

Investigating the role of modifiable risk factors on the causal pathway to Alzheimer's Disease



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Motivation:

- Currently no treatments to stop, reverse, or fully prevent AD.
- Research consistently reports educational factors like years of schooling & intelligence to show protective association with AD, but it remains unclear how these interact with biology to influence risk.
- Blood metabolites can provide vital clues to how factors like the above influence biology.
- As metabolites are also easily measurable, they offer particular efficacy for tracking disease progress, monitoring intervention strategies, and as direct treatment targets - but **ONLY if they are causally linked to AD.**

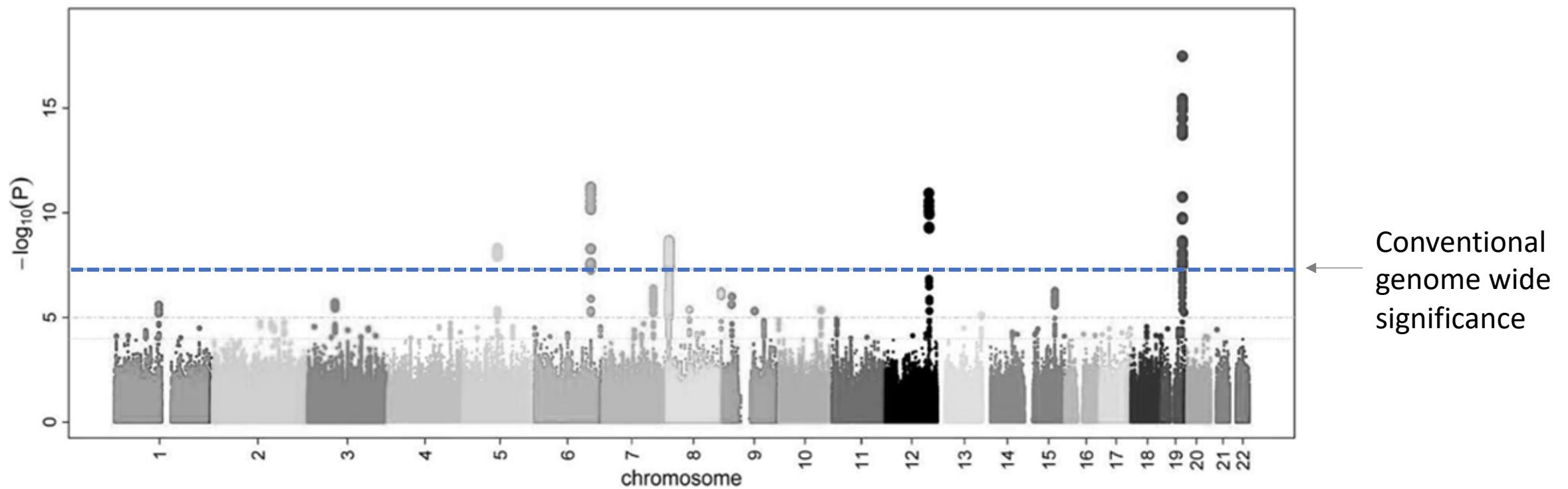
Aims:

1. Harness use of polygenic risk scores to identify metabolites which genetically predict AD status.
2. Disentangle causal relationships between these metabolites and AD.
3. Incorporate information relating to schooling and intelligence to:
 - a) Reconfirm previous reports of protective associations
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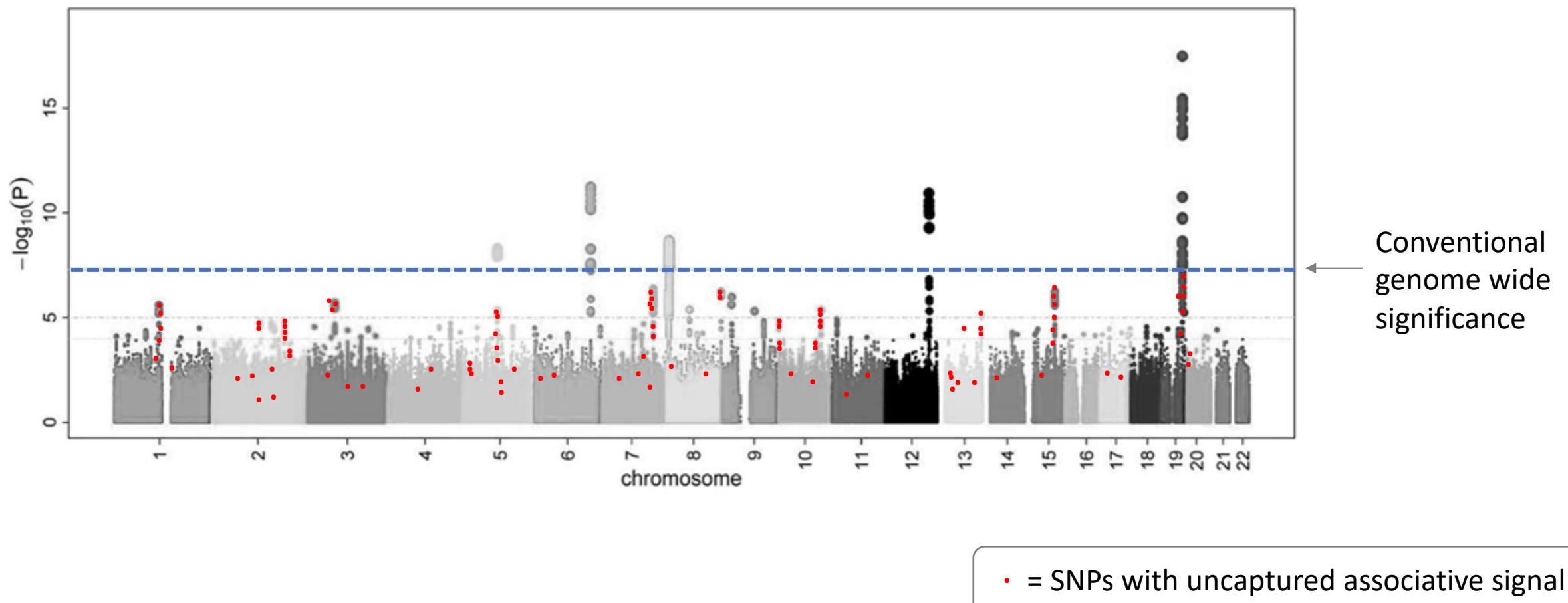
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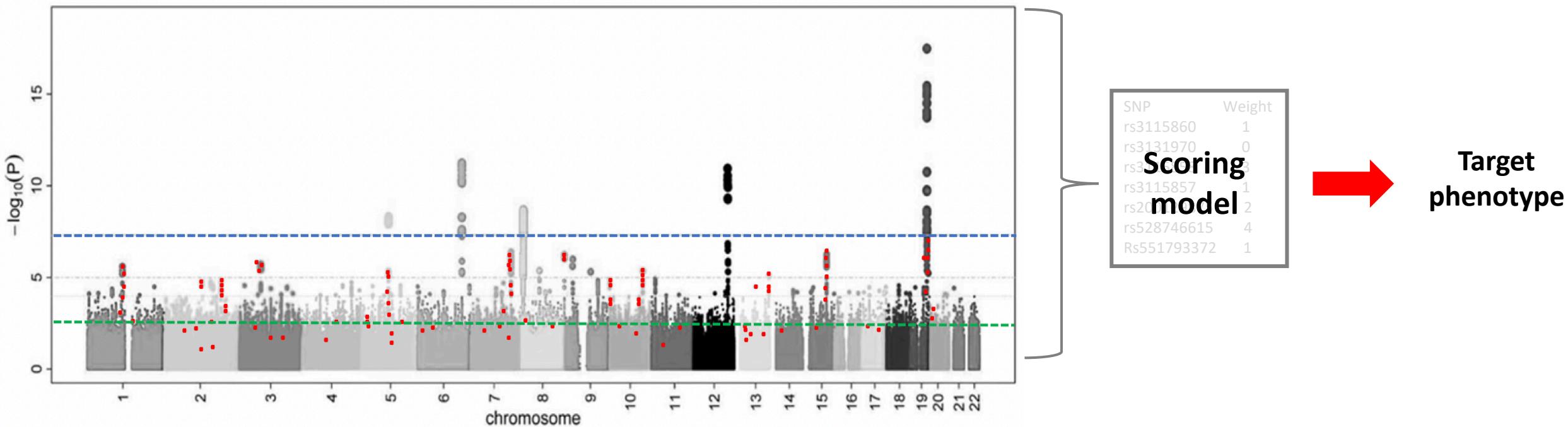
Context: What is a Polygenic Score?



