

# Disentangling independent and mediated causal relationships between blood metabolites and Alzheimer's Disease

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Edinburgh University Journal Club | Dec 2020

# Background

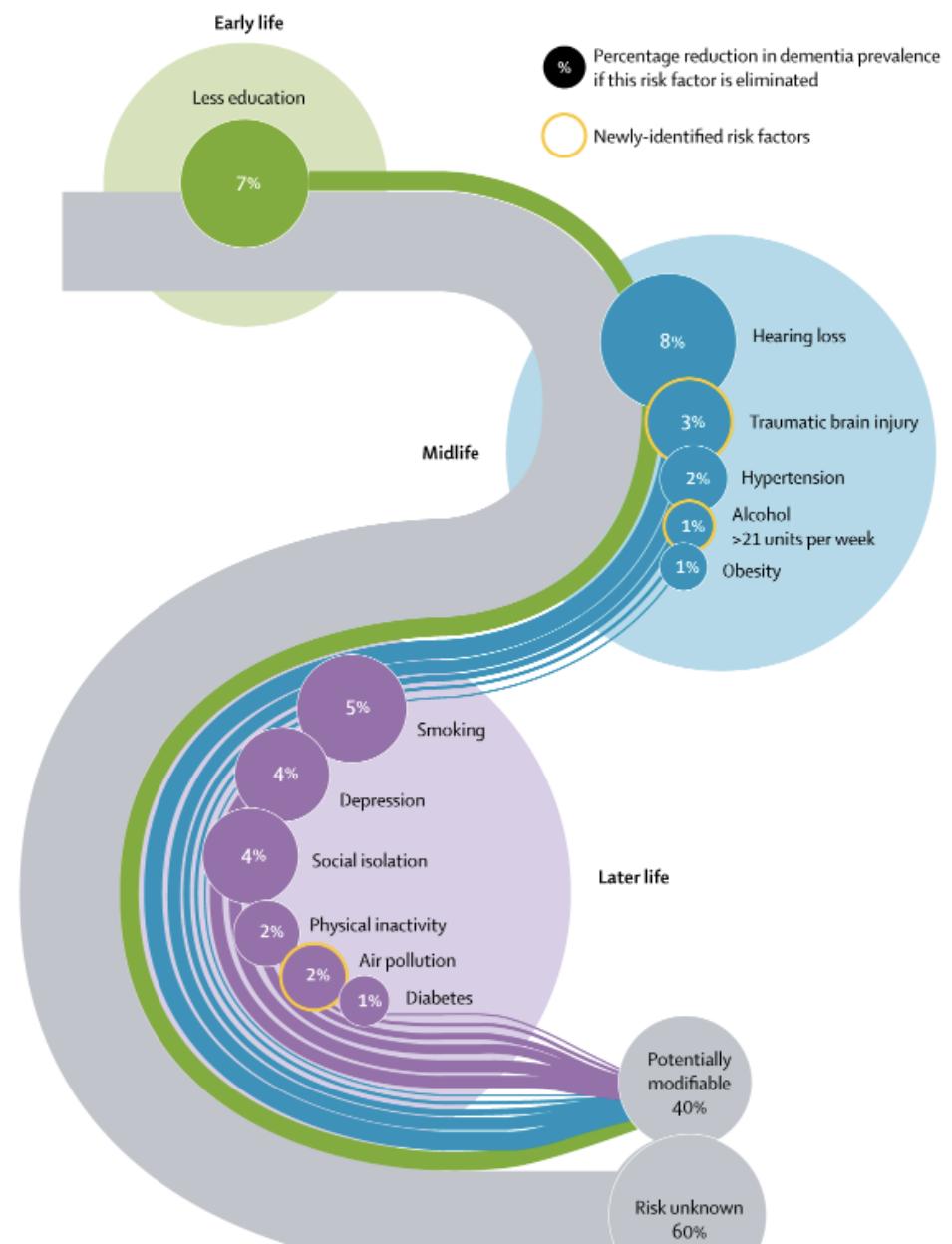
# Late-onset Alzheimer's Disease

- 47 million individuals worldwide.
- Recently overtook heart disease as the leading cause of death in the UK.
- Neurodegeneration → cognitive decline → death.
- Unclear aetiology / incomplete understanding of interlinking pathways into disease.
- No disease modifying treatments



## Risk factors for dementia

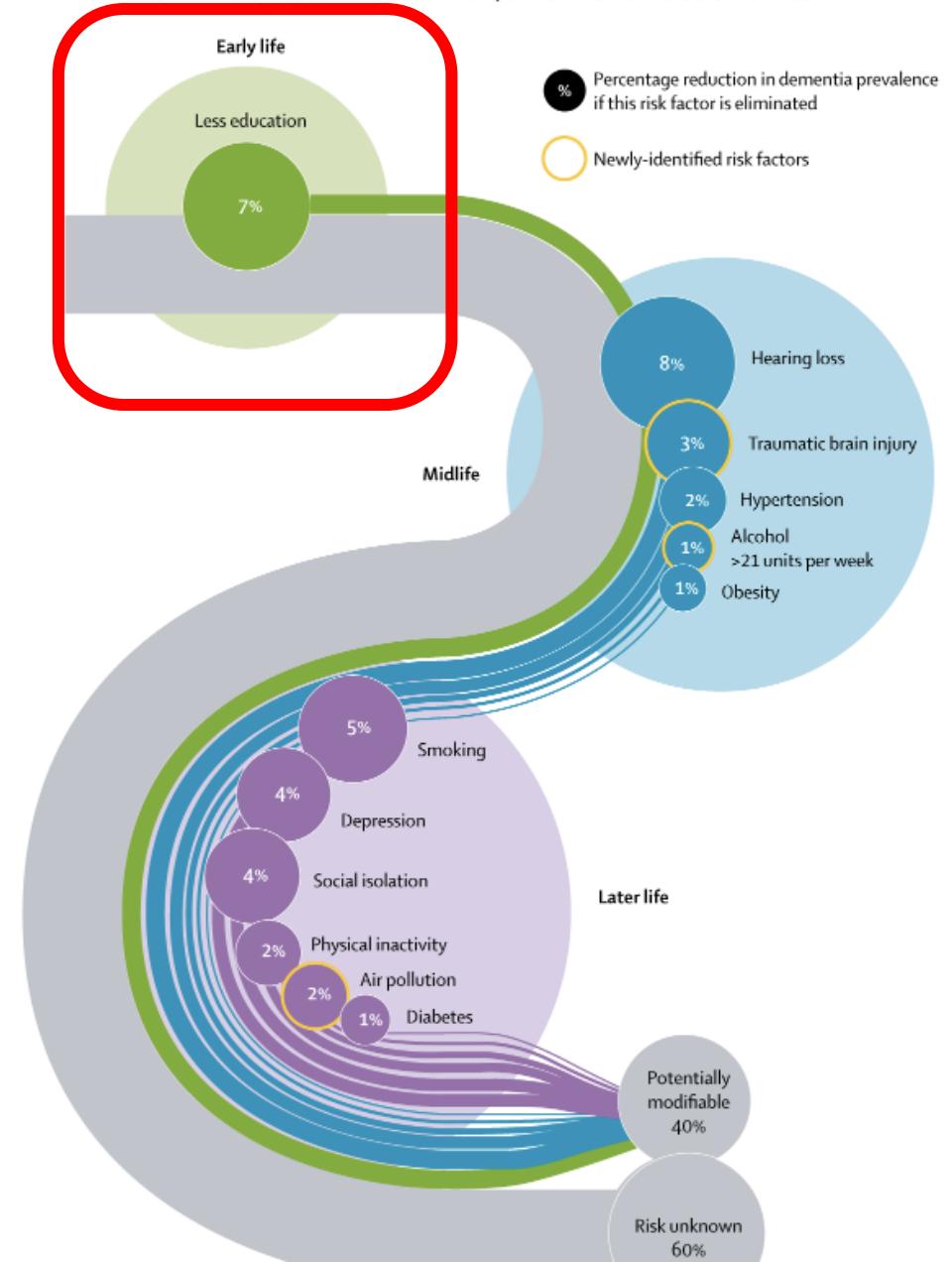
An update to the Lancet Commission on Dementia prevention, intervention, and care presents a life-course model showing that 12 potentially modifiable risk factors account for around 40% of worldwide dementias



Lancet Report  
Livingstone et al., 2020

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# Blood metabolites

- Small molecular weight compounds (lipids, amino acids etc) in blood.
- Cross-talk between genome and environmental influences.
- Easily accessible.
- Potentially modifiable.
- Previously implicated in cognitive processing and AD – particularly lipid

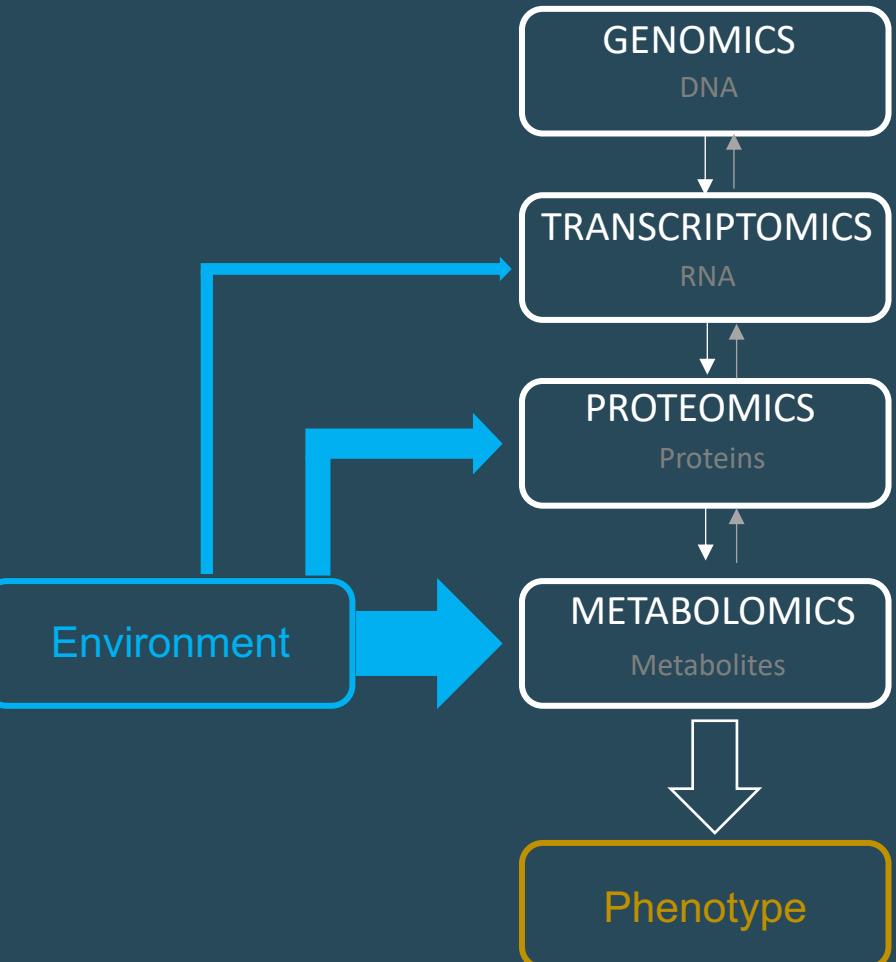


Image adapted from Tolstikov, 2016.

# **Study Aims**

1

Harness the use of polygenic scoring to identify, from a wider set of available metabolites, those demonstrating plausible **genetic overlap** with AD.

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Interrogate **causal relationships** using univariable Mendelian randomization.

Metabolite  $\leftrightarrow$  Alzheimer's Disease

Metabolite  $\leftrightarrow$  Educational attainment

Metabolite  $\leftrightarrow$  Intelligence

Educational attainment  $\leftrightarrow$  Alzheimer's Disease

Intelligence  $\leftrightarrow$  Alzheimer's Disease

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3

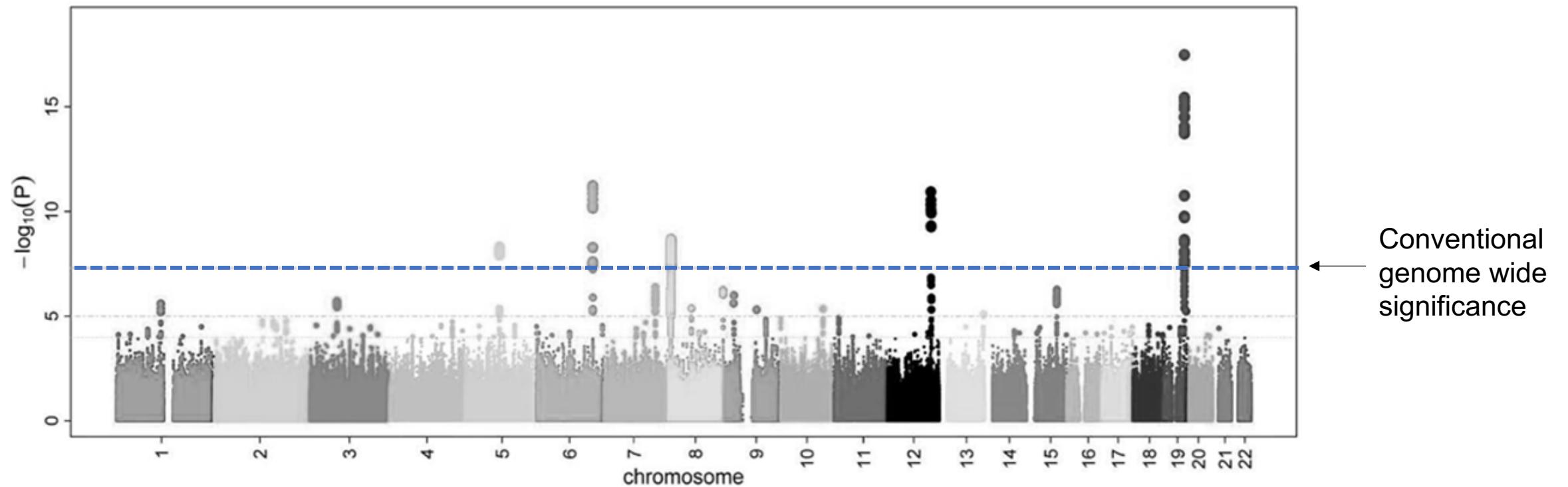
Incorporate multivariable methodology to disentangle **mediating relationships**.

