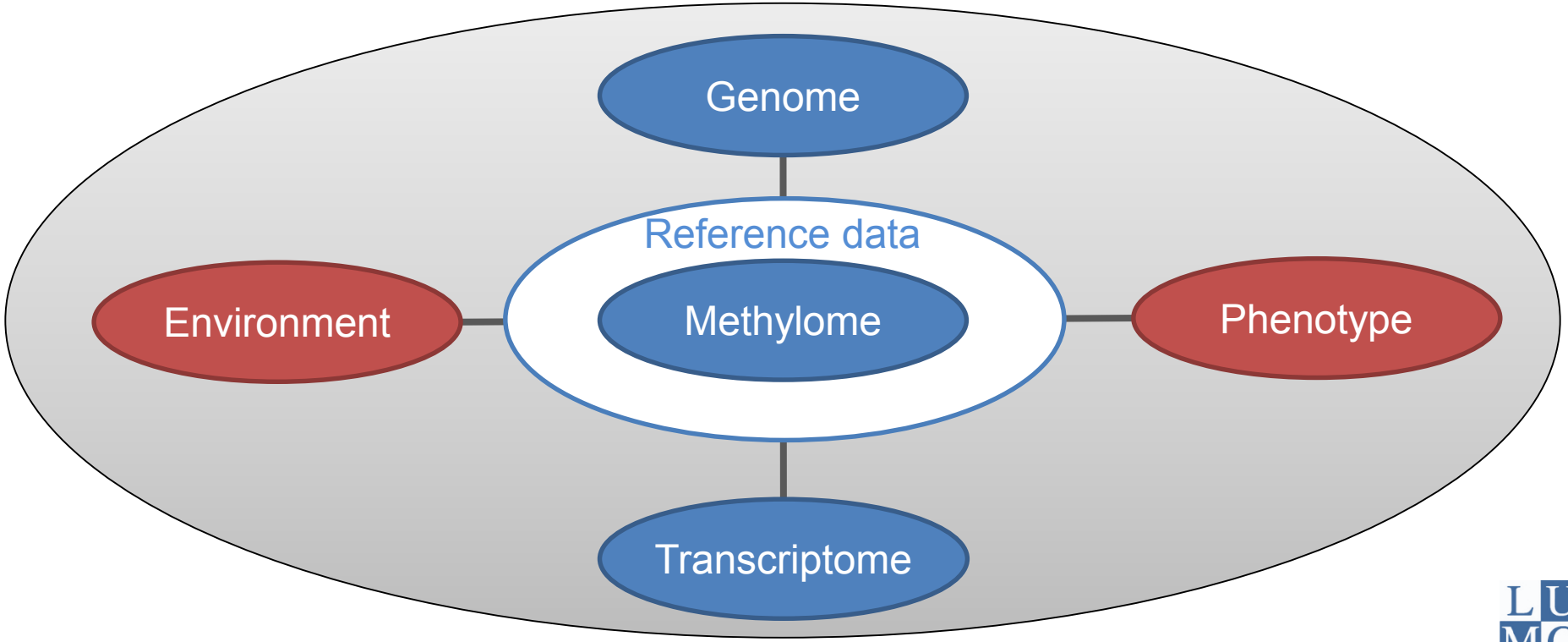


Beware of assumptions

Pleiotropy



Integrative Genomics



Population Genomics

The human as ‘model organism’:
Exploiting natural variation in large-scale population studies

- Genome biology
- Disease mechanisms
- Biomarkers