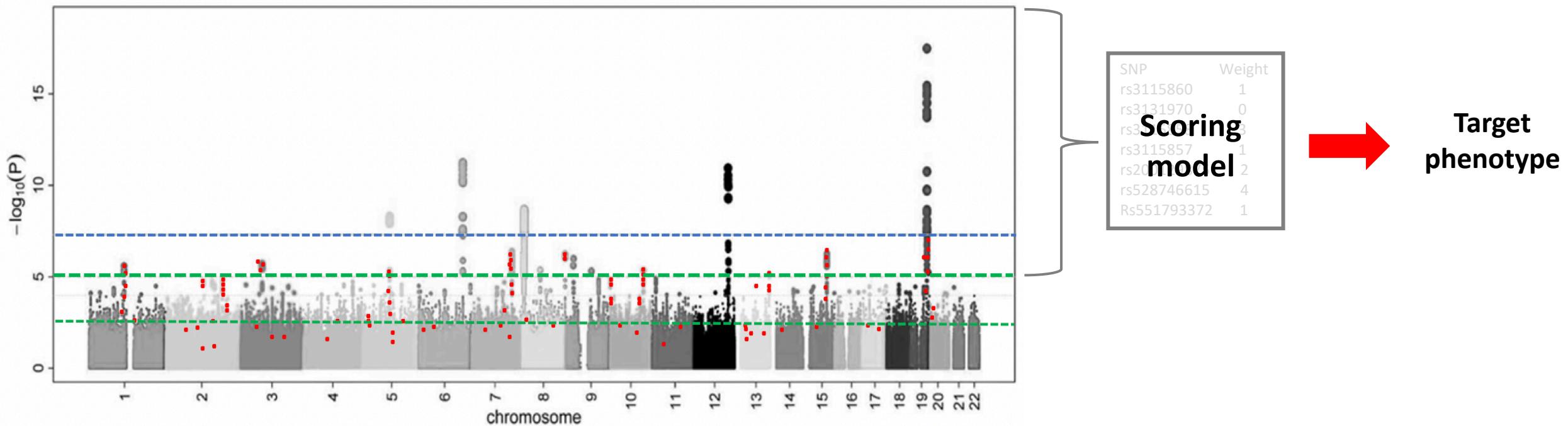
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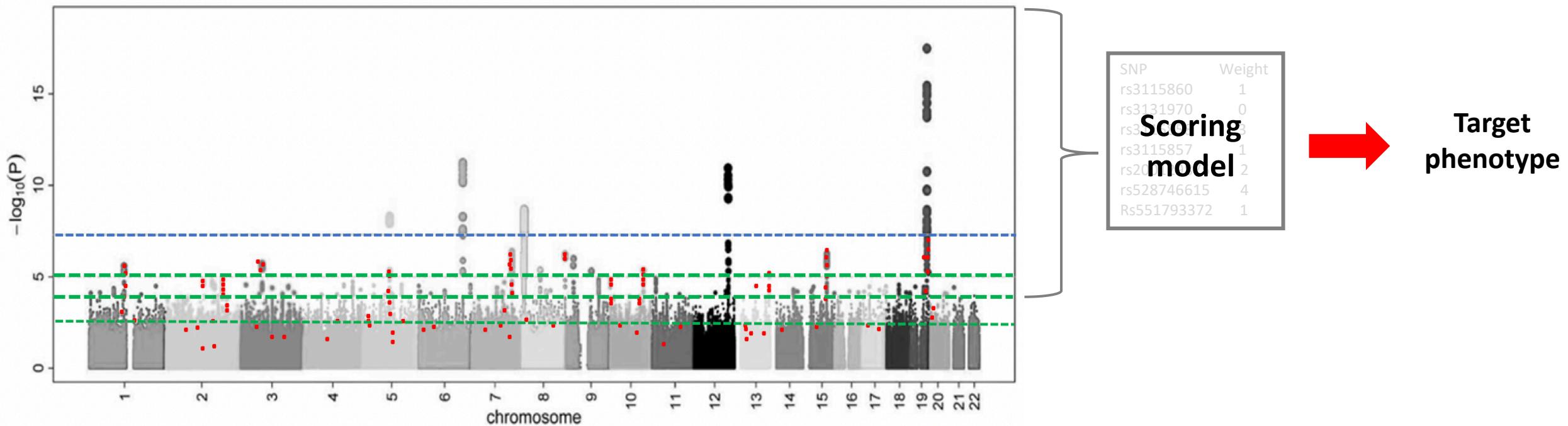
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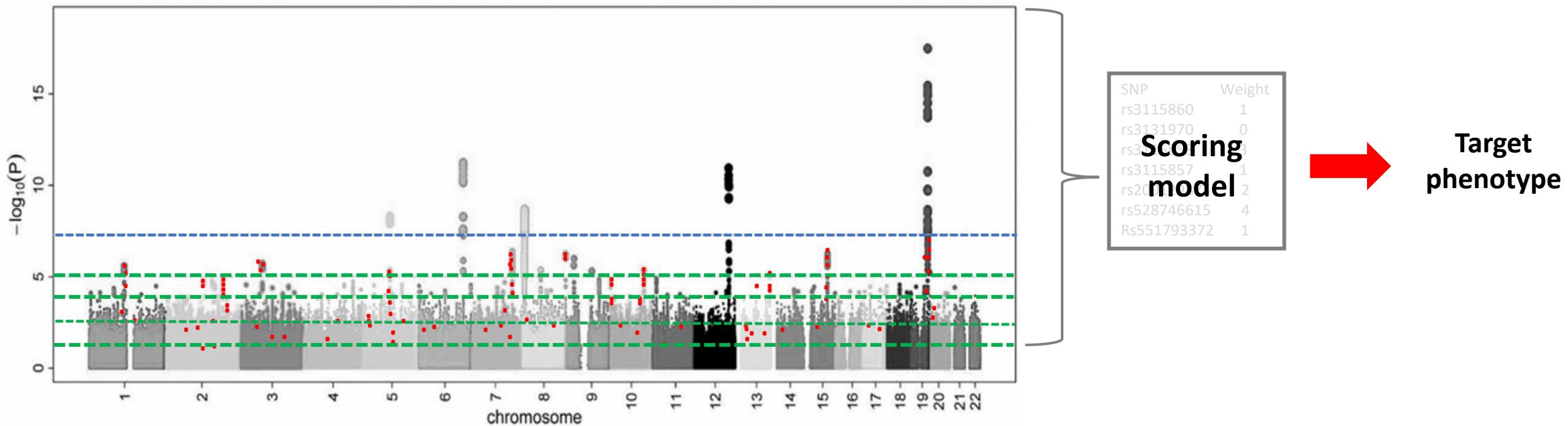
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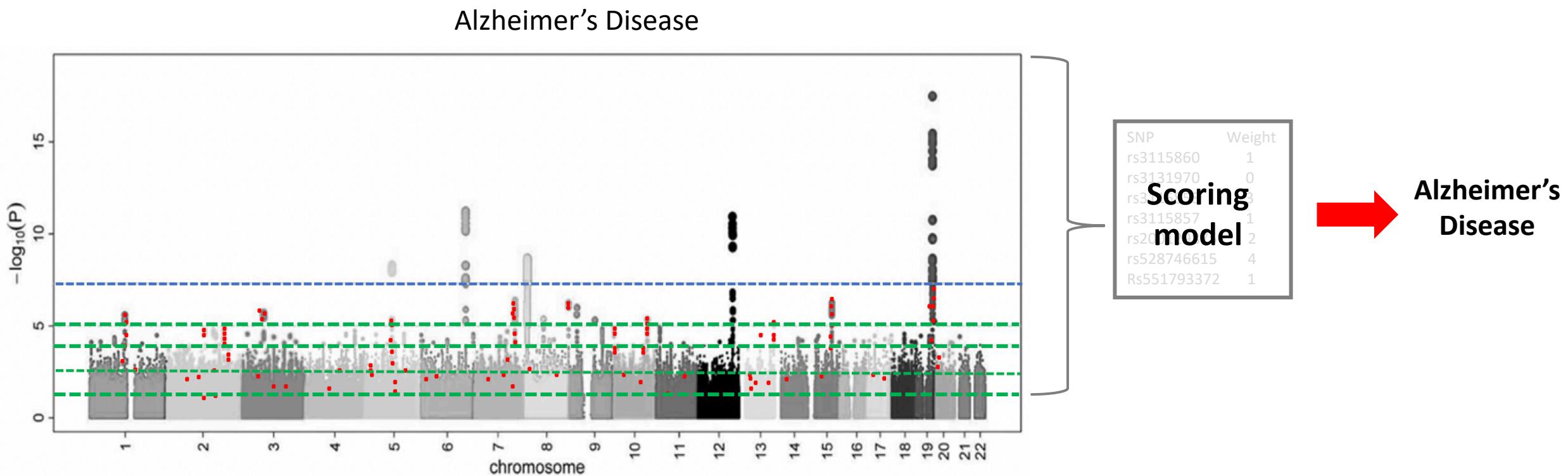
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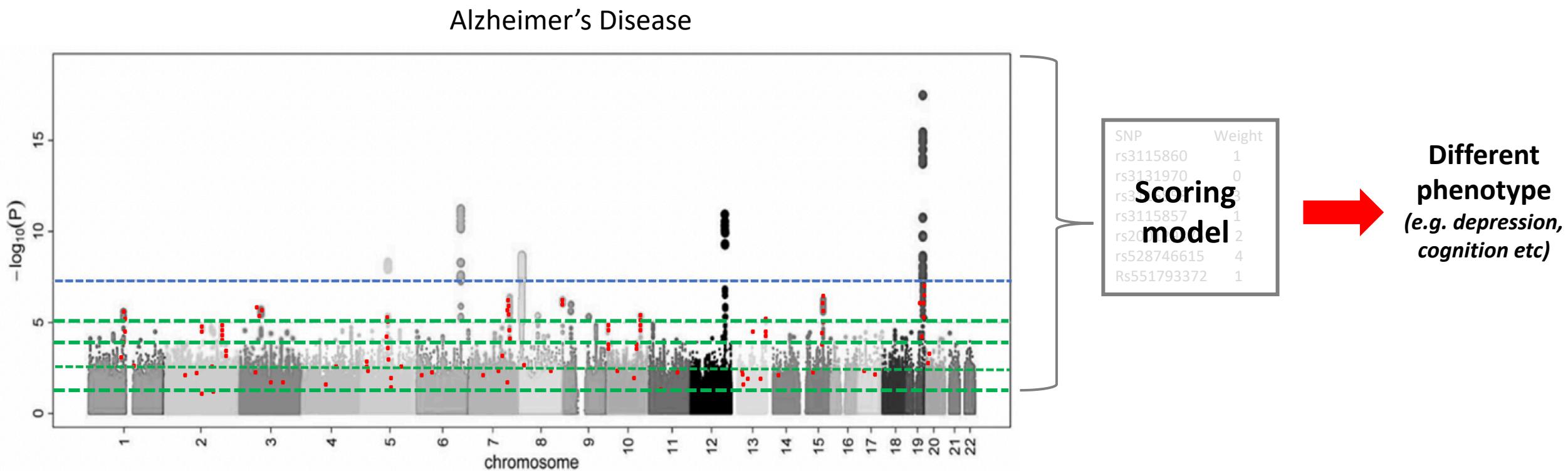
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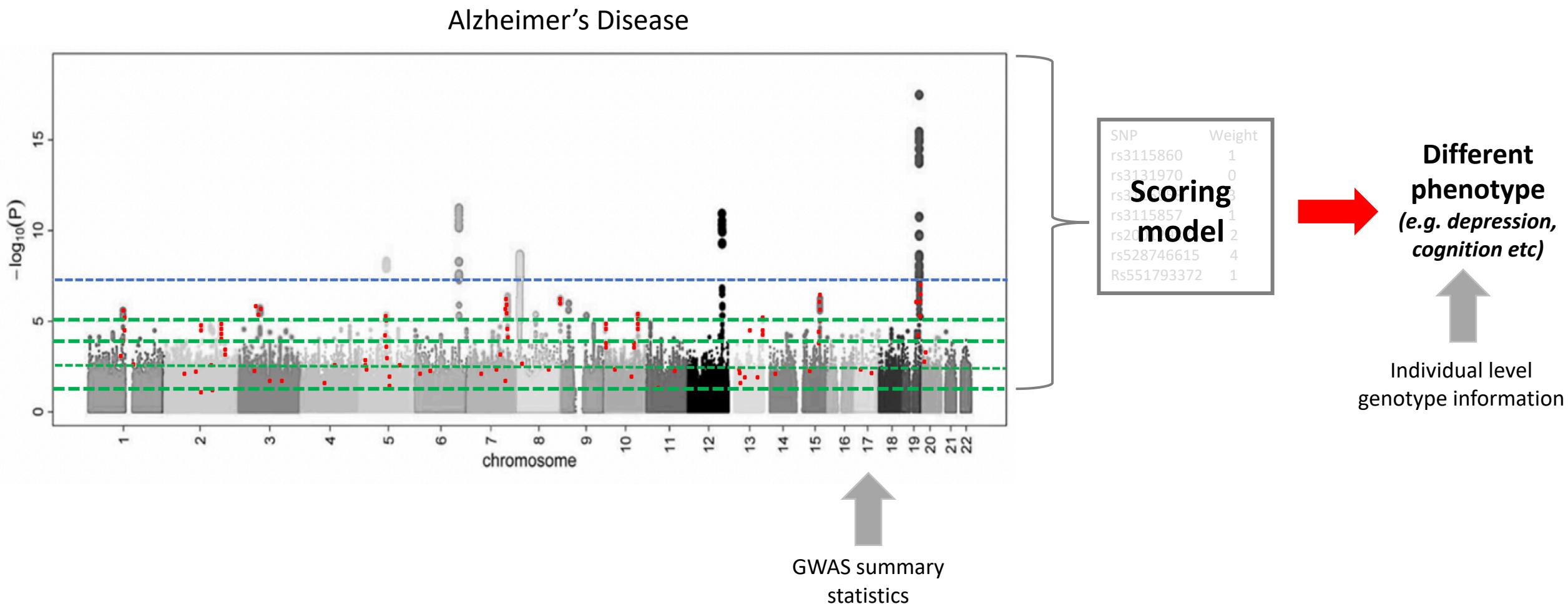
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Harness use of polygenic risk scores to identify metabolites which genetically predict AD status.