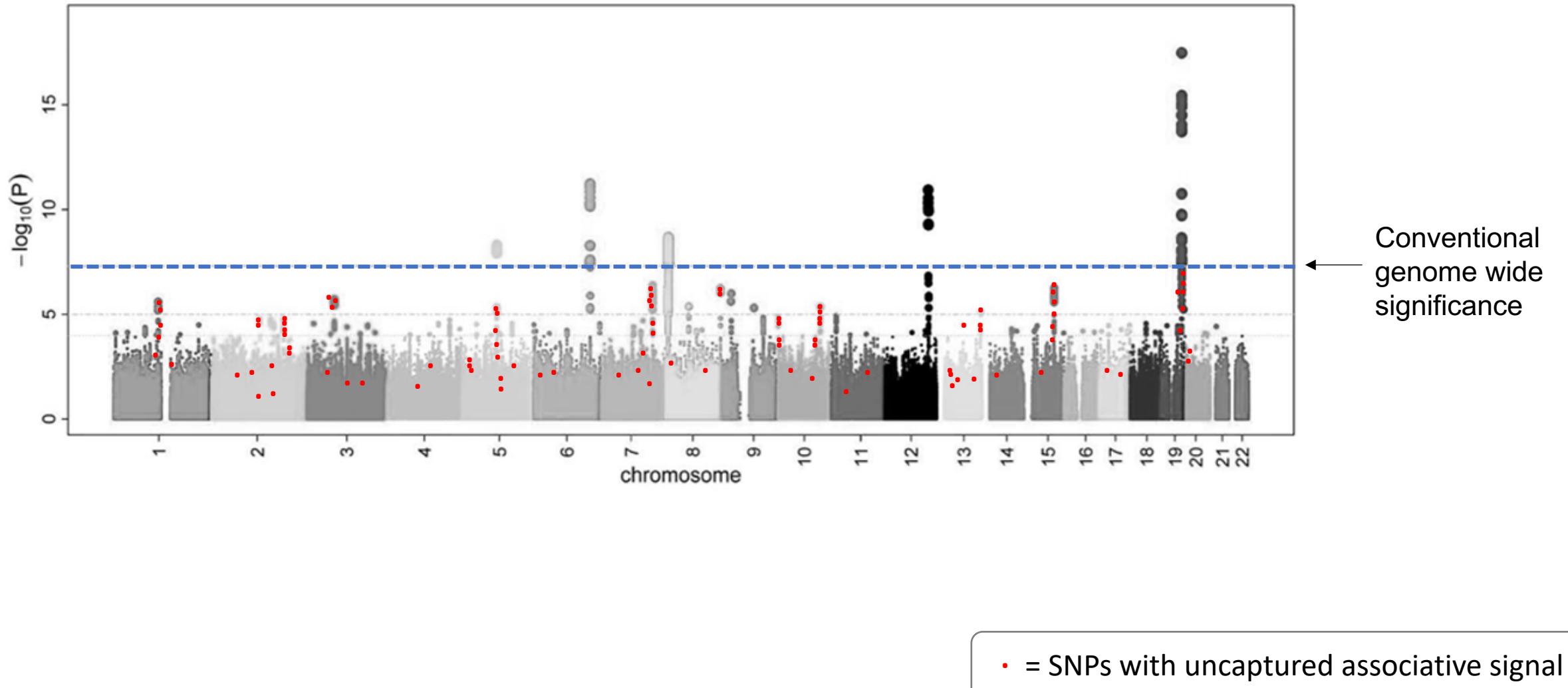
# Methods

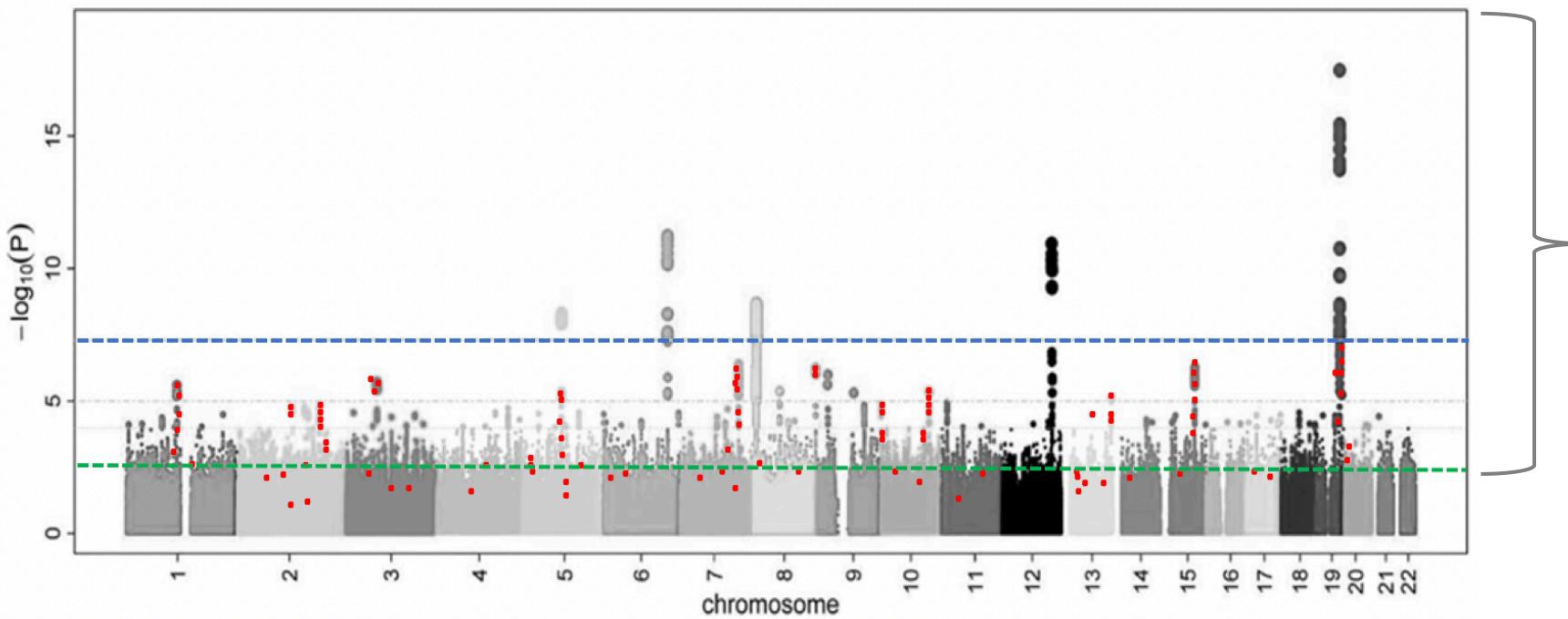
## Cross Trait Polygenic Scoring

**Context**

What is a Polygenic Score?





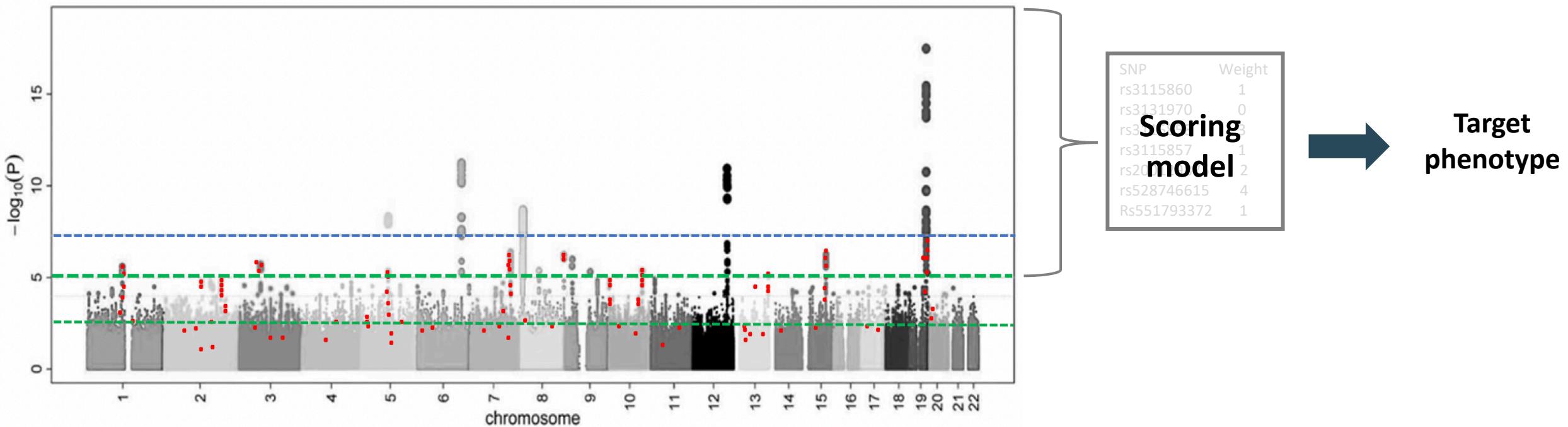


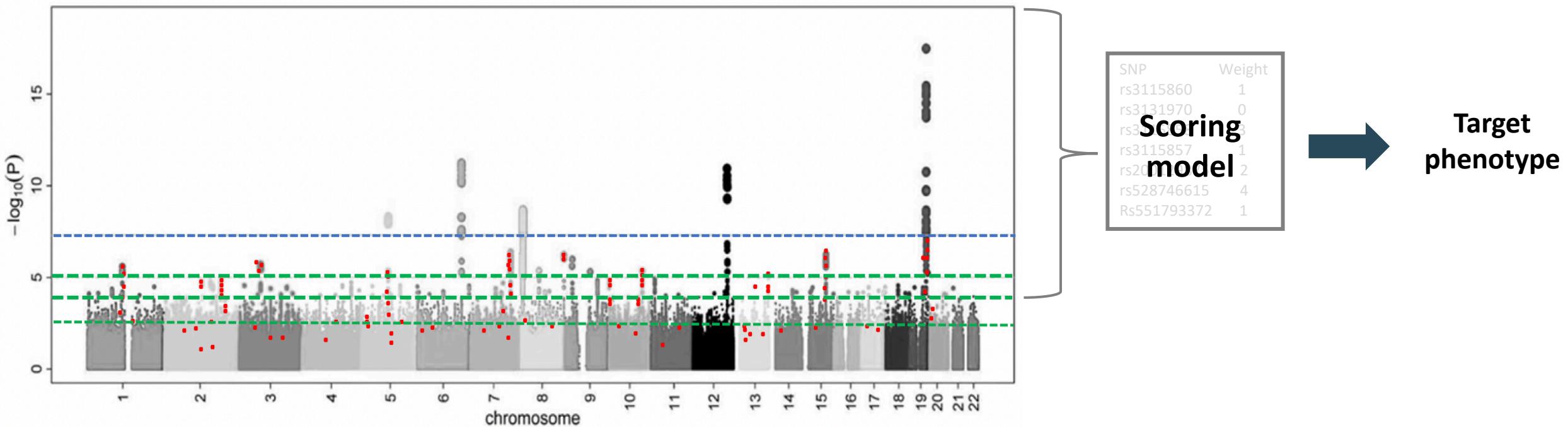
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rs3115860	1
rs3131970	0
rs3115857	3
rs2073955	1
rs528746615	2
Rs551793372	4

