

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

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BACKGROUND

- There are currently no treatments to stop, reverse, or fully prevent AD.
- Educational factors like years of schooling & intelligence show protective associations with AD, and vascular factors such as hypertension show positive associations; but it remains unclear how these interact with biology to influence risk.
- Blood metabolites are small molecules found in blood, levels of which reflect the interplay between genetic instruction and environmental influence. Thus, they can provide vital clues to how factors like the above influence biology.
- Blood metabolites are also easily measurable, offering accessible sources to track disease progress & monitor efficacy of intervention strategies. But **ONLY if they are causally linked to AD**.

AIMS

- Harness use of polygenic risk scores to identify metabolites which genetically predict AD status.
- Disentangle causal relationships between these metabolites and AD.
- Identify any causal association between metabolites and:
 - Schooling Years
 - Intelligence
 - Blood Pressure
- Investigate whether associations found between metabolites and a b or c influence:
 - Casual associations between metabolite levels & AD.
 - Casual associations between a b or c and AD.

WORKFLOW

1. Assess Genetic Overlap using Cross-Trait Polygenic Risk Scoring

- Base Datasets: **106 metabolite PRS models** generated using GWAS data from Kettunen et al., 2016 (N=24,925).
- Each PRS model applied to **3 raw AD target datasets**:
 - AddNeuroMed (N=648)
 - ADNI (N=886)
 - 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 greatest genetic overlap with AD → MR

2. Disentangle Causality using Univariable Mendelian Randomization

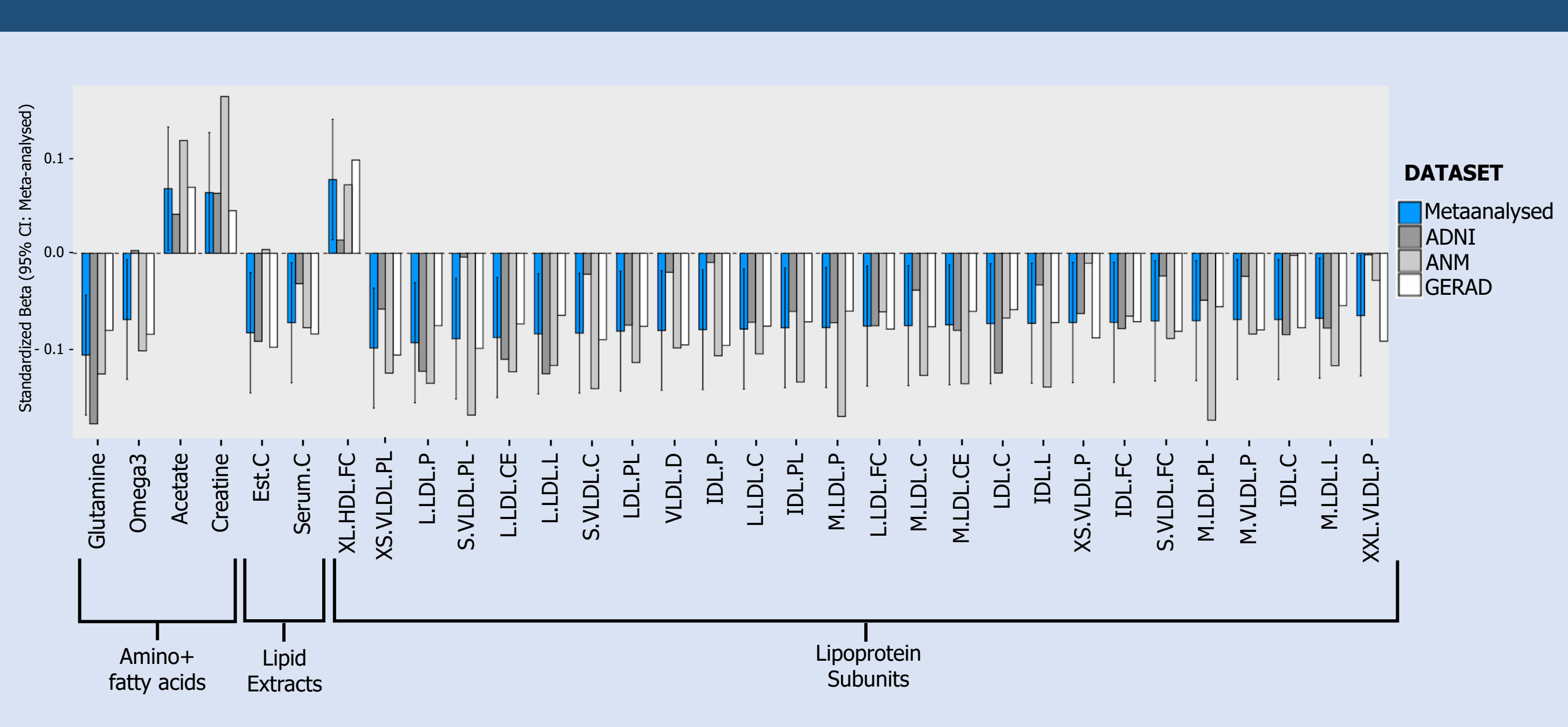
- Bi-directional 2-sample inverse variance weighted (IVW) MR (excluding ApoE) for:

metabolite ↔ AD
metabolite ↔ years of schooling
metabolite ↔ Intelligence
metabolite ↔ diastolic blood-pressure
metabolite ↔ systolic blood-pressure
years of schooling ↔ AD
intelligence ↔ AD
diastolic blood pressure ↔ AD
systolic blood pressure ↔ AD
- Robust methods: MR egger | weighted median.
- Sensitivity analyses: leave-one-out | MR-PRESSO | Cochran’s Q.
- Metabolites showing causal assoc with schooling, intelligence and blood pressure → MV-MR