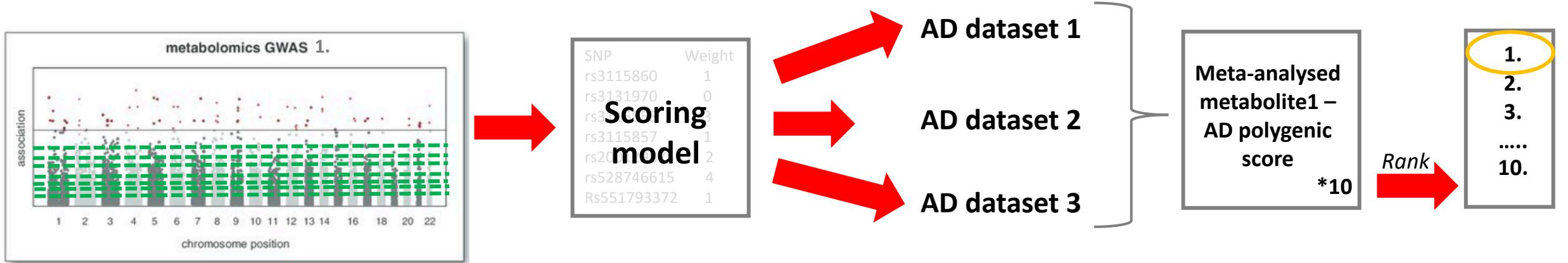
- Cross-trait Polygenic Risk Scores.
- Base Datasets:
106 metabolite GWAS datasets from Kettunen et al., 2016. 
- 10 p-value thresholds:
 $5e^{-8}$ | $1e^{-5}$ | $1e^{-4}$ | 0.0001 | 0.001 | 0.01 | 0.05 | 0.1 | 0.2 | 0.5 | 1
- Target Datasets:
3 raw AD datasets (106*3):
 1. AddNeuroMed ($N=648$)
 2. ADNI ($N=886$)
 3. GERAD ($N=3191$).
- Covariates:
Top 7 PCs, age, sex | ApoE genomic region removed.
- Random-effects **meta-analysis** in R using the metafor package.
- Metabolites showing most significant genetic association with AD → MR

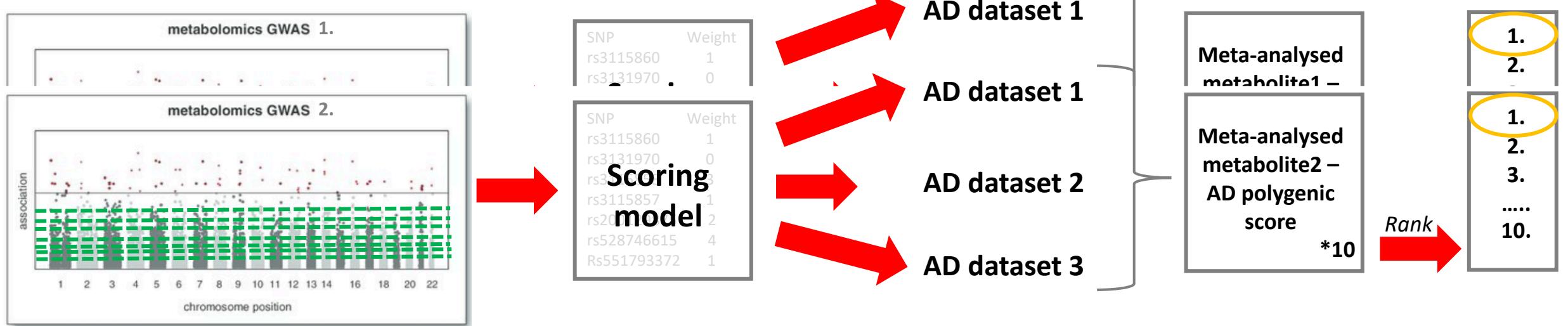
Genome-wide study for circulating metabolites identifies 62 loci and reveals novel systemic effects of LPA