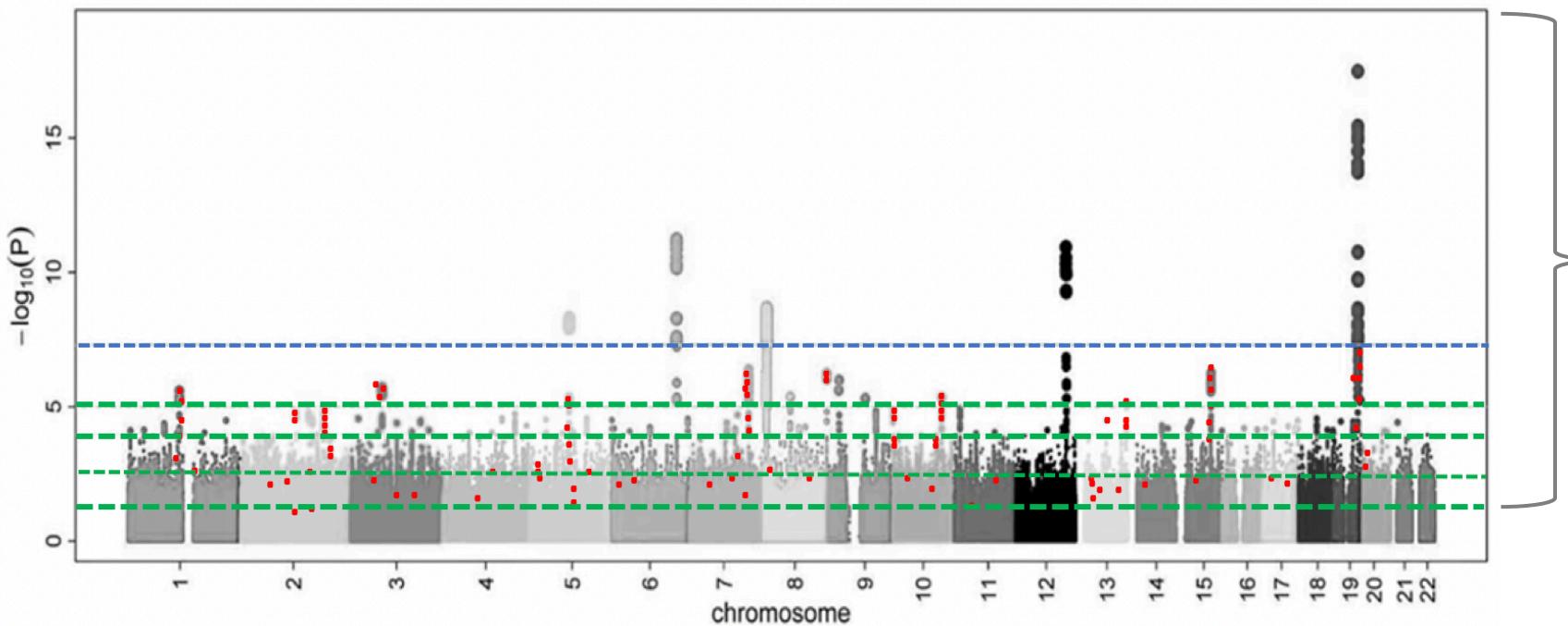
**Scoring  
model**



**Target  
phenotype**







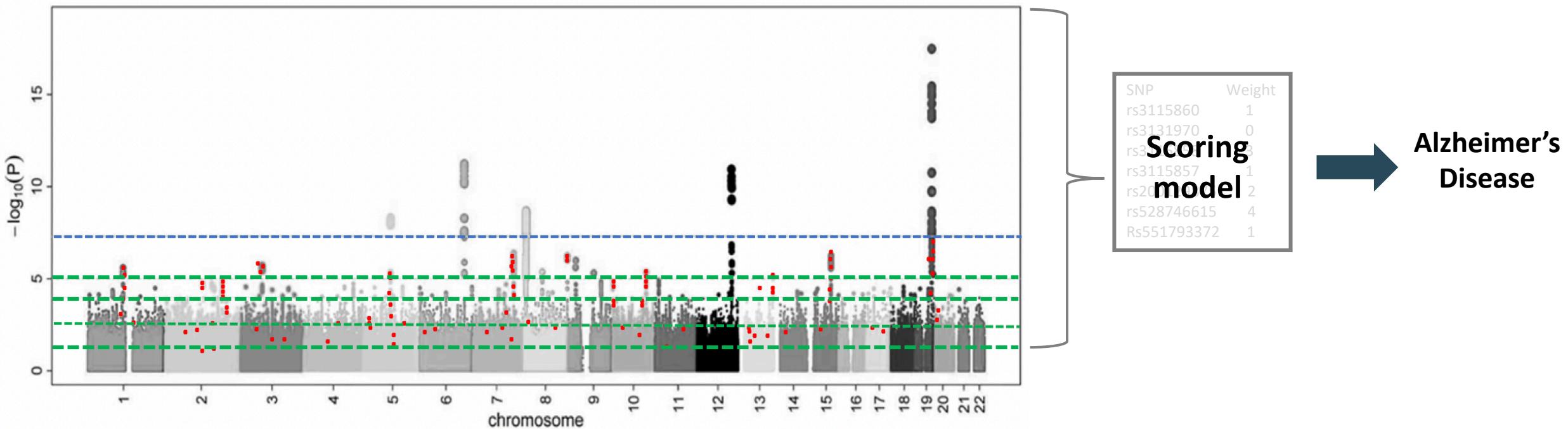
SNP	Weight
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**Scoring  
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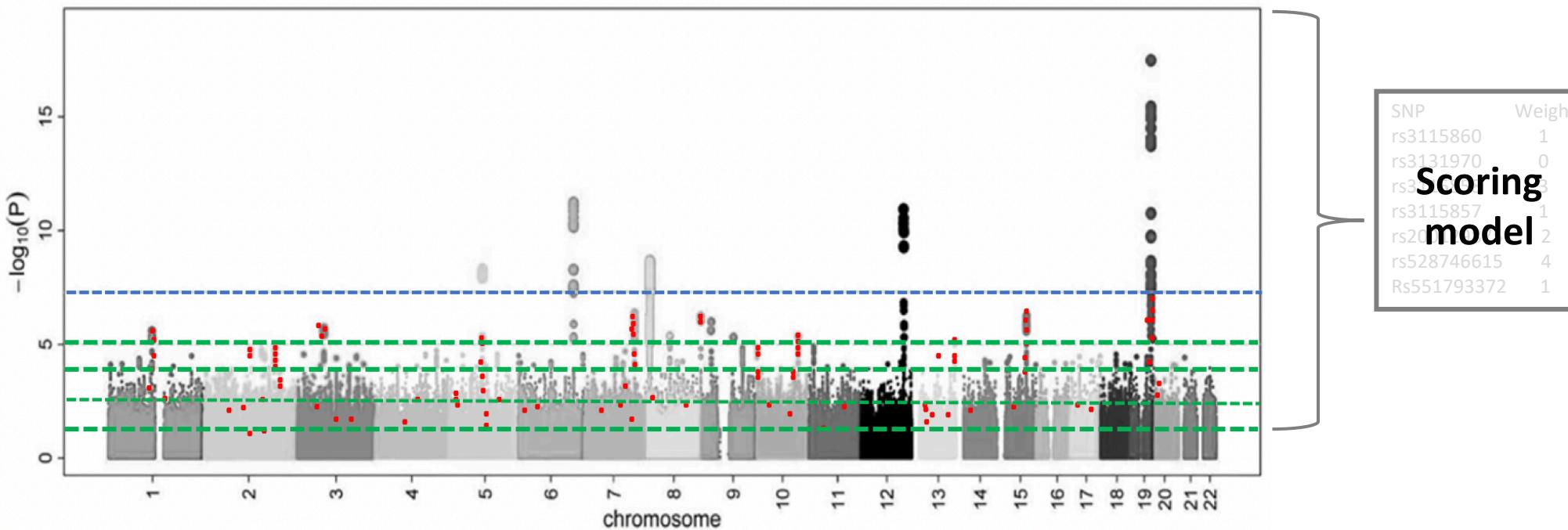


**Target  
phenotype**

## Alzheimer's Disease

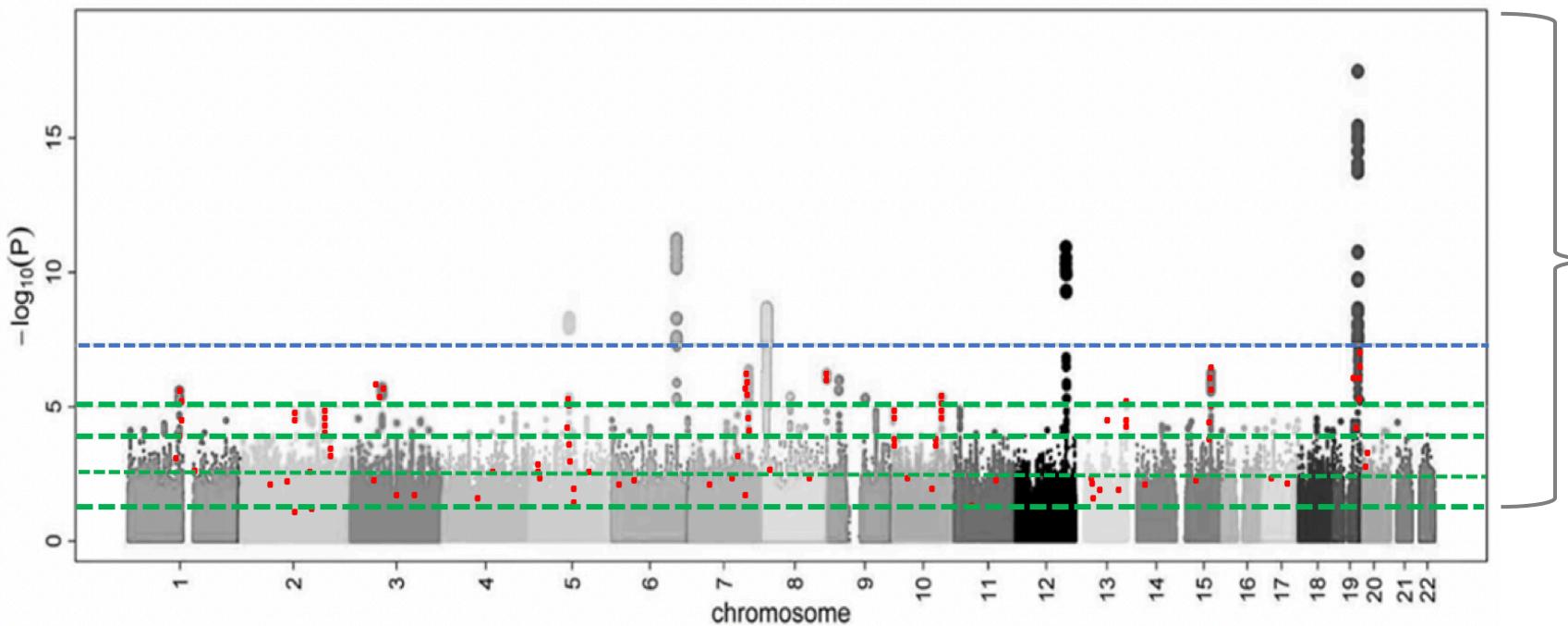


## Alzheimer's Disease



Different phenotype  
(e.g. depression,  
obesity etc)

## Alzheimer's Disease



SNP	Weight
rs3115860	1
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Rs551793372	1

**Scoring  
model**



**Different phenotype**  
(e.g. depression,  
obesity etc)



Individual level  
genotype information

1

Harness the use of **polygenic scoring** to identify, from a wider set of available **metabolites**, those demonstrating plausible **genetic overlap** with **AD**.

# Base Datasets

Blood metabolites:

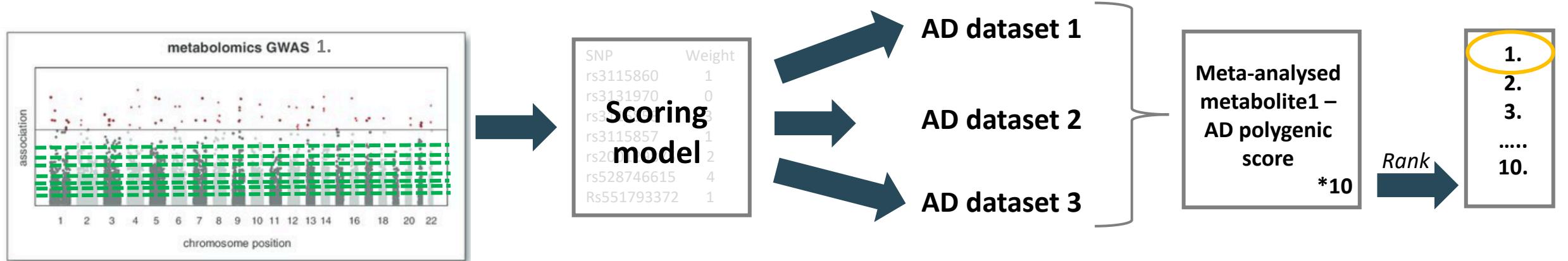
- 106 metabolite GWASs, Kettunen et al., 2016.  
(N=24,925)
- 10 p-value thresholds  
 $5e^{-8}$  |  $1e^{-5}$  |  $1e^{-4}$  | 0.0001 | 0.001 | 0.01 | 0.05 | 0.1 | 0.2 | 0.5 | 1

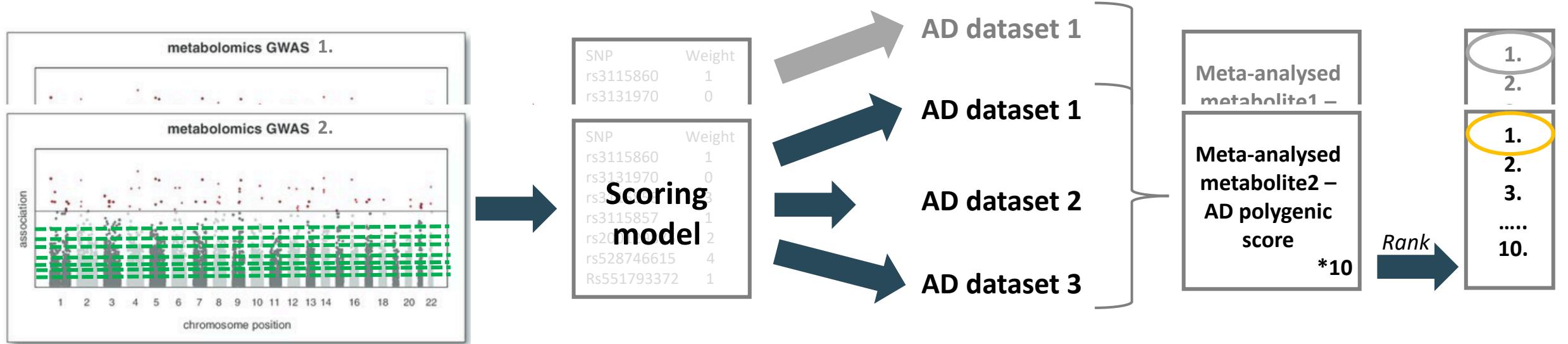
# Target Datasets

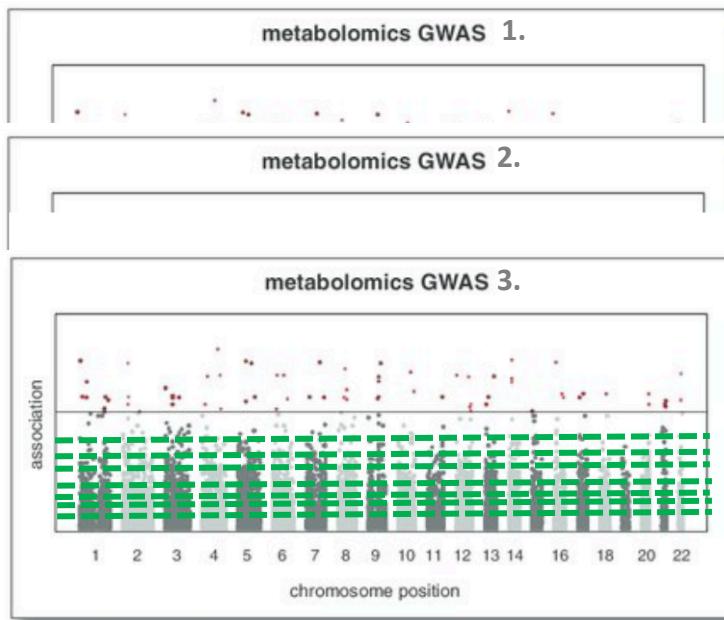
Alzheimer's:

1. AddNeuroMed N=648)
2. ADNI (N=886)
3. GERAD (N=3191)

All models adjusted for 7 PCs, age, sex. ApoE genomic region removed.





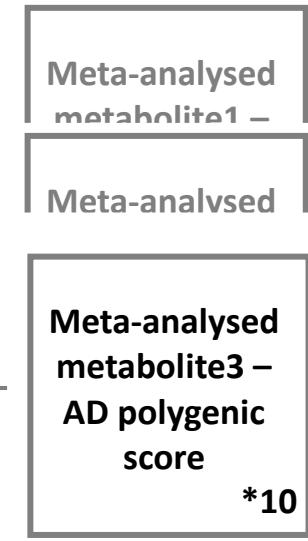
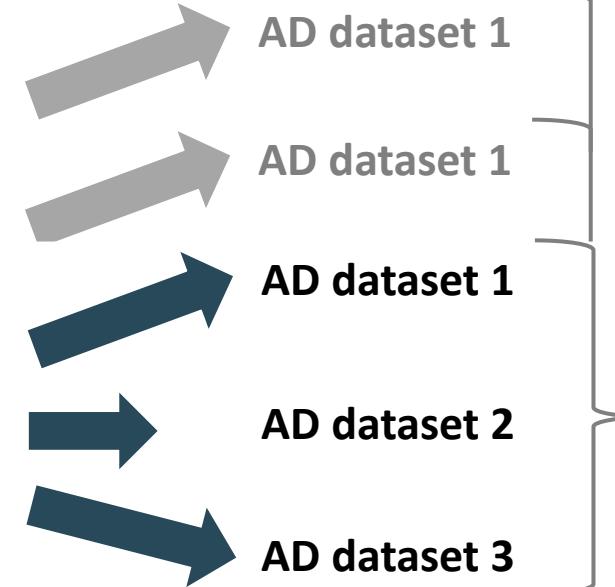