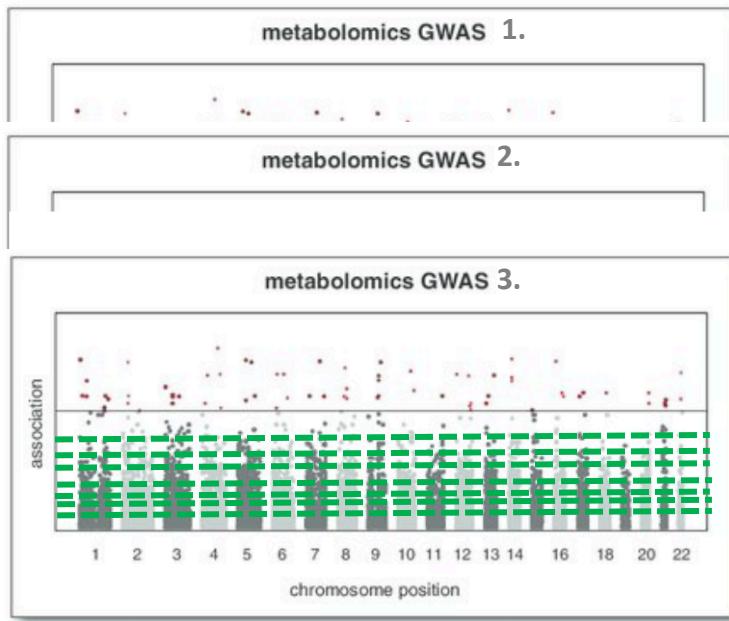
Johannes Kettunen, Ayşe Demirkar [...] Mika Ala-Korpela

Nature Communications 7, Article number: 11122 (2016) | Download Citation ↴

- 123 GWAS datasets available.
- 17 removed due to low h^2 .
- Blood metabolites extracted via Nuclear Magnetic Resonance.
- Total N = 24,925





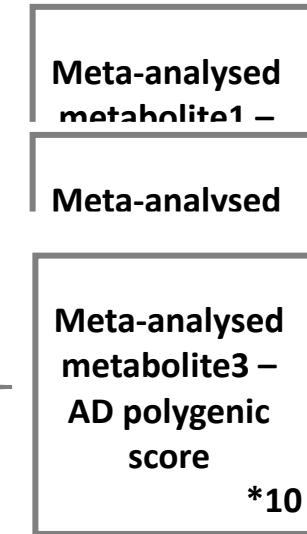


SNP	Weight
rs3115860	1
rs3131970	0

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rs3115860	1

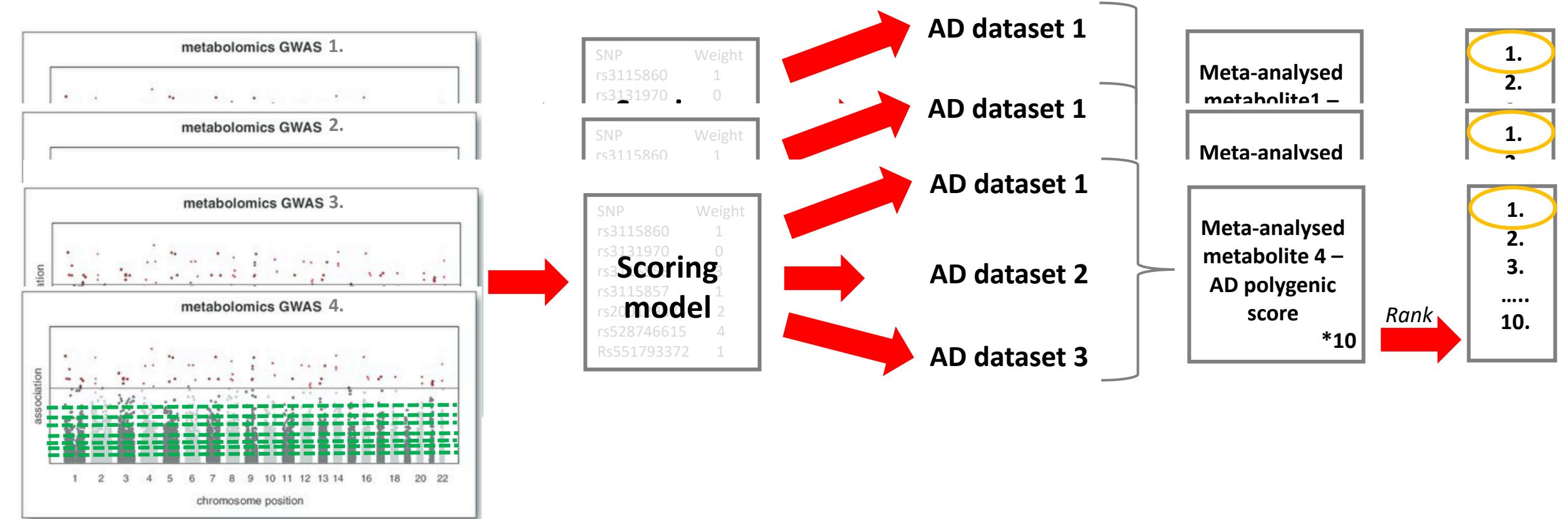
SNP	Weight
rs3115860	1
rs3131970	0
rs3115857	1
rs3115857	1
rs2073640	2
rs528746615	4
Rs551793372	1