SNP	Weight
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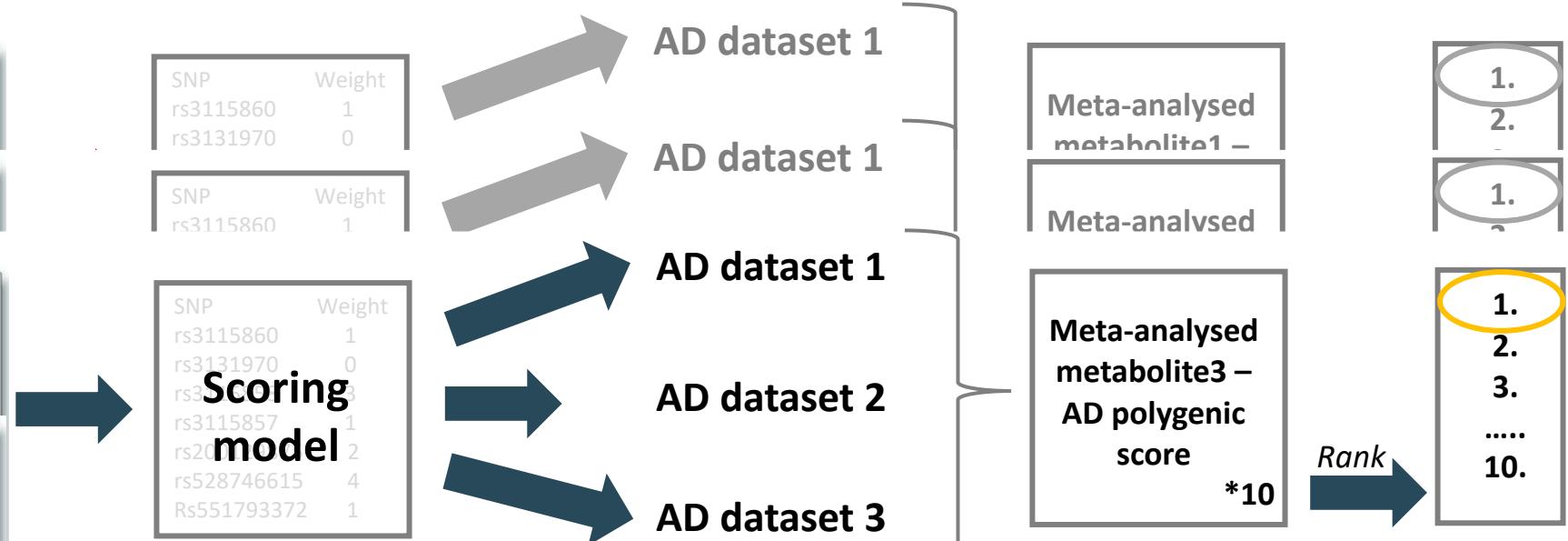
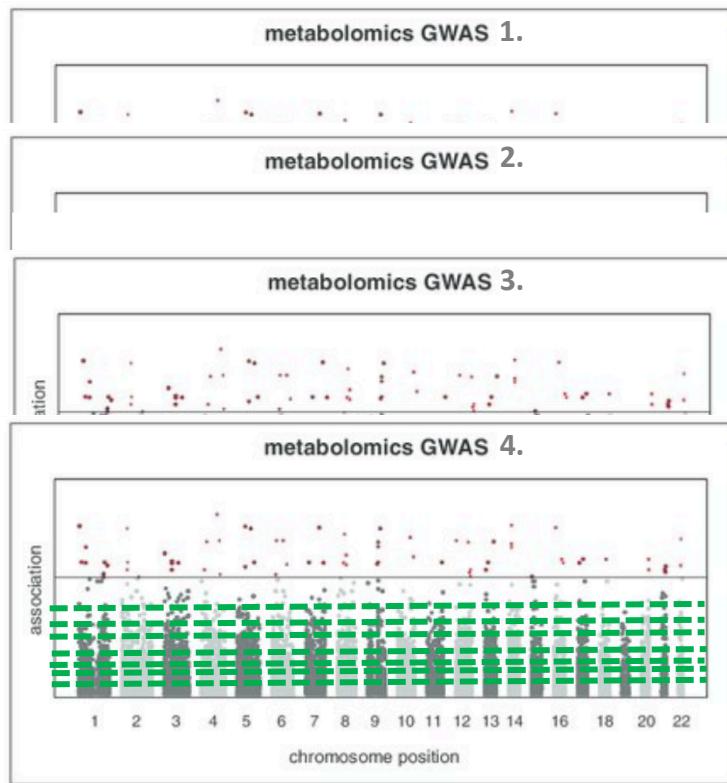
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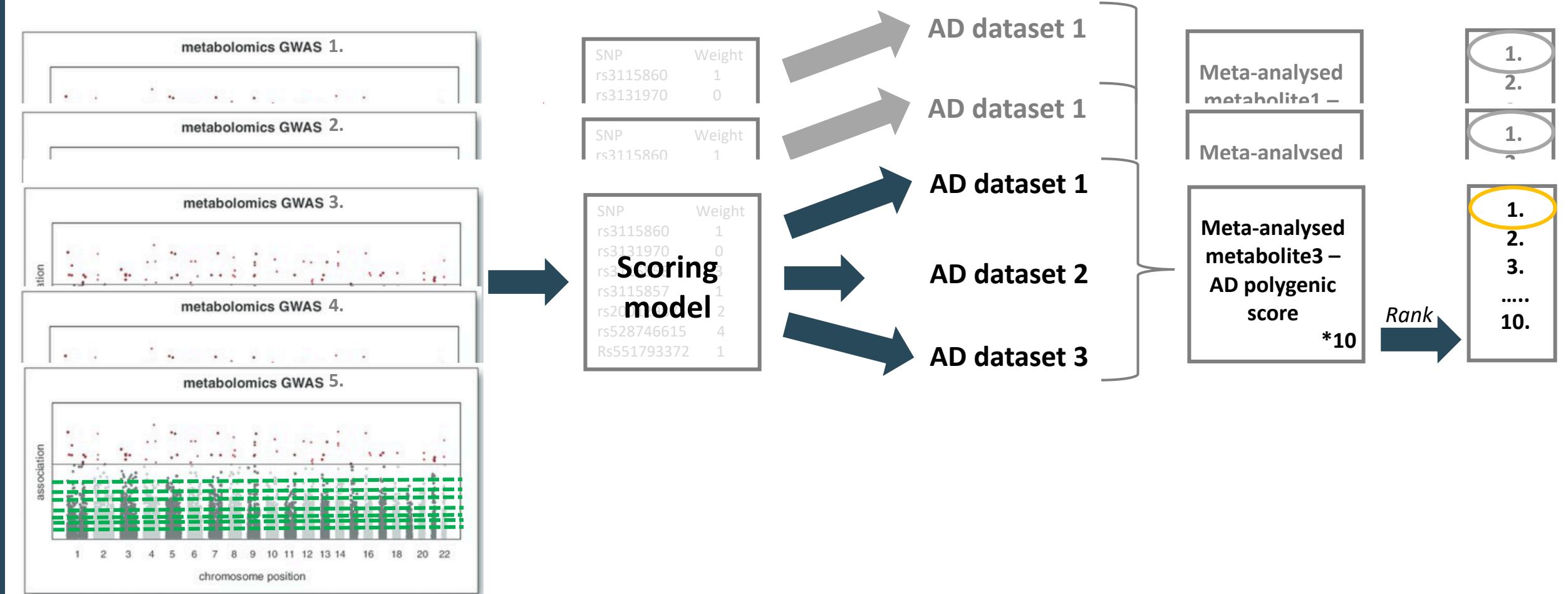
## Scoring model

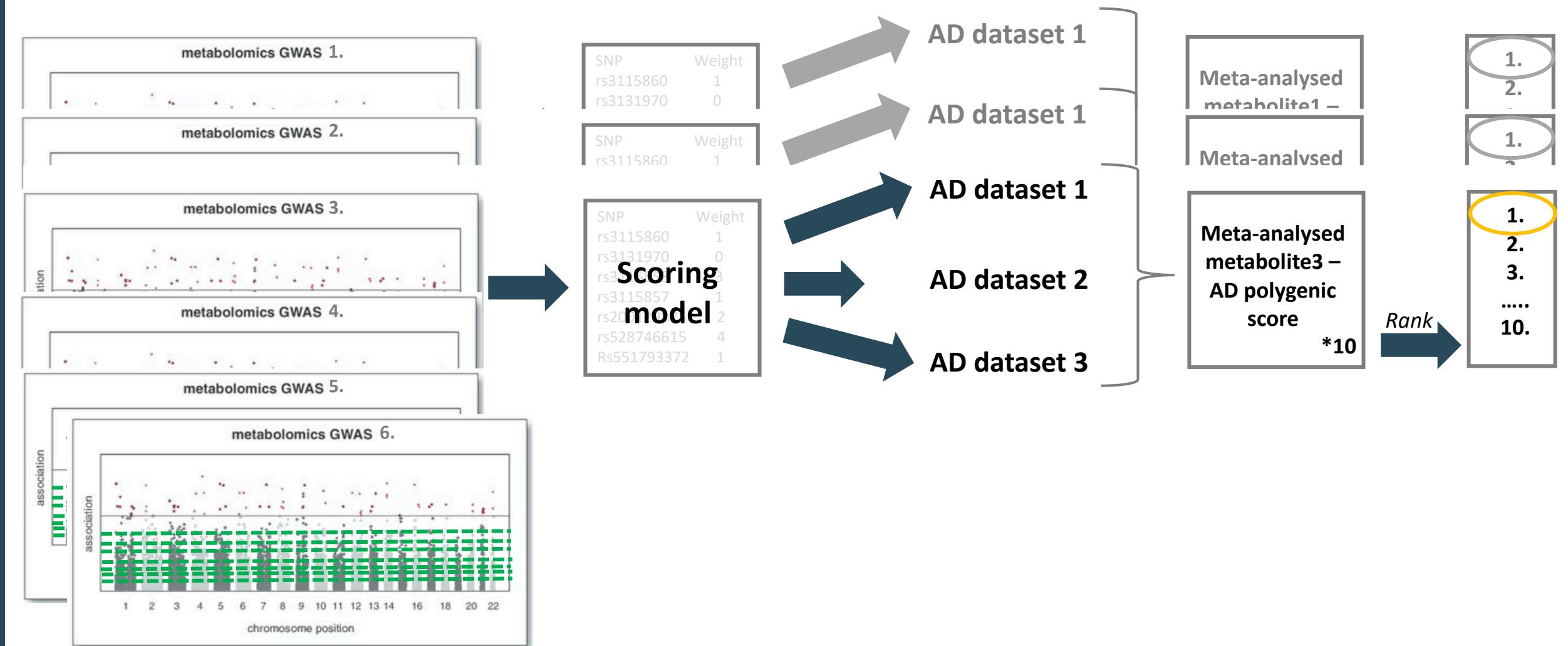


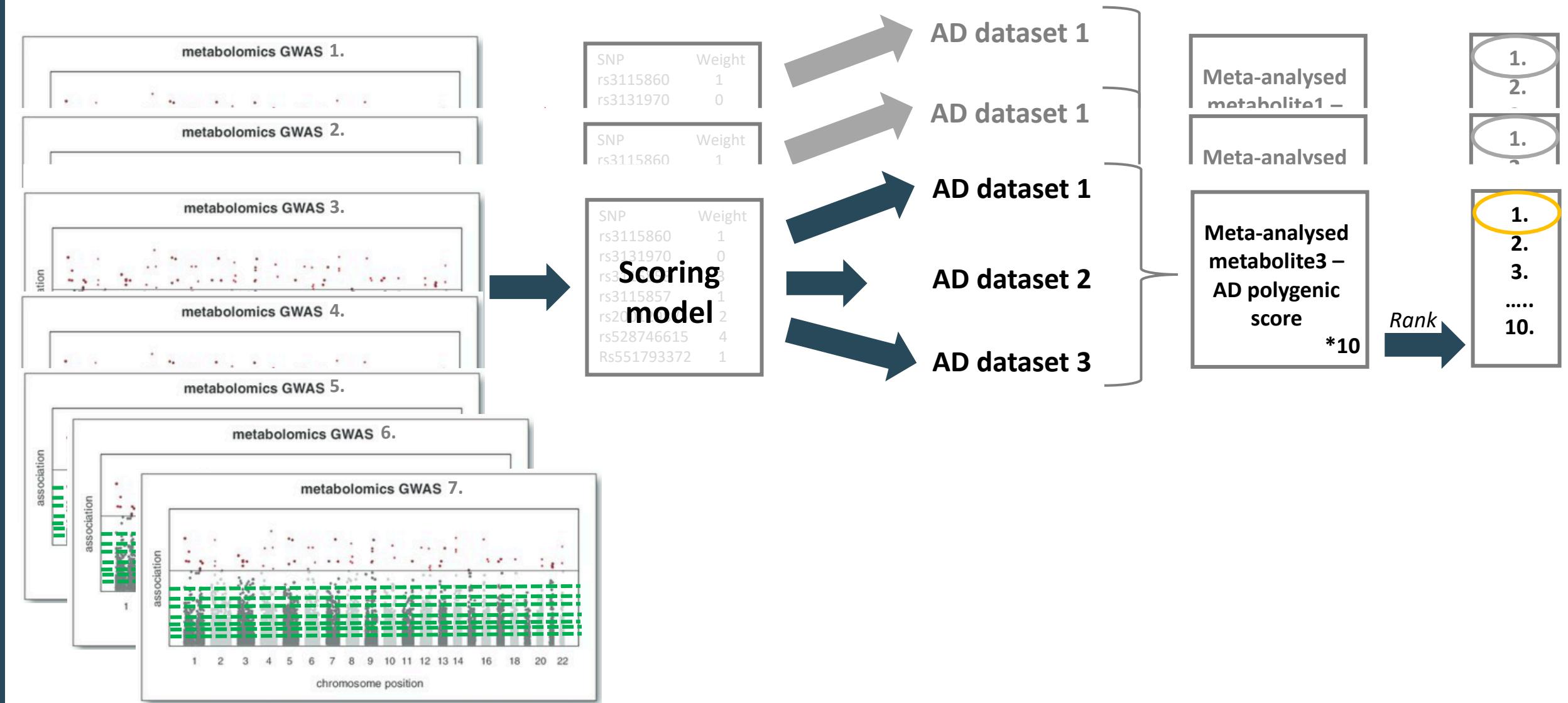
Rank

1.
2.
3.
.....
10.