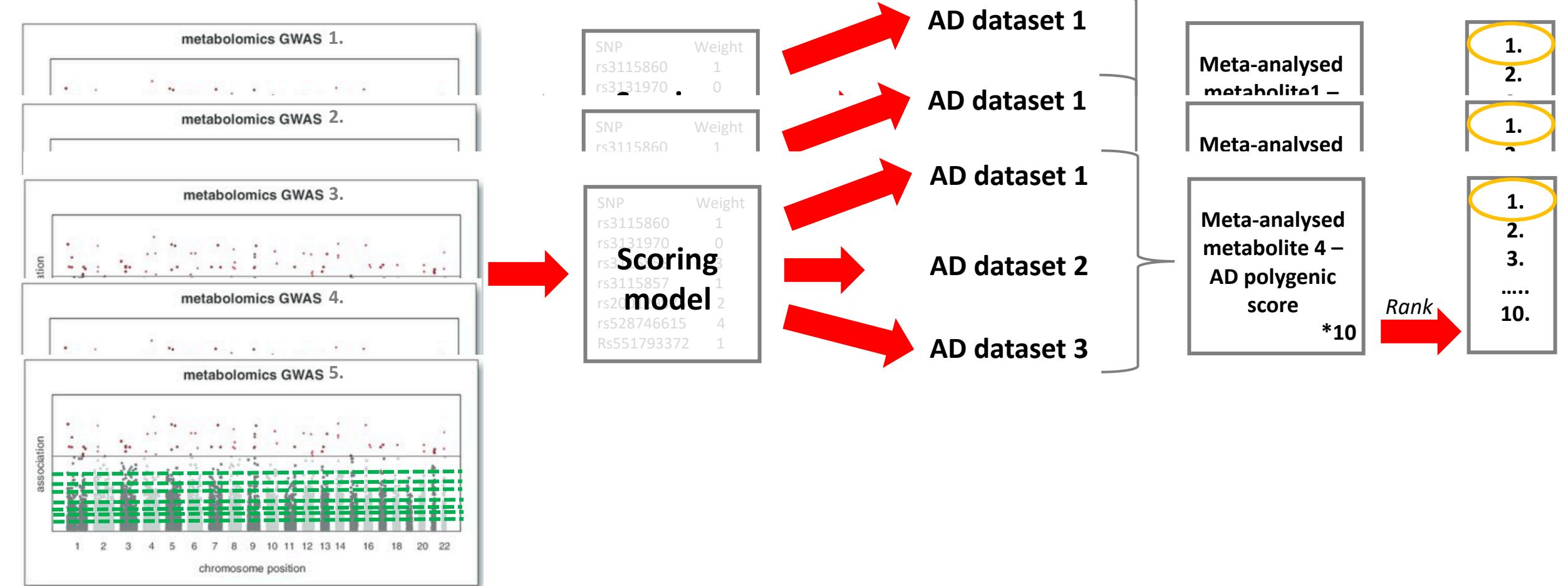
Scoring model

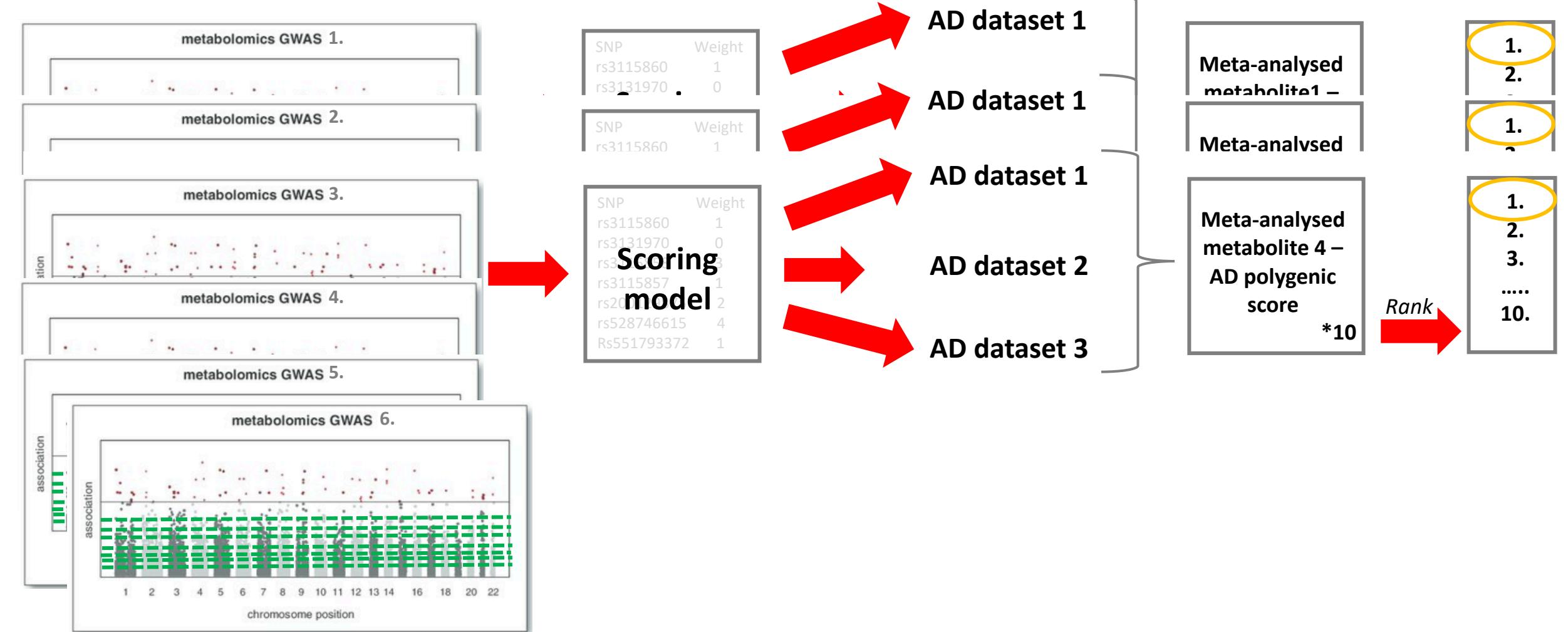


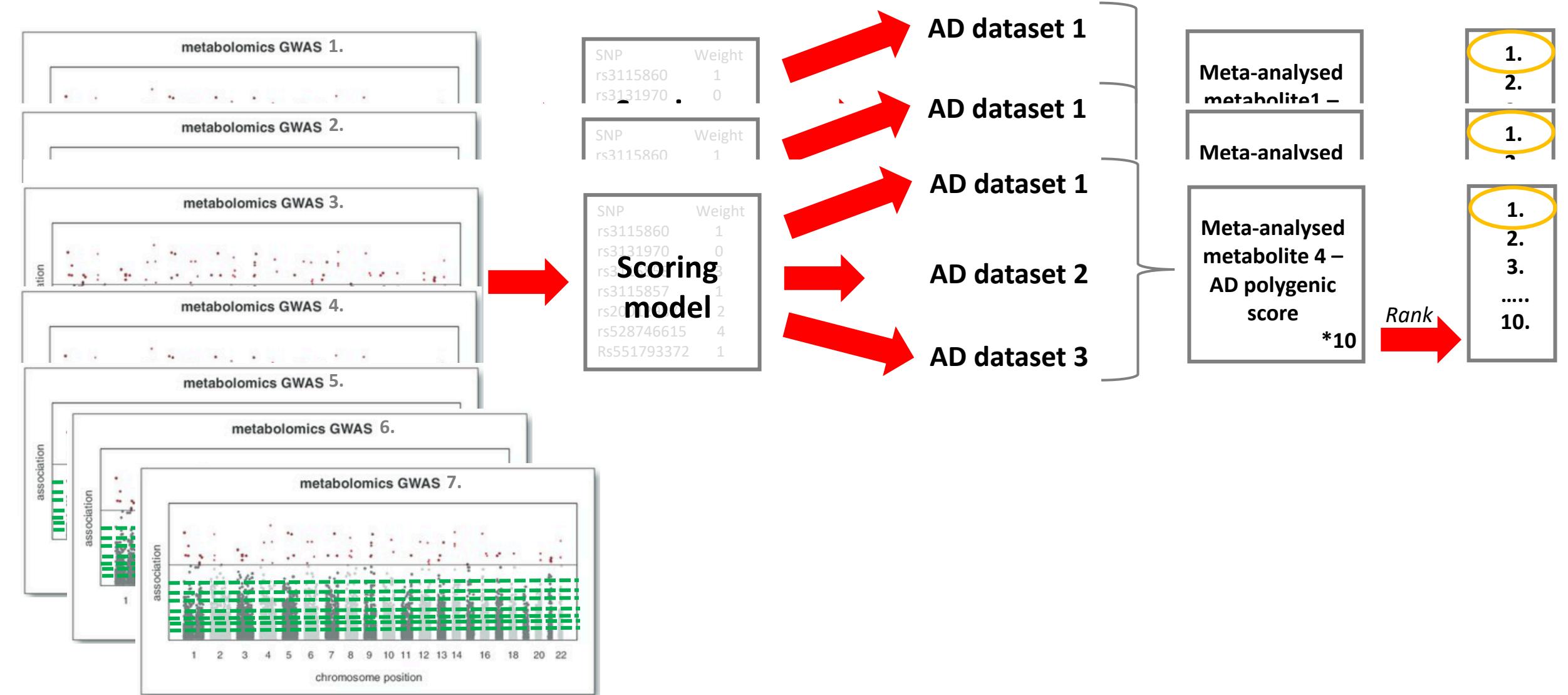
Rank

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- 1.
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 - 1.
 - 1.
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 - 10.