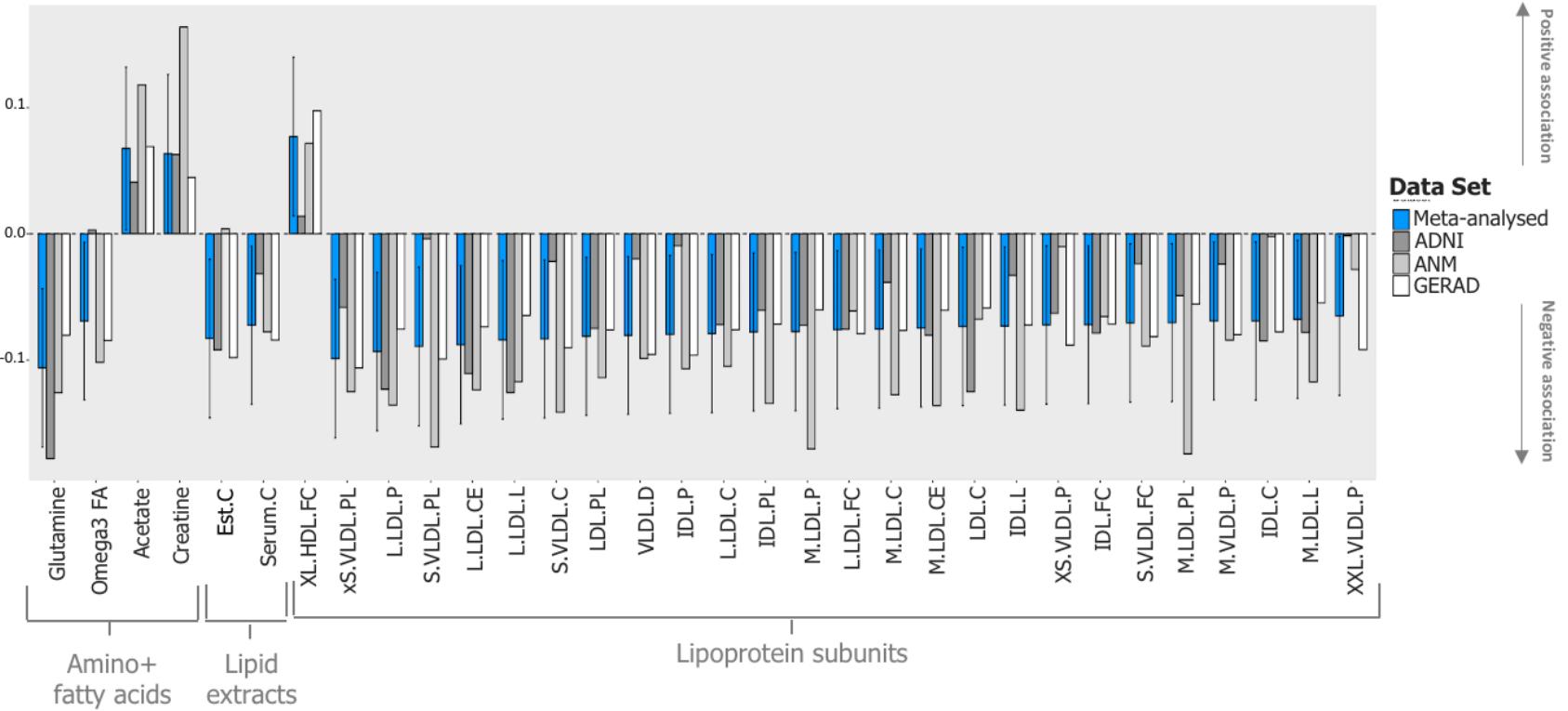


.... Metabolomics GWAS 106

# Results

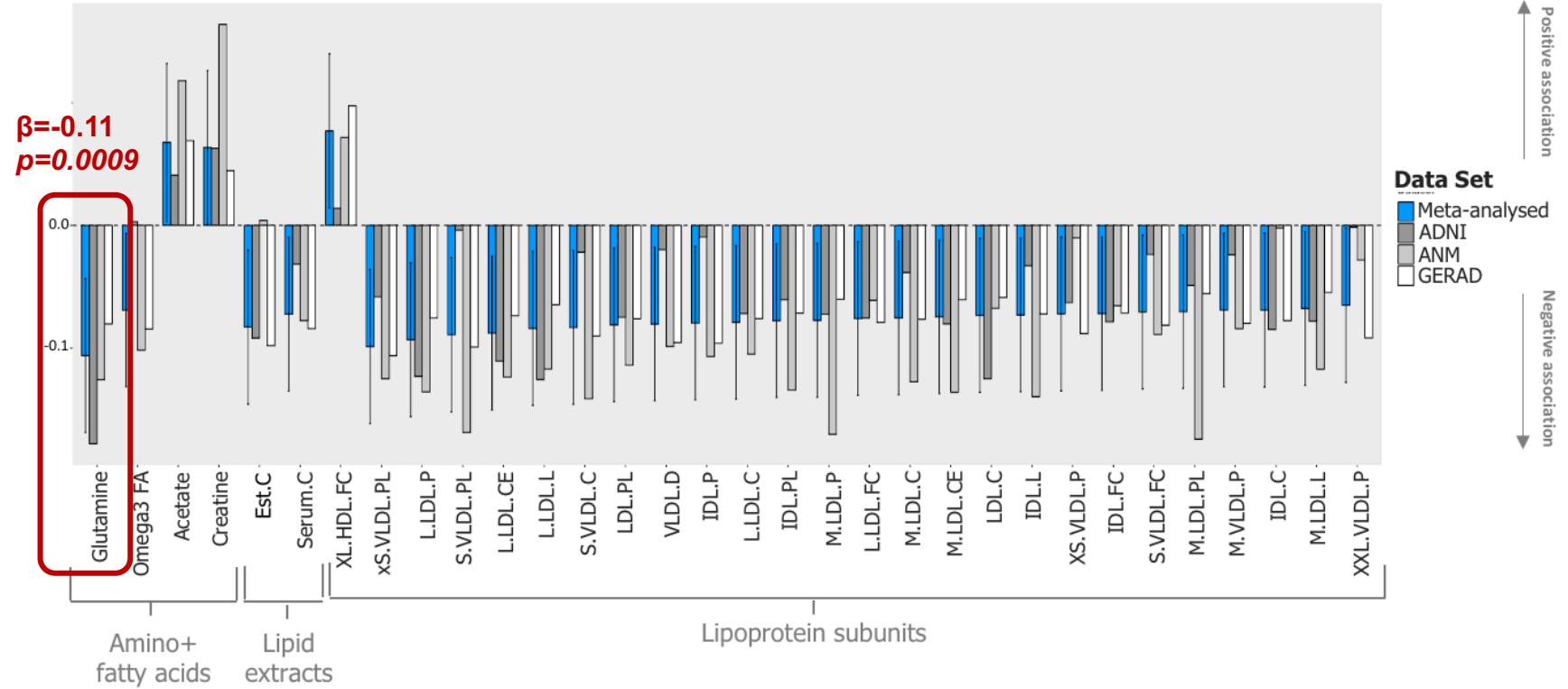
## Cross Trait Polygenic Scoring

# 34 blood metabolites demonstrated suggestive polygenic overlap with Alzheimer's



Results exclude ApoE

**34 blood  
metabolites  
demonstrated  
suggestive  
polygenic overlap  
with Alzheimer's**



*Results exclude ApoE*

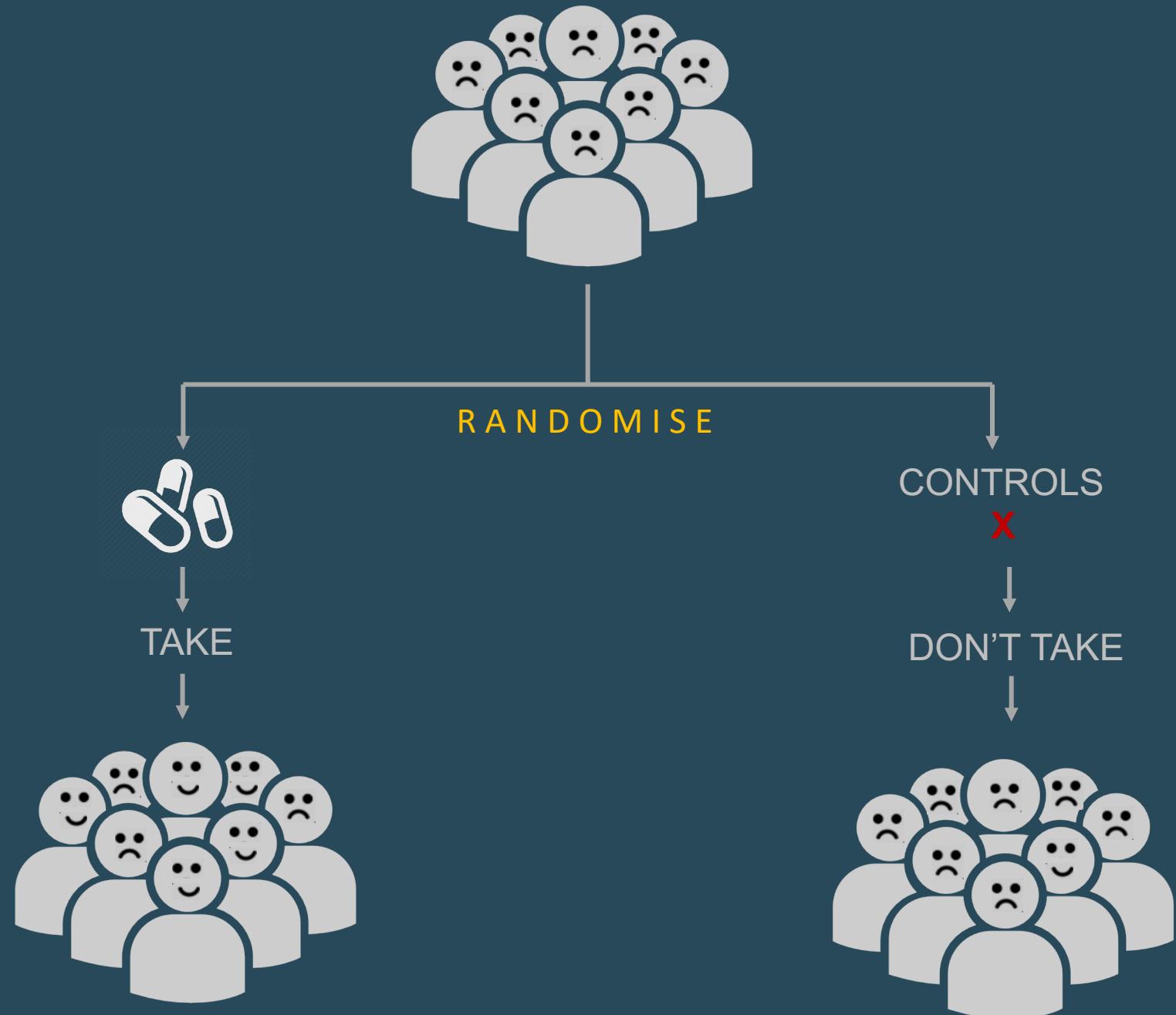
# Methods

## Mendelian Randomization

## Context

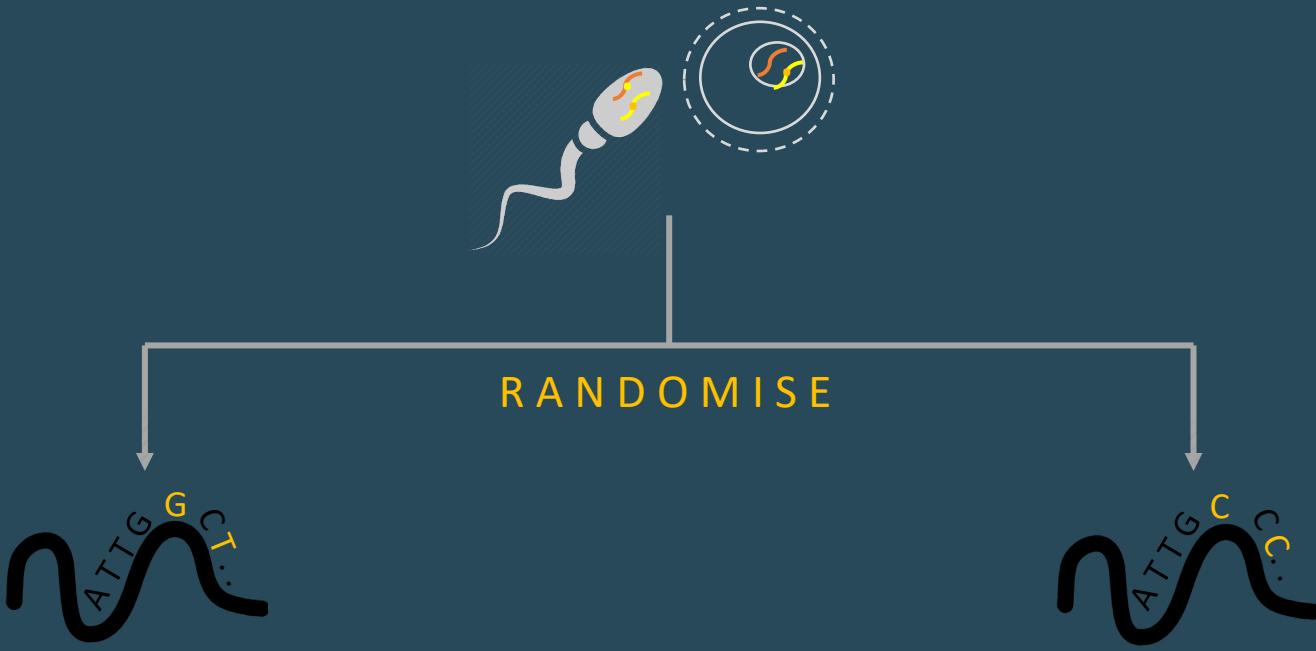
What is Mendelian randomization?