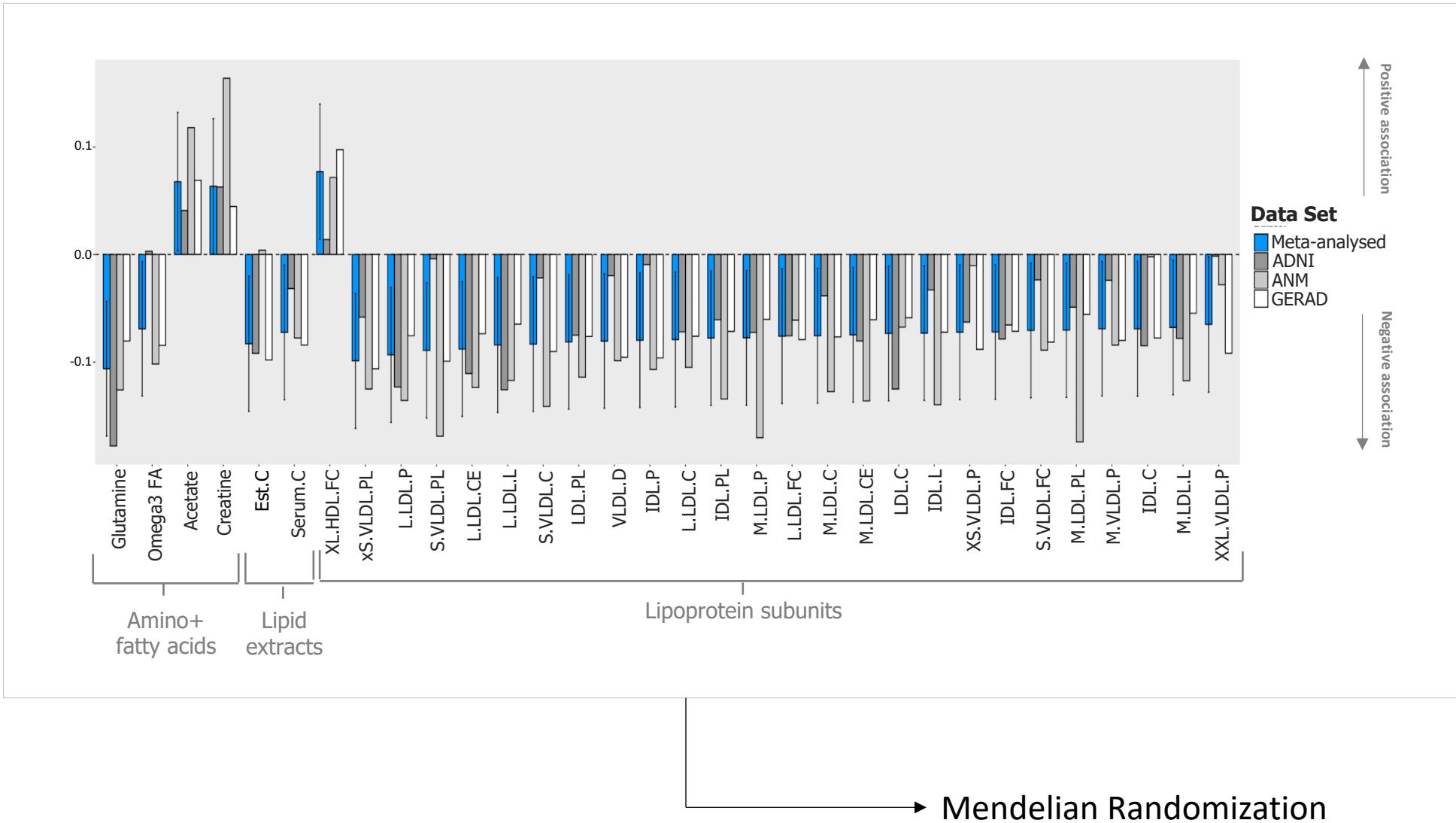






.... Metabolomics GWAS 106

Results: Polygenic Scores



34 metabolite-AD
genetic associations at
 $p < 0.05$

Majority nominal
associations =
lipoprotein subunits.

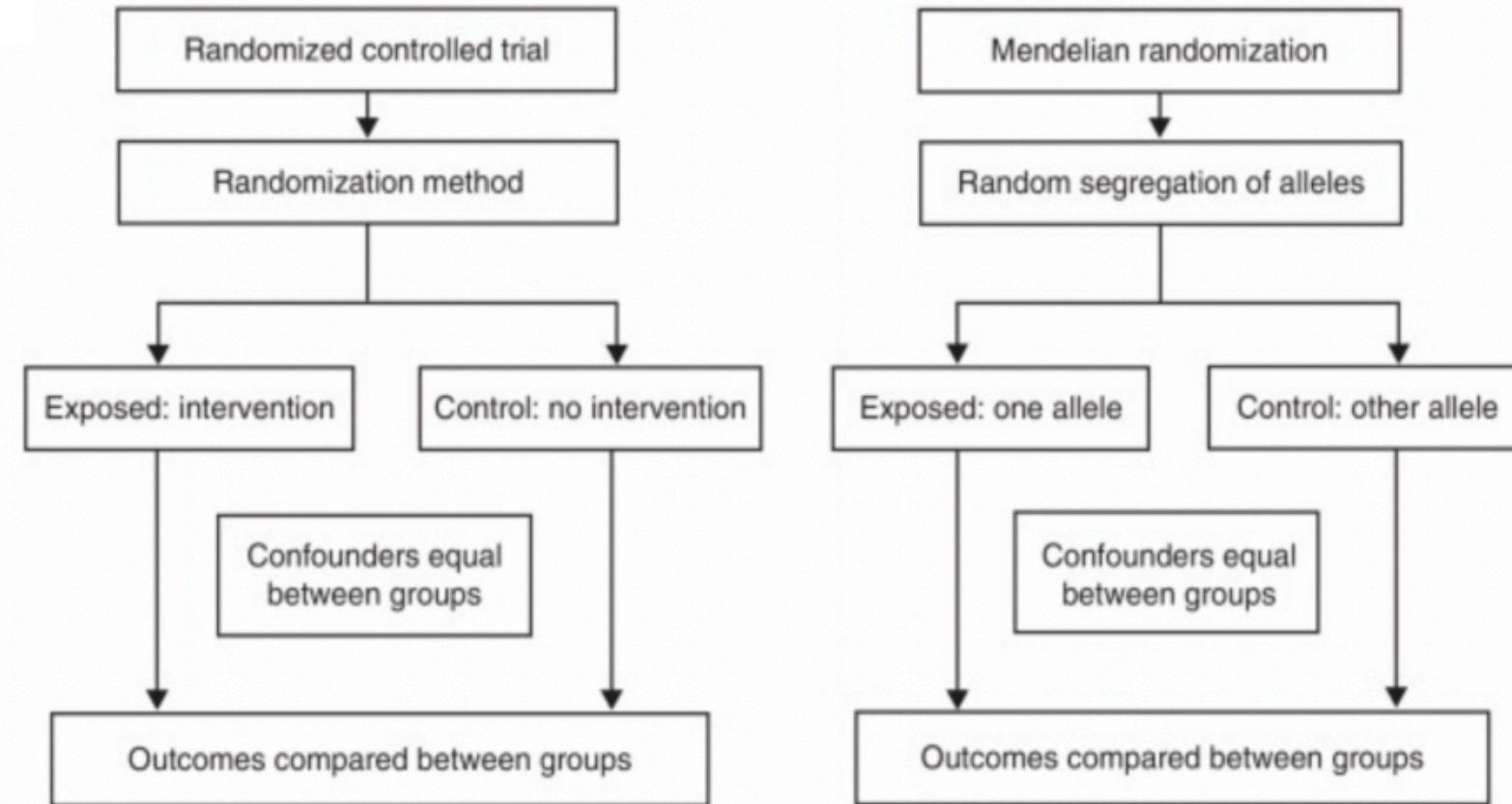
No association reached
multiple testing
significance ($p < 0.0001$)

Glutamine = most sig
genetic association with
AD ($\beta=-0.11$, $se=0.03$,
 $p=0.0009$)

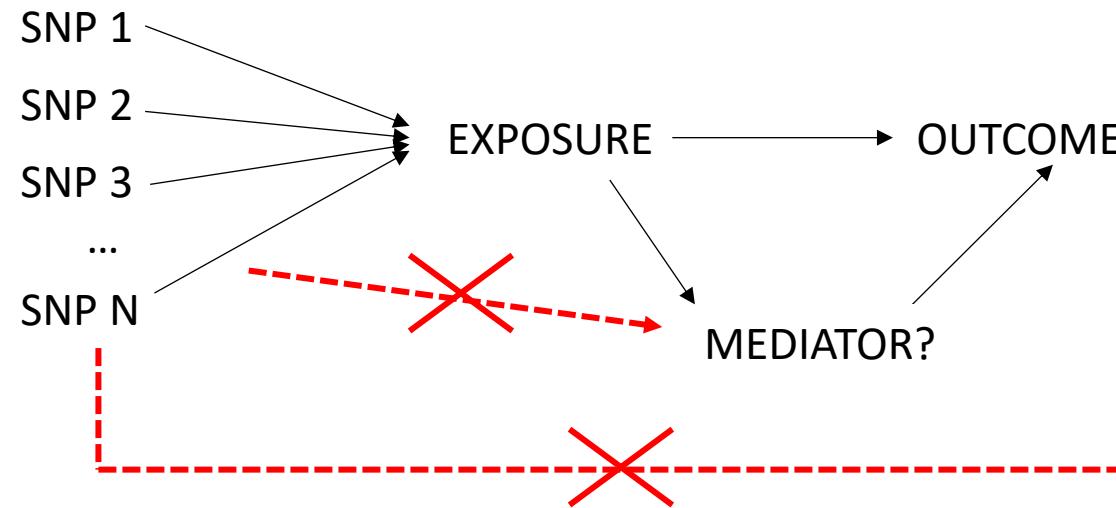
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Mendelian Randomization Framework



Mendelian Randomization Framework



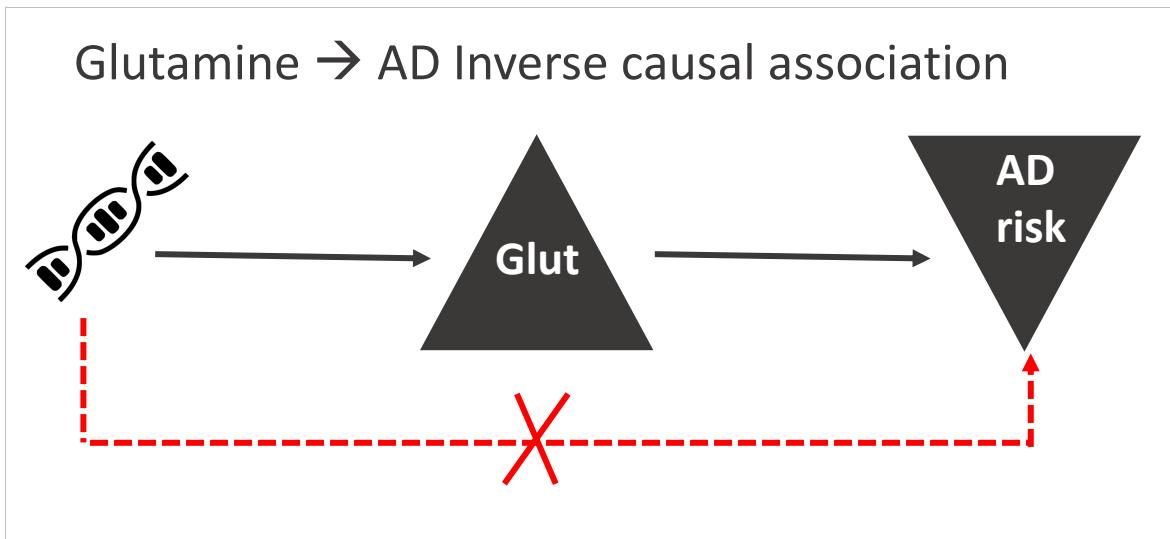
Disentangle causal relationships between these metabolites and AD.