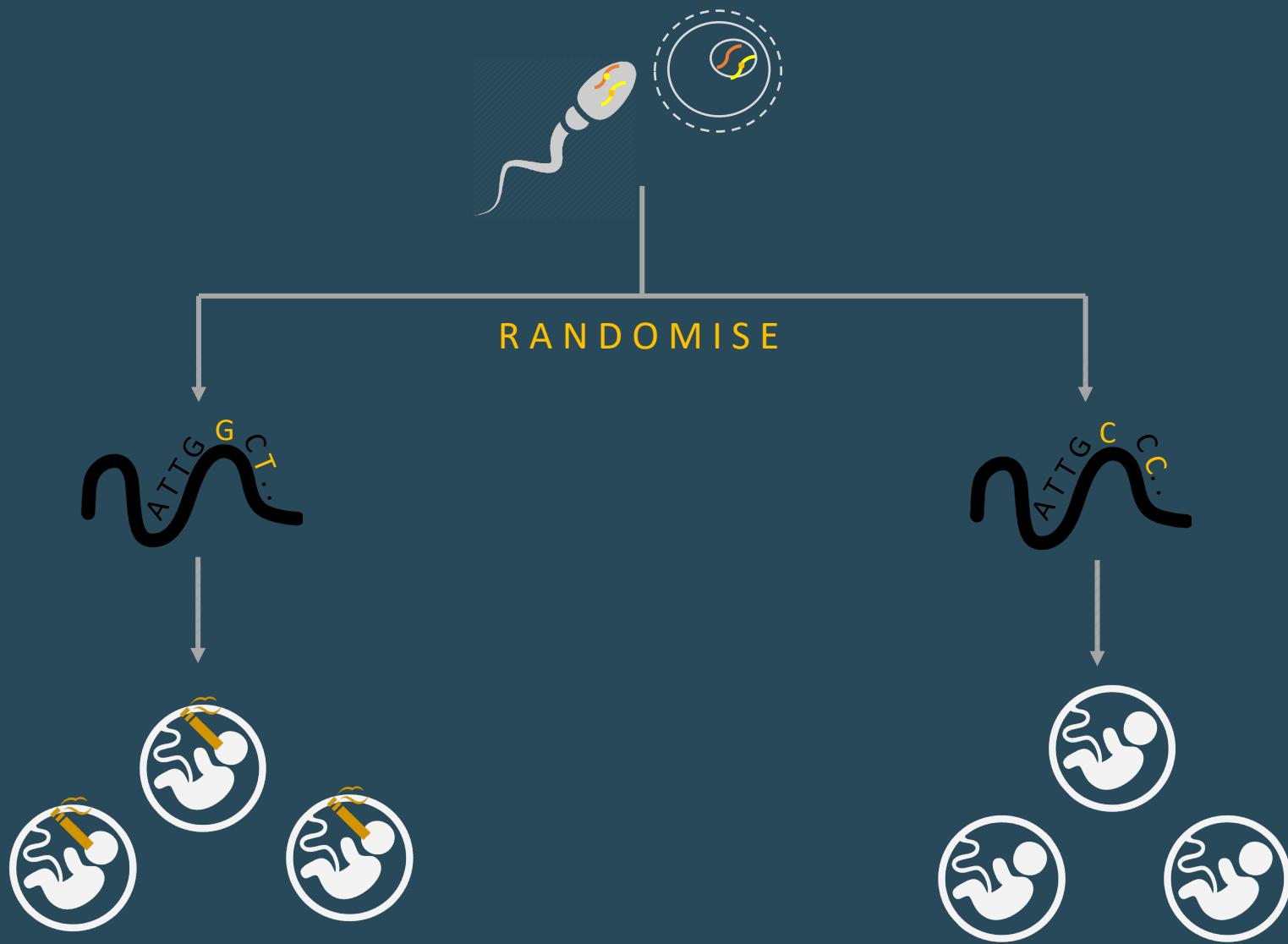
**Randomized Control Trials...**

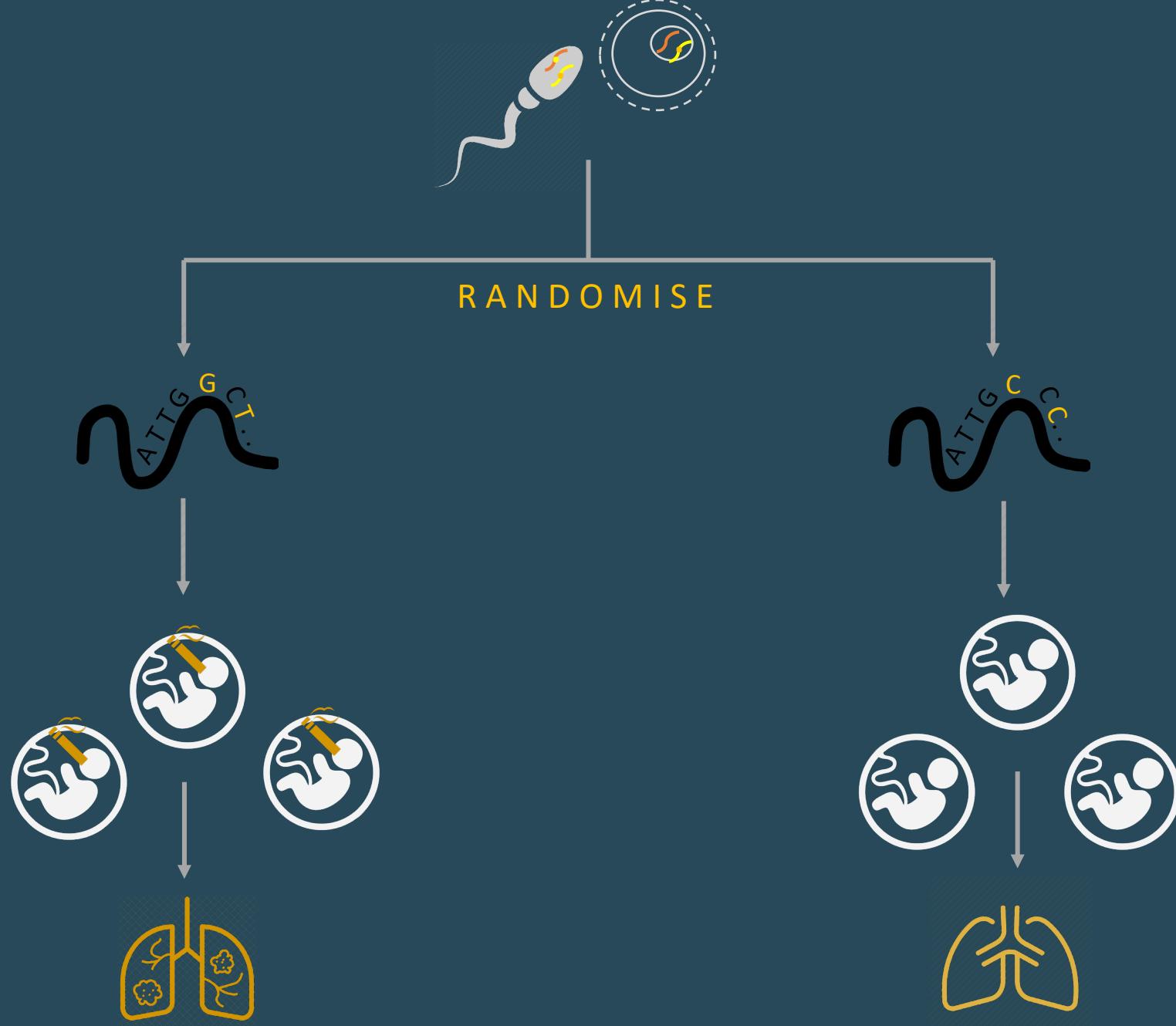


**Our Genetics = Natures Randomizer...**

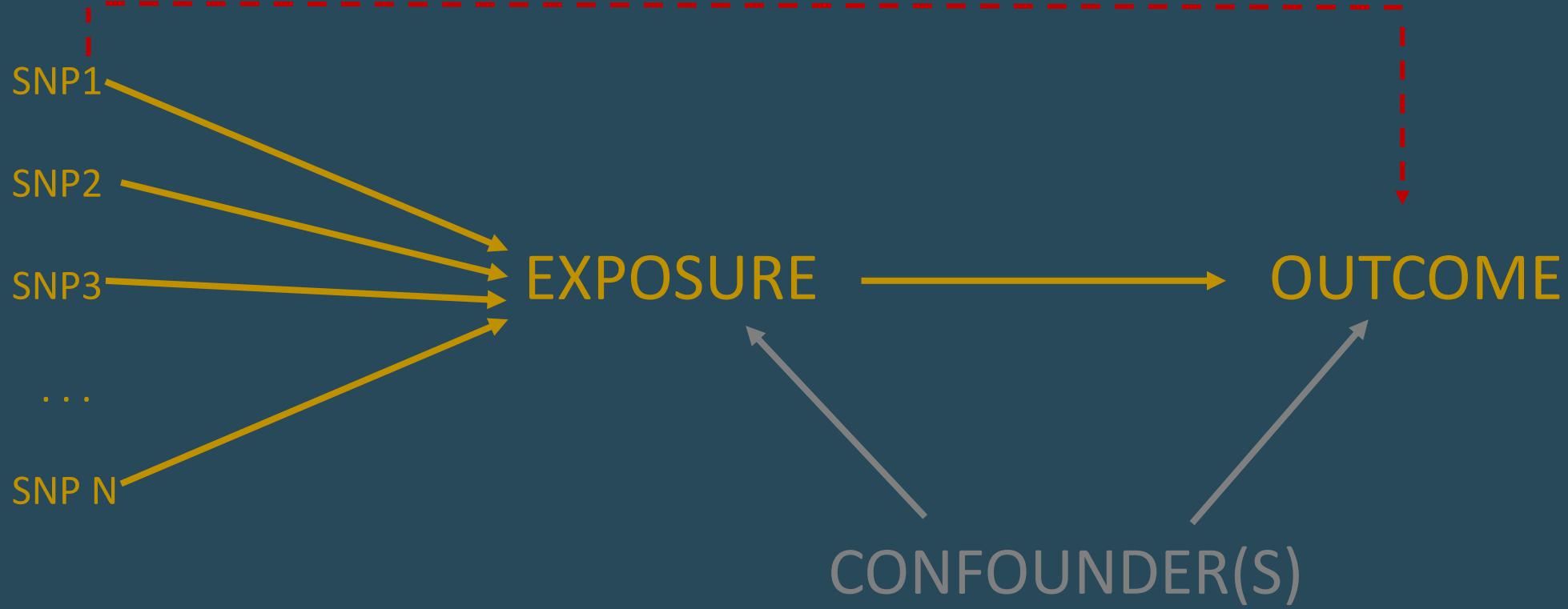


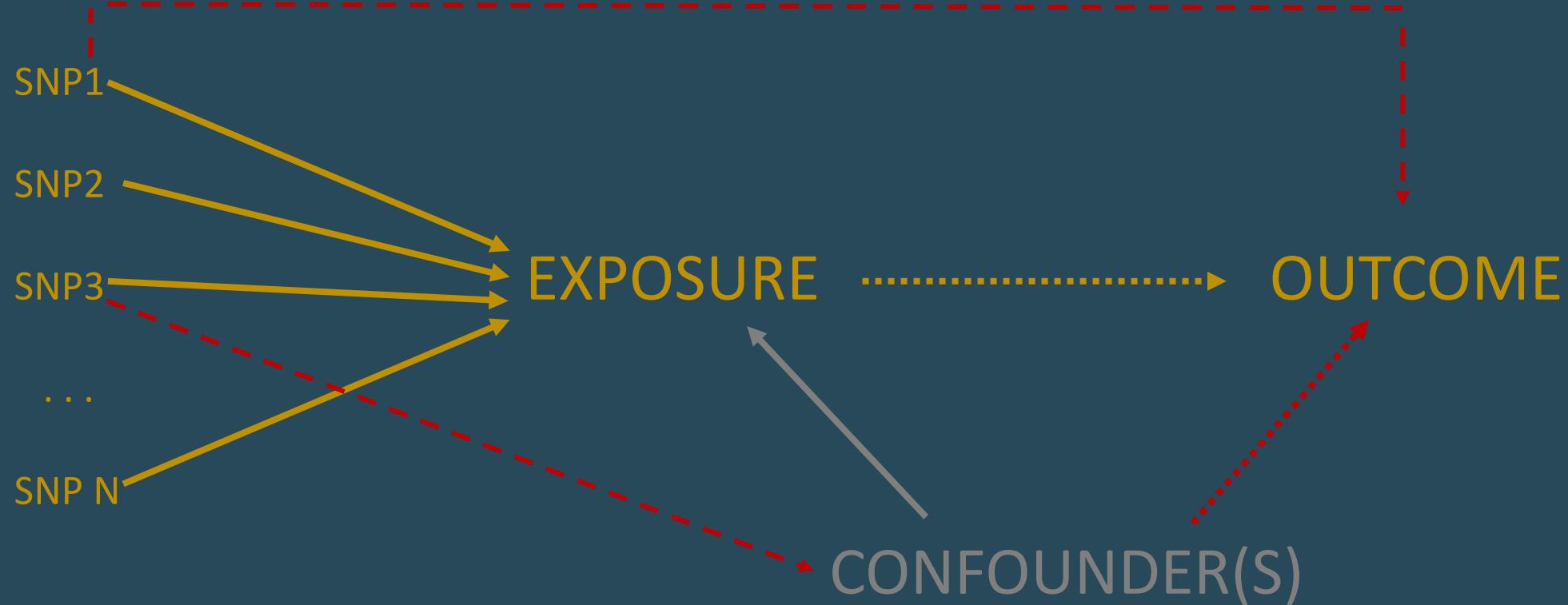




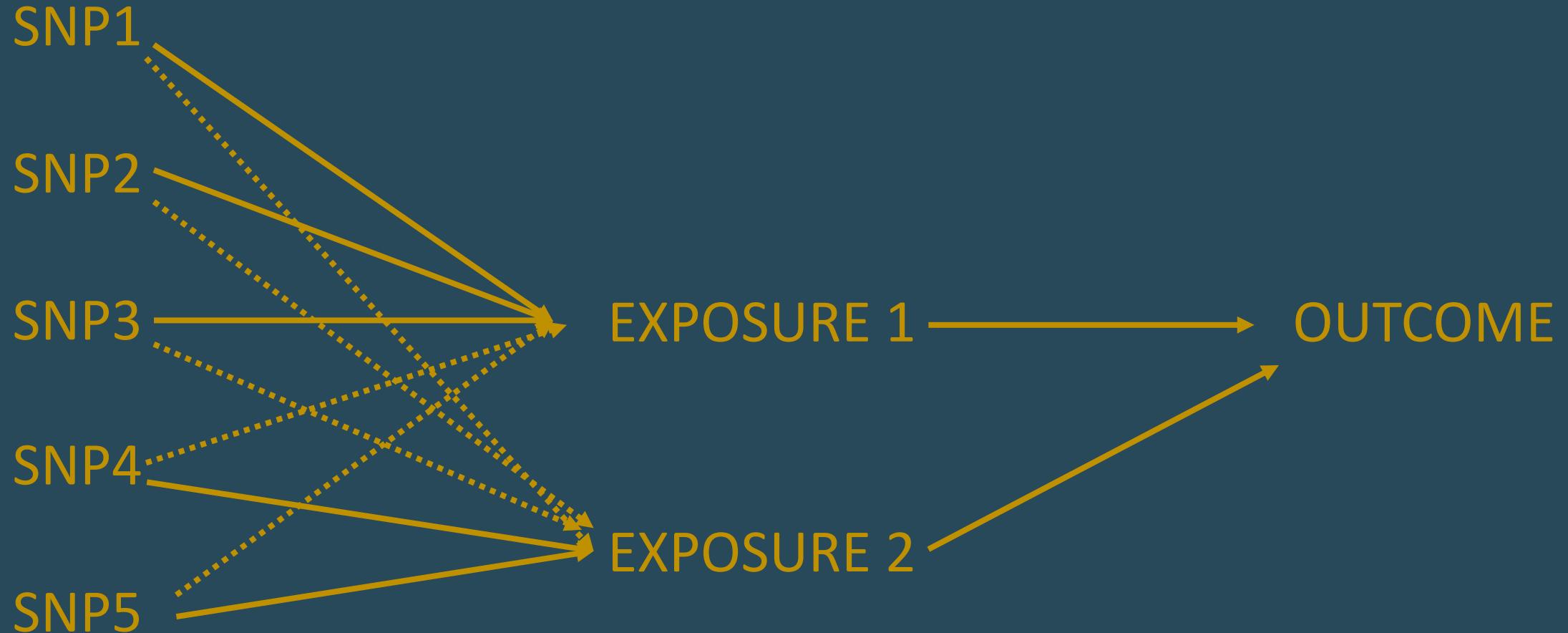


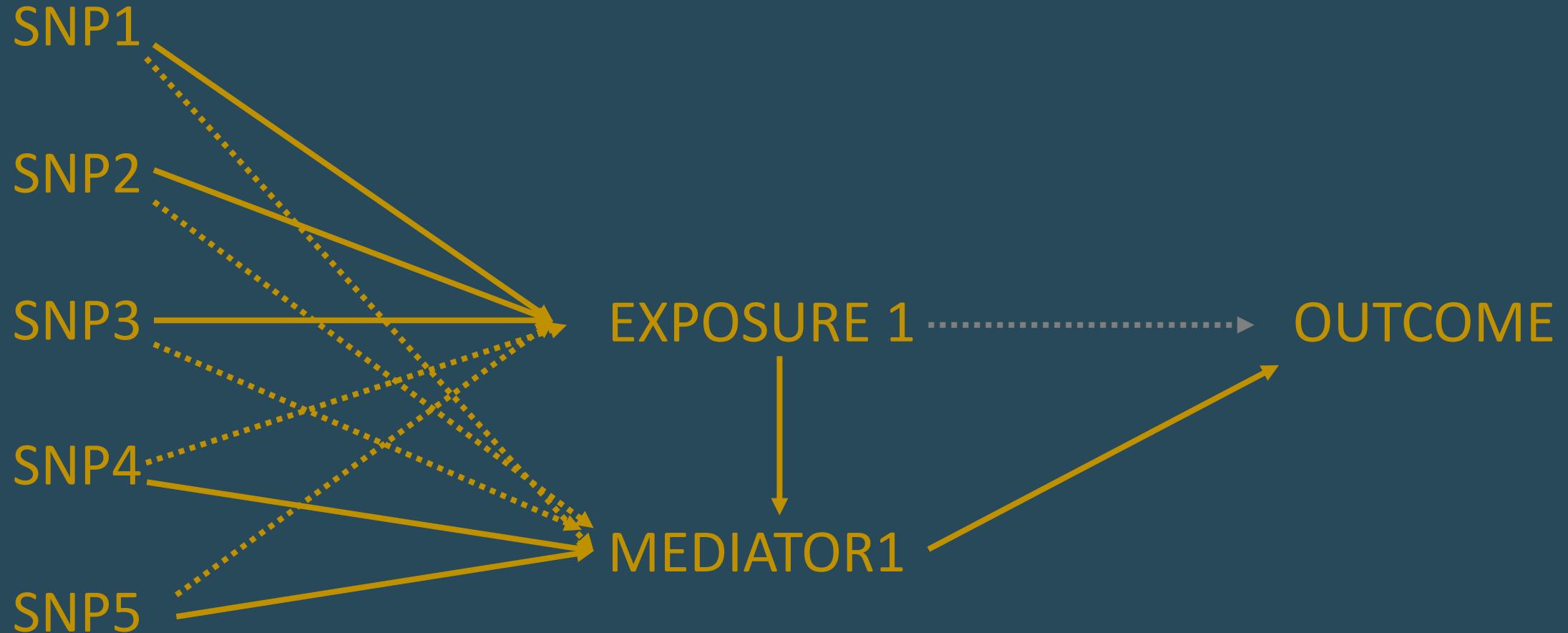
# Univariable MR Framework

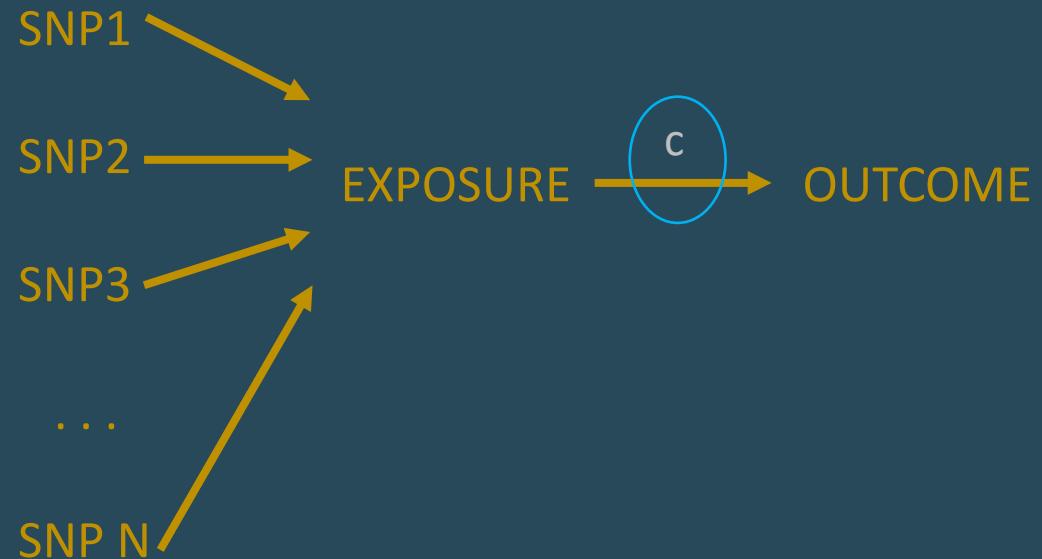




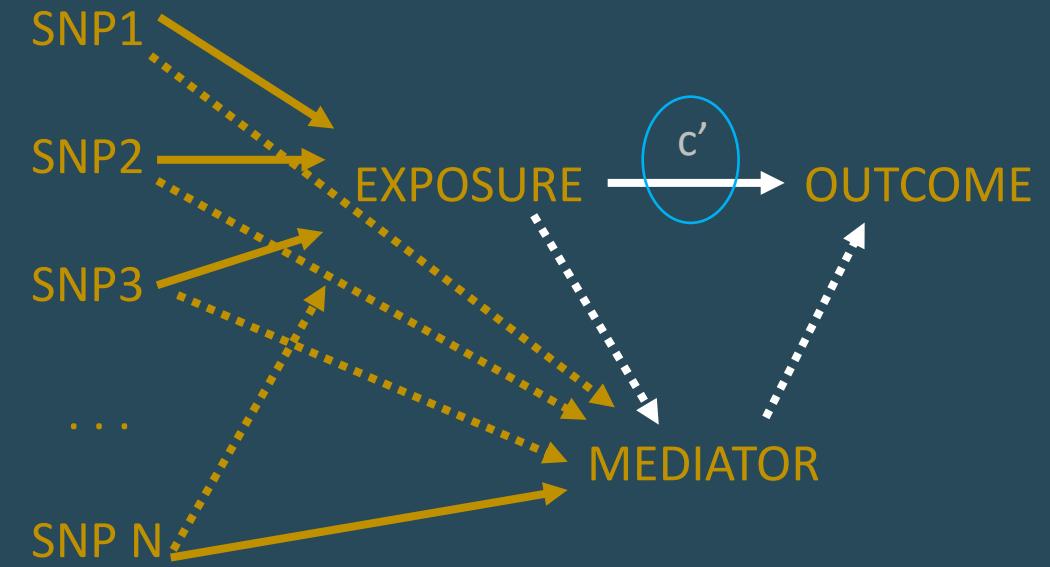
# Multivariable MR Framework (for mediation)



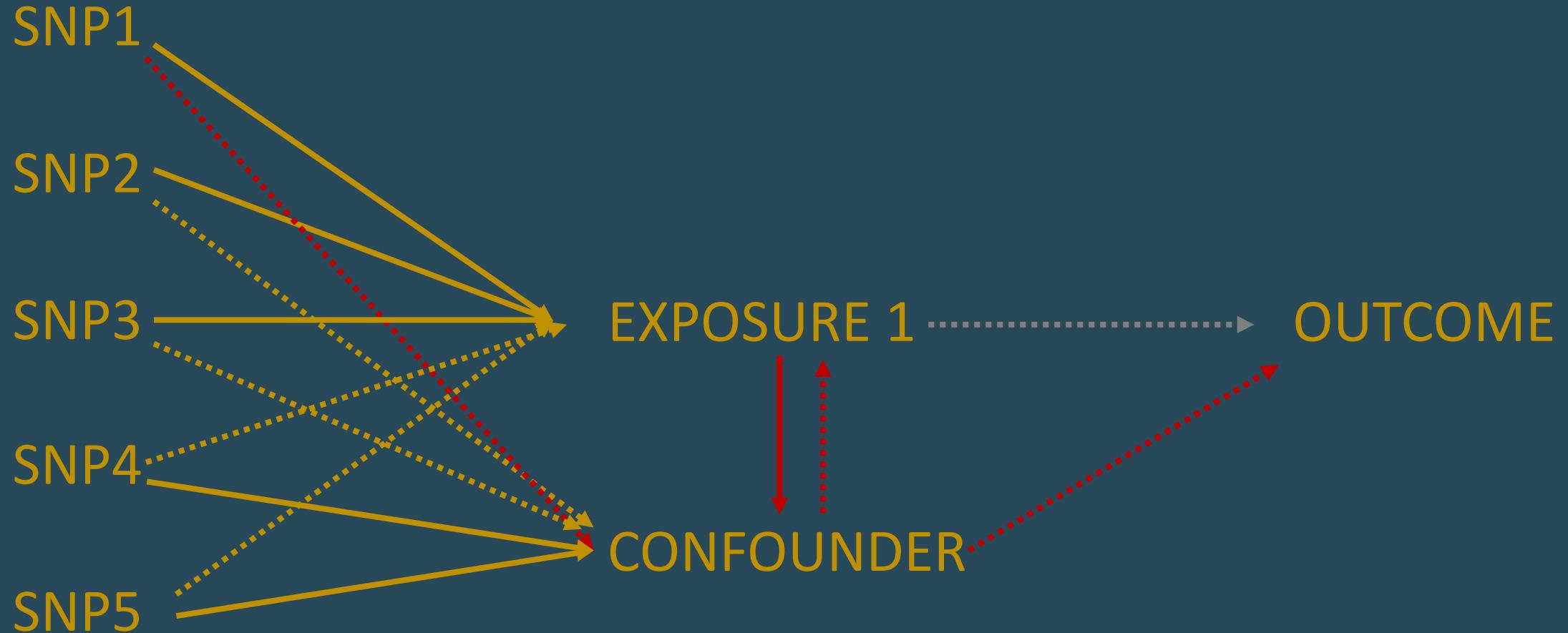




UNIVARIABLE MR:TOTAL EFFECT



MULTIVARIABLE MR: DIRECT EFFECT



2

## Interrogate **causal relationships** using univariable **Mendelian randomization**.

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Educational attainment  $\leftrightarrow$  Alzheimer's Disease

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## Incorporate multivariable methodology to disentangle **mediating relationships**.

# Bi-directional inverse variance weighted (IVW) MR.

- ApoE excluded.
- Sensitivity analyses: MR egger | weighted median | leave-one-out | Cochran's Q.

## DATASETS:

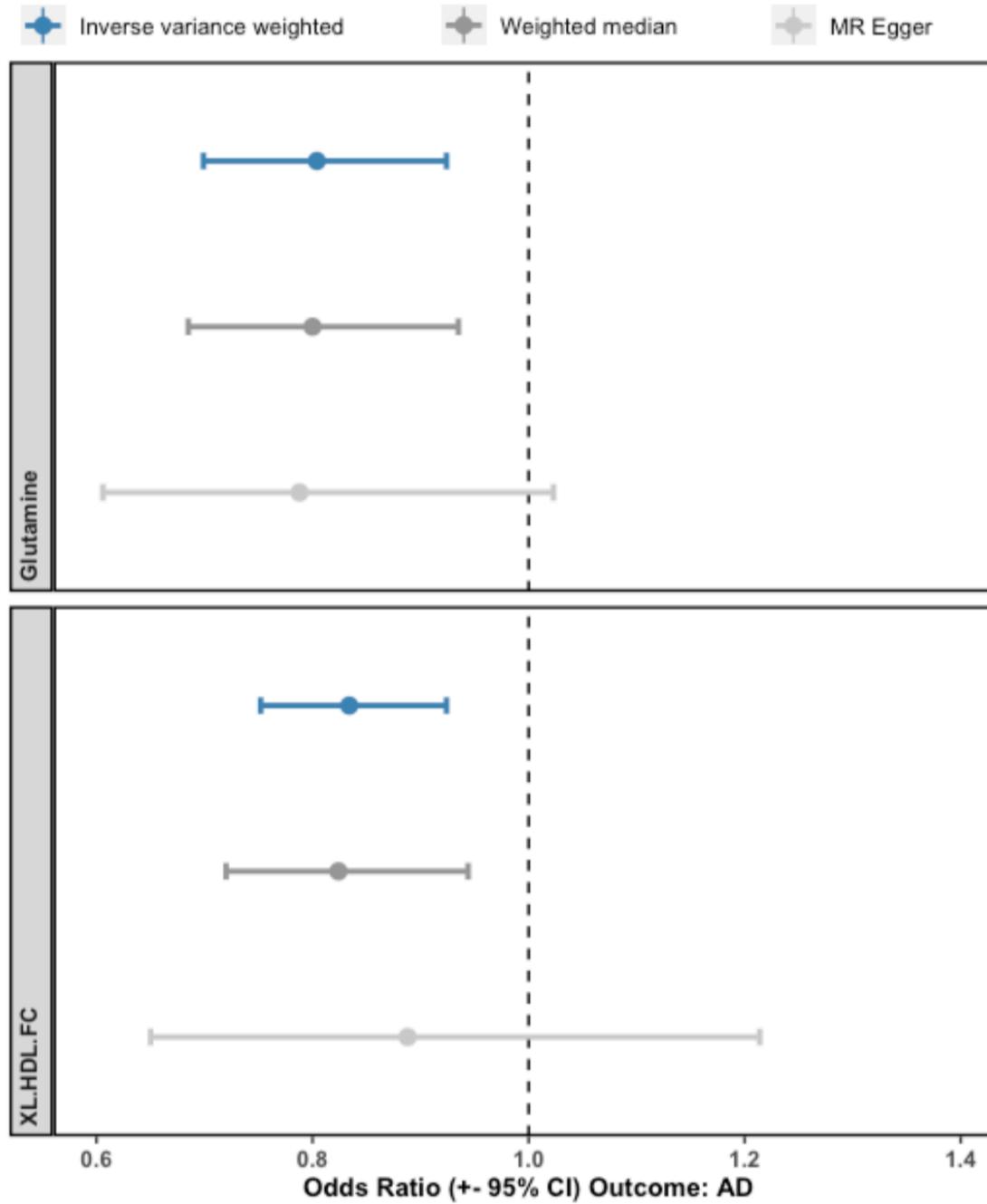
Phenotype	Dataset (year published)	Sample N
Metabolites (1...34)	Kettunen et al. (2016)	24,925
Alzheimer's Disease	Kunkle et al. (2019)	94,437
Educational Attainment	Lee et al. (2018)	1.1 million
Intelligence	Savage et al. (2018)	269,867

*Univariable  
associations used  
to inform  
mediation / what  
taken forward for  
MVMR*

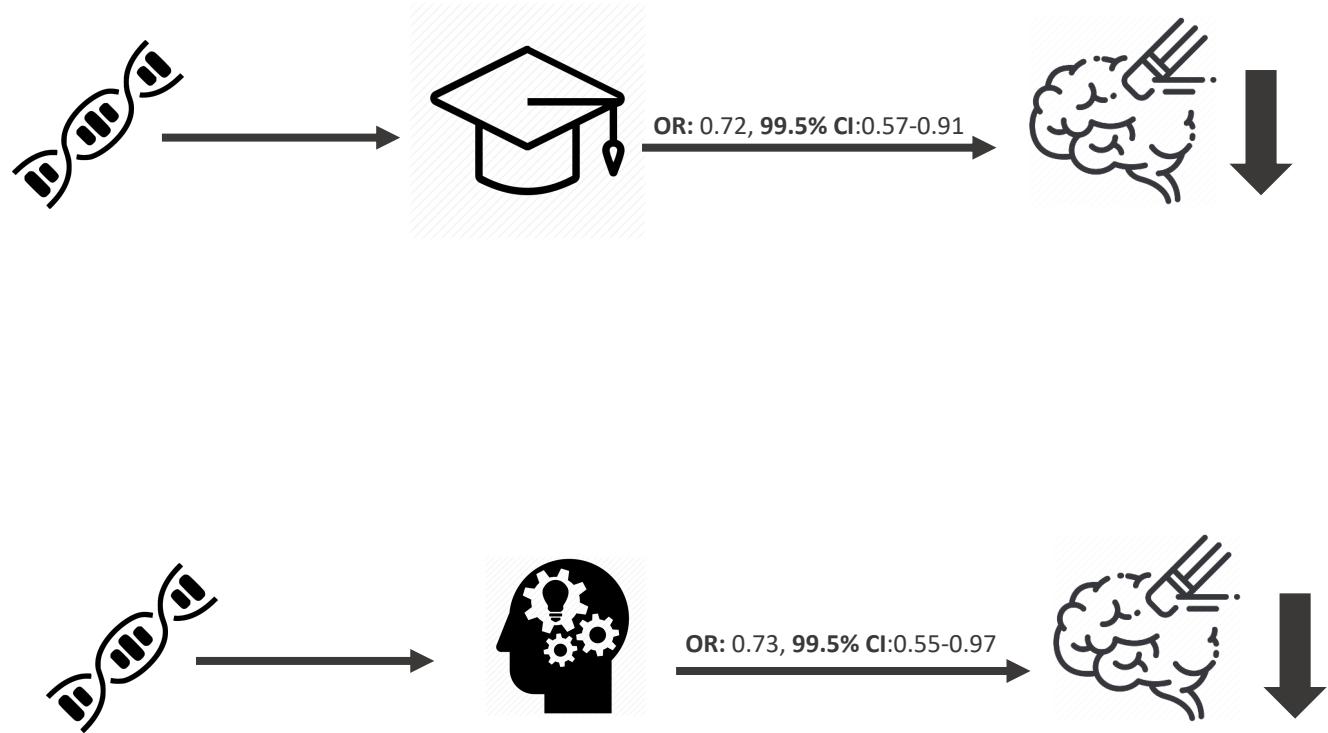
# **Results**

## Mendelian Randomization

# Evidence of a **protective** causal effect of **glutamine** and **XL.HDL.FC** on **Alzheimer's Disease.**



# A protective effect of both educational attainment and intelligence on Alzheimer's Disease.

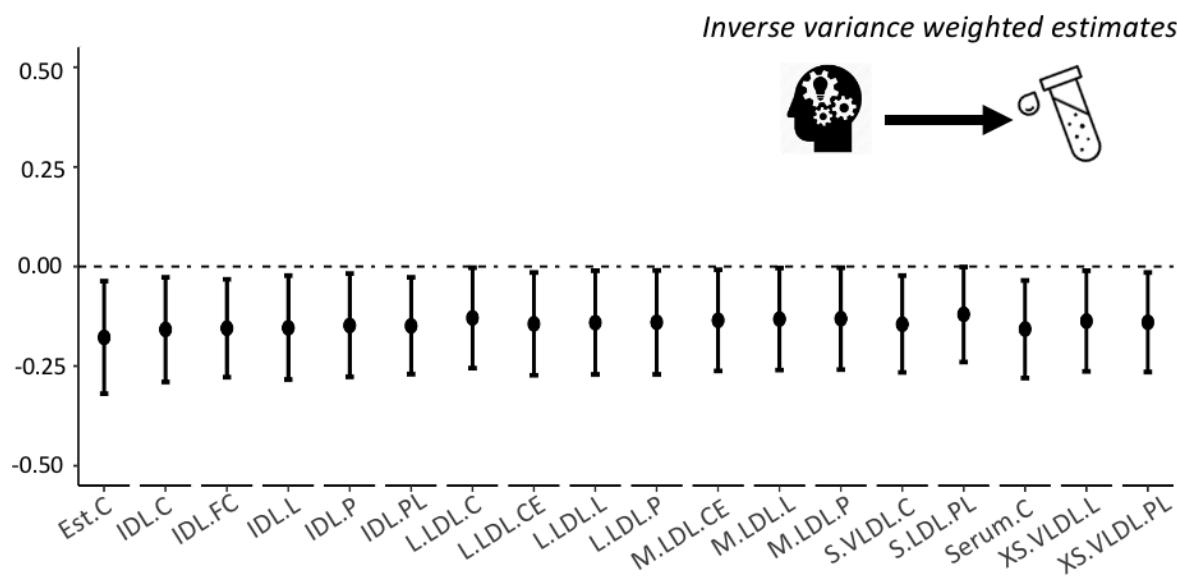


99.5% CIs represent window for adjusted alpha=0.005, to reflect multiple testing.