- Bi-directional inverse variance weighted (IVW) univariable MR.
- ApoE excluded.
- Robust methods: MR egger | weighted median.
- Sensitivity analyses: leave-one-out | MR-PRESSO | Cochran's Q.
- **DATASETS:**

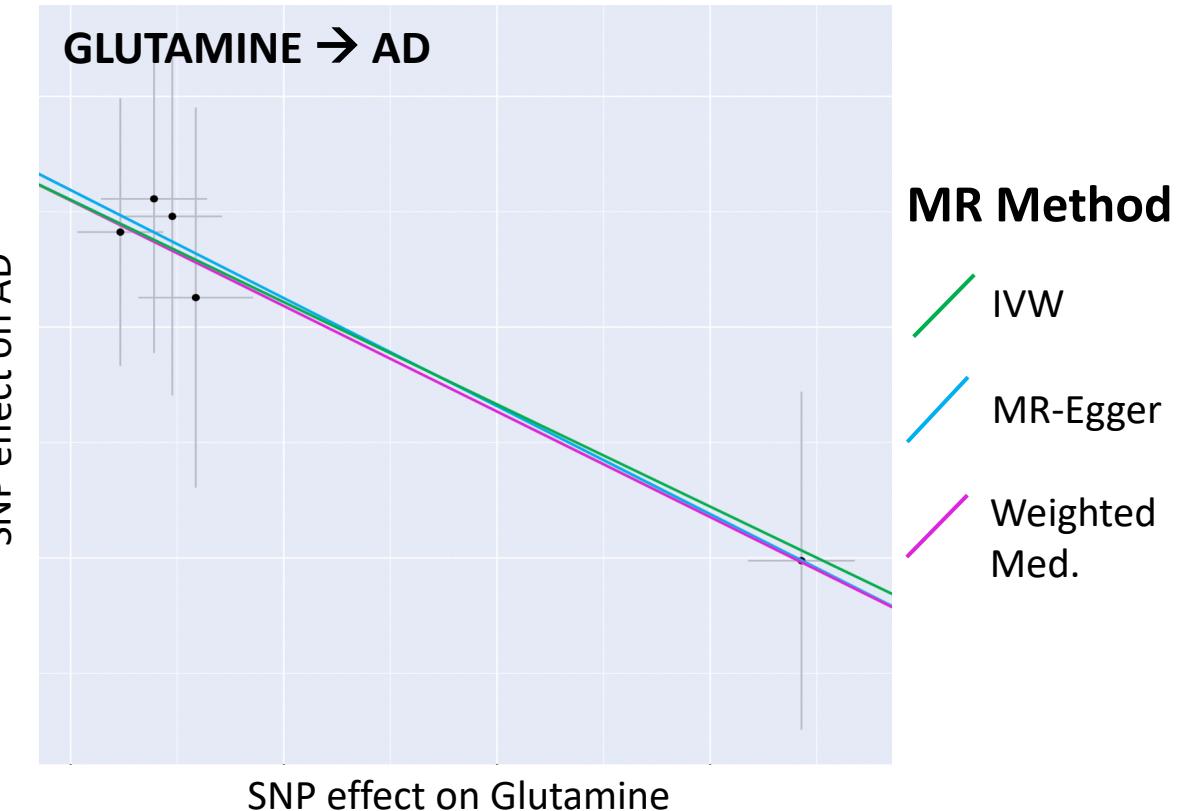
Metabolites: Kettunen et al., 2016. $N=24,925$

Alzheimer's Disease: Kunkle et al., 2019. $N=94,437$

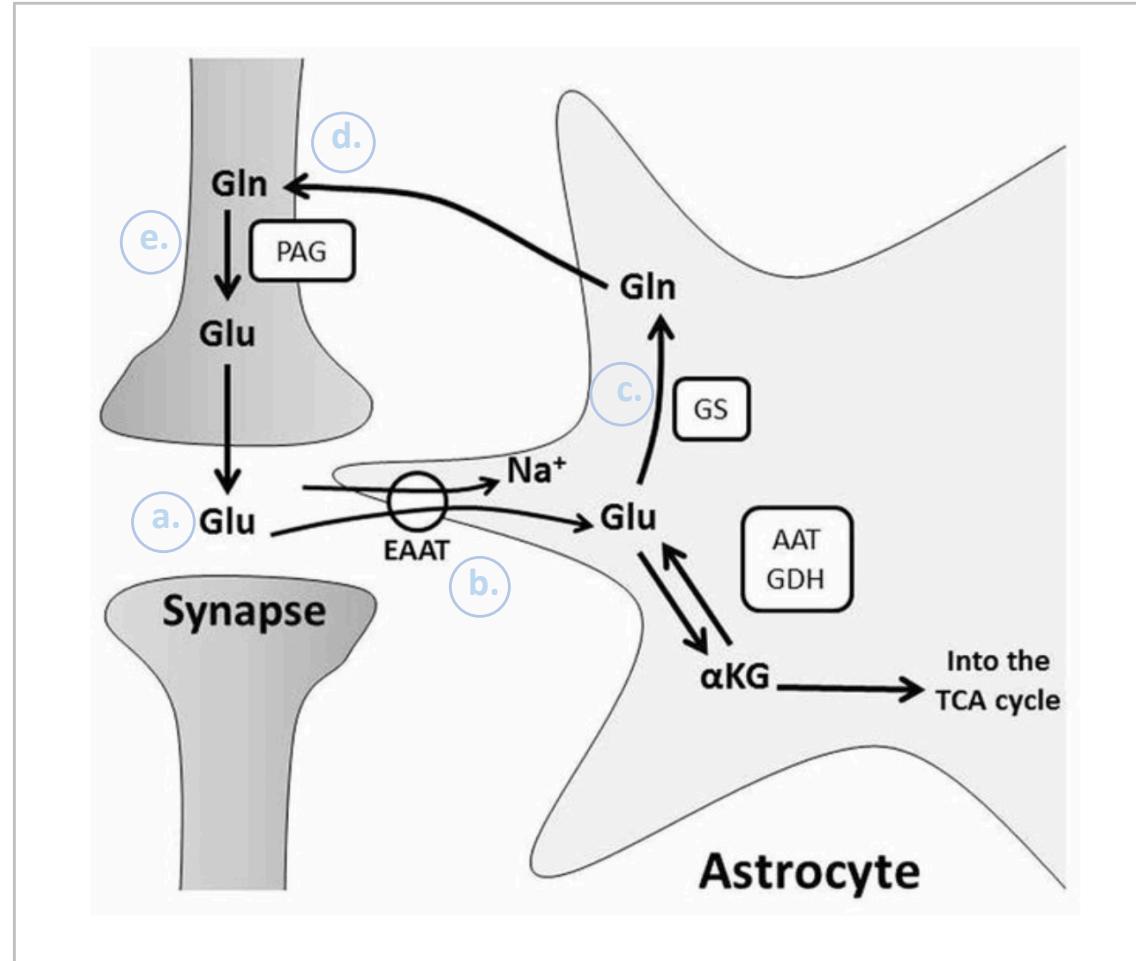
Higher levels of GLUTAMINE may be PROTECTIVE against Alzheimer's Disease Risk



- Glutamine = only sig metabolite → AD causal association (MR-IVW $\beta = -0.22, p=0.001$)
- No AD → metabolite causal association



Glutamine is Implicated in Neurotransmission



Glutamate-glutamine cycle:

- During neurotransmission: glutamate(Glu) = released from pre-synaptic cell into synaptic cleft(a).
- Astrocytes re-uptake any remaining Glu(b) and convert to glutamine (Gln) (c).
- Gln = released back into extracellular space where it is re-up-taken by pre-synaptic cells(d)
- Presynaptic cell metabolize Gln back into Glu(e) and package into synaptic vesicles ready for next round of neurotransmission.
- This cycle is critical for regulating appropriate neurotransmission within the CNS

(image adapted from Stobart & Anderson., 2013)

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Incorporate information relating to schooling and intelligence...

- Bi-directional inverse variance weighted (IVW) univariable MR for:

metabolite \longleftrightarrow AD

years of schooling \longleftrightarrow AD

intelligence \longleftrightarrow AD

metabolite \longleftrightarrow years of schooling

metabolite \longleftrightarrow Intelligence

- Multivariable MR to investigate mediating relationships:

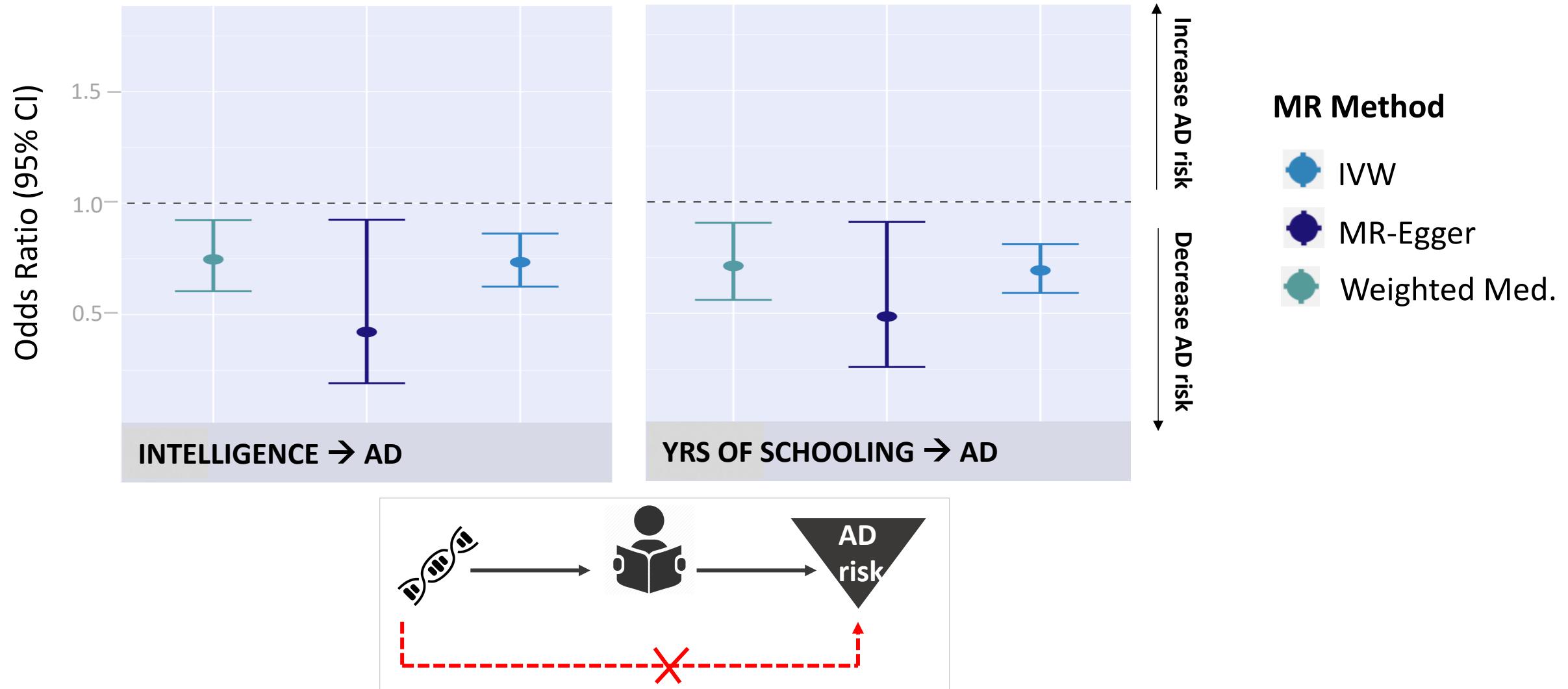
One metabolite at a time, educational factors added to MR model to test direct impact of each metabolite (exposure) on AD holding educational factors (mediator) constant, and vice versa.

- **DATASETS:**

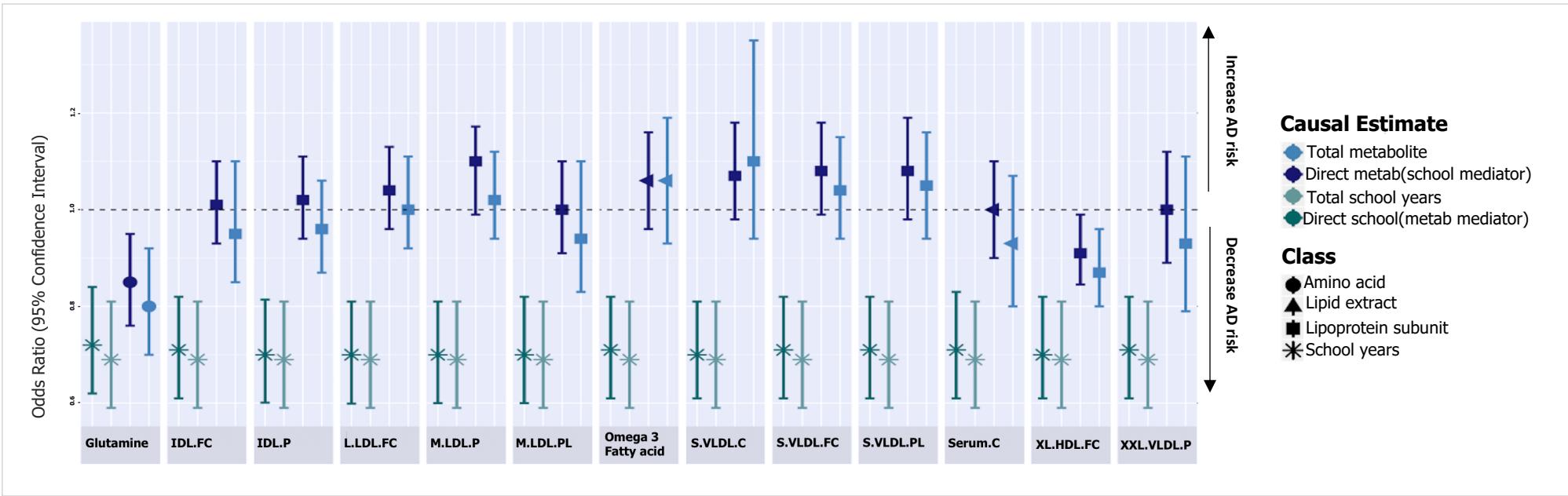
School Years: Lee et al., 2018. N=1.1million

Intelligence: Savage et al., 2018. N=269,867

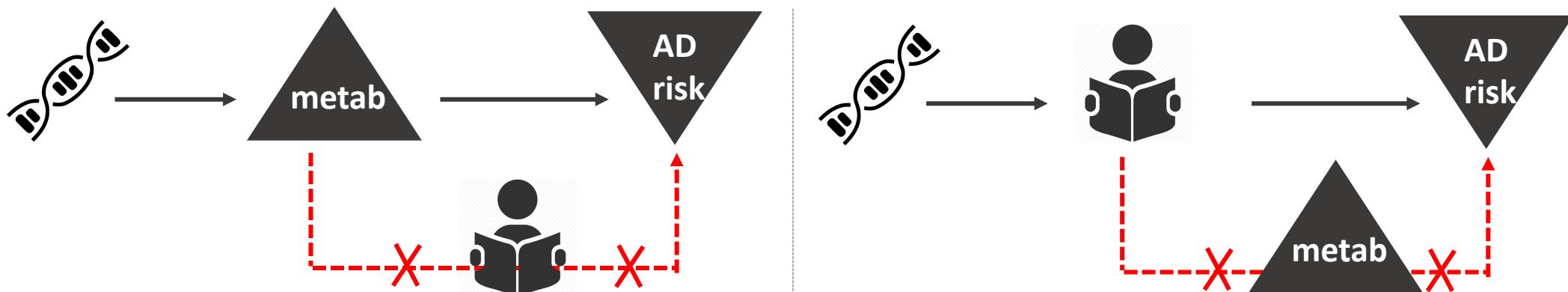
Greater no. of SCHOOL YRS and HIGHER INTELLIGENCE may also be PROTECTIVE against AD risk.



No mediating effects. Suggests INDEPENDENT causal pathways



- No sig change on metab → AD when school = mediator (blue).
- No sig change on school → AD when any metab = mediator (green).



Summary

- Glutamine & educational factors both show a causally protective effect on AD but the effect of one does not mitigate or exacerbate the effect of the other.
- Glutamine = abundant in brain & crucial for neurotransmission so offers efficacy as direct AD treatment target, but more research needed.
- Signal for other metabolites likely attenuated by removal of ApoE – future studies should seek to incorporate effect of ApoE into models.
- How educational factors influence biology to impact AD risk still elusive.

Collaborators:

SGDP Statistical Genetics Unit
Cristina Legido-Quigley



THANK YOU!



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Ammar Al-Chalabi

Funders:
van Geest