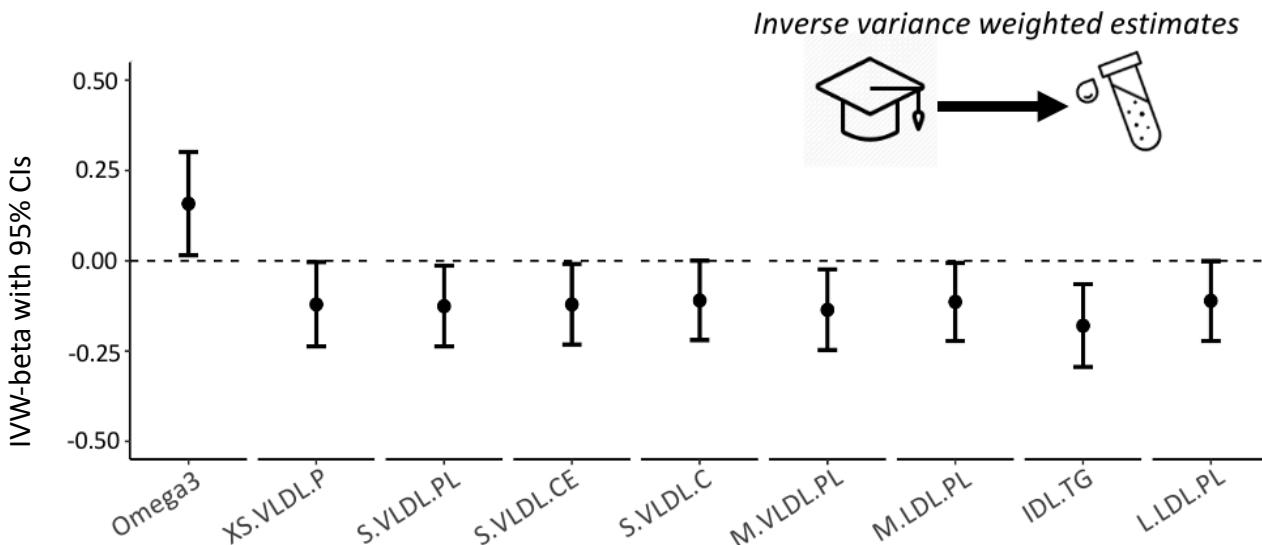
No evidence that either of these metabolites were causally linked to either educational attainment or intelligence, however.



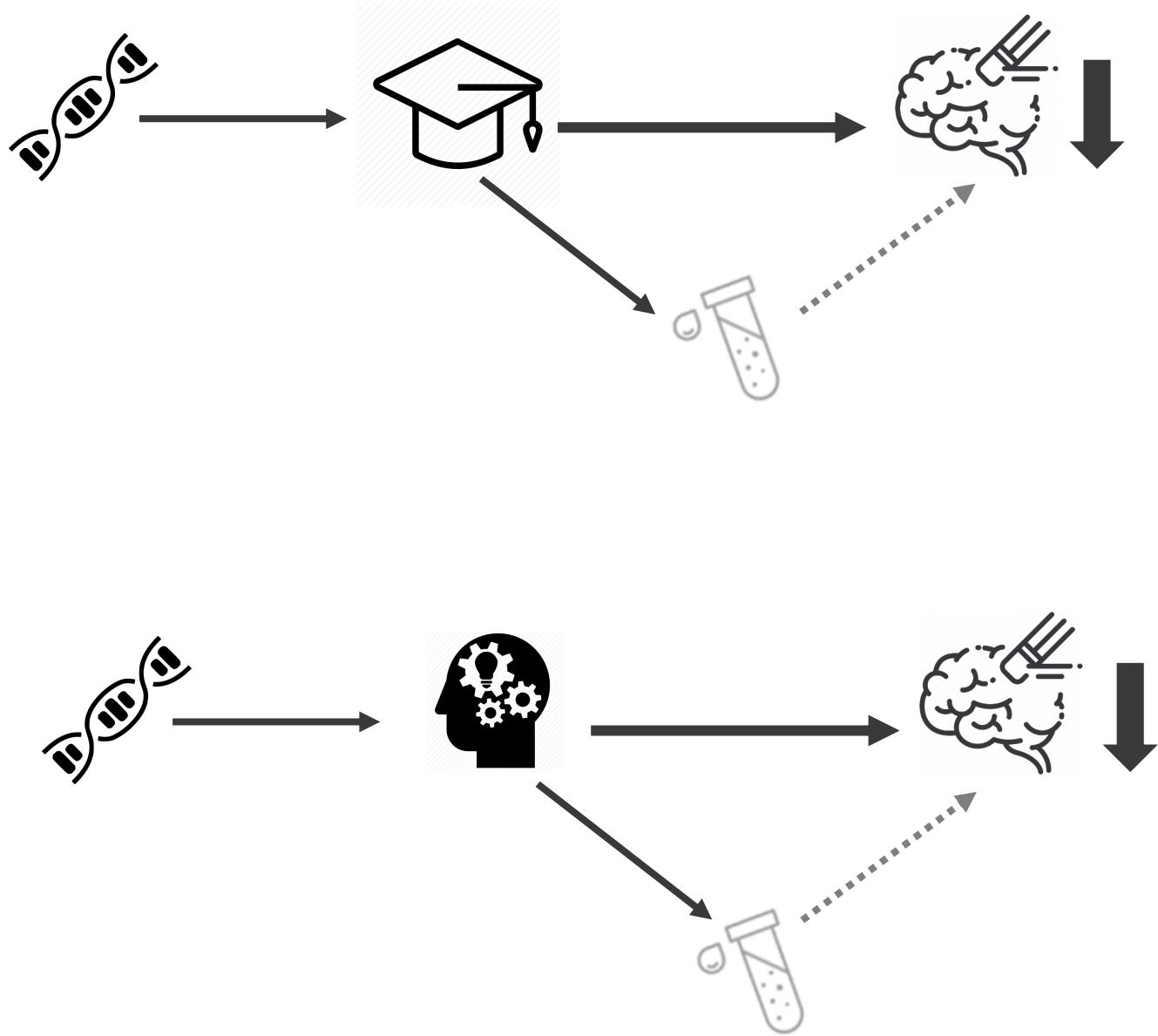
**18 lipid-related metabolites show evidence of a causal association with intelligence.**



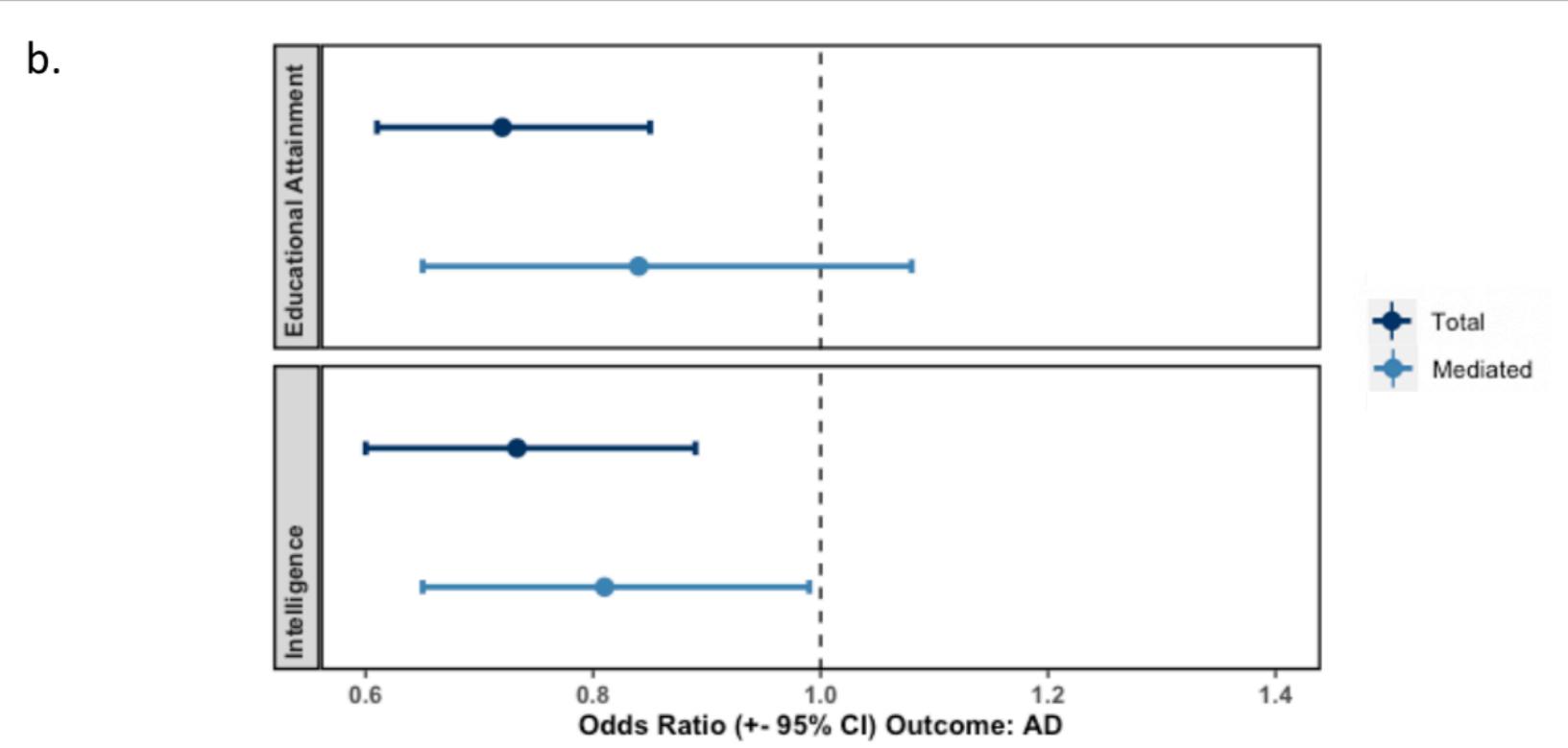
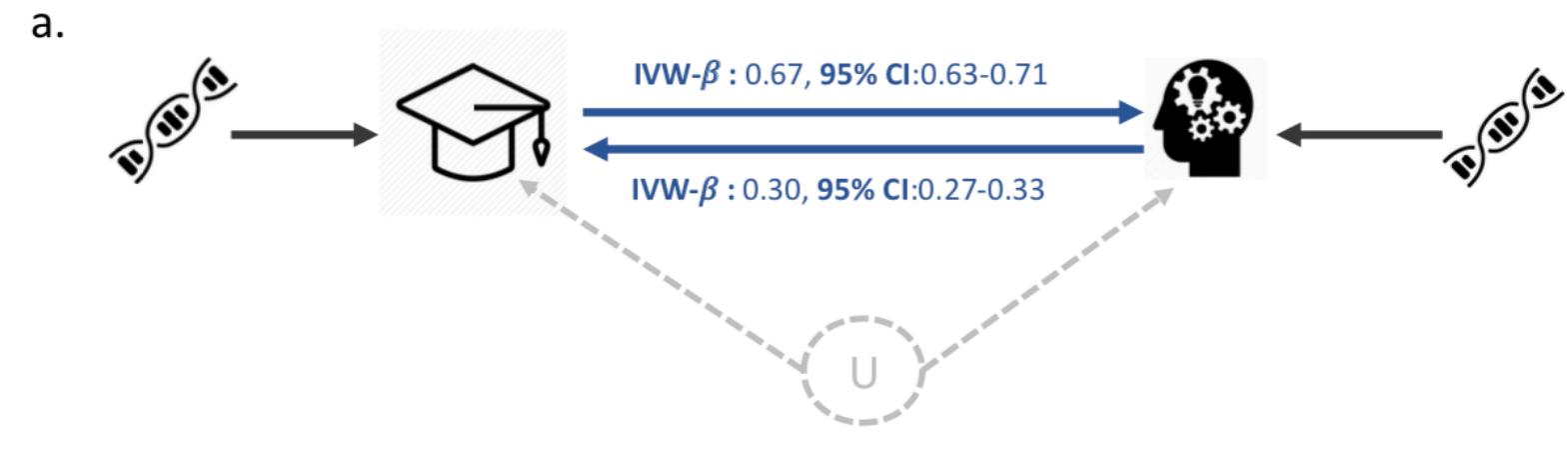
**9 lipid-related metabolites show evidence of causal association with educational attainment.**



However...  
**No evidence** that  
any of these  
**metabolites**  
**mediated** the  
causal effects  
observed for either  
of our cognition  
factors on **AD**.



**Bidirectional mediation between education and intelligence with regards to their effect on AD was observed, though stronger mediation via intelligence was found.**



# **Summary**

## and next steps

## Combining knowledge across polygenic scores, multivariable and univariable MR, our results:

- Identified two blood metabolites – glutamine and XL.HDL.FC – to show evidence of a protective effect on AD.
- Like previous studies, confirmed a protective effect of both education and intelligence on AD.
- Biological mechanisms underpinning the relationship between education and intelligence on AD, however, remain elusive, with no evidence of mediation via any of our metabolites.
- However, the effect of educational attainment on AD was almost entirely driven by positive changes that educational attainment has on intelligence.

### Next:

Disentangling wider, multi-modal risk factors (depression, other omics etc) and understanding how these connect along the AD causal pathway will be an important future endeavor if we hope to appropriately inform treatment strategies.

This study provides some initial puzzle pieces to the AD causal jigsaw, which will be important for informing this wider multi-modal work.

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**Thank You!**

**Questions?**

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Marcus Richards<sup>e</sup>, Pak Sham<sup>f</sup>, Cristina Legido-Quigley<sup>g</sup>, Richard Dobson<sup>abh</sup>, Petra Proitsi<sup>a</sup>



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## References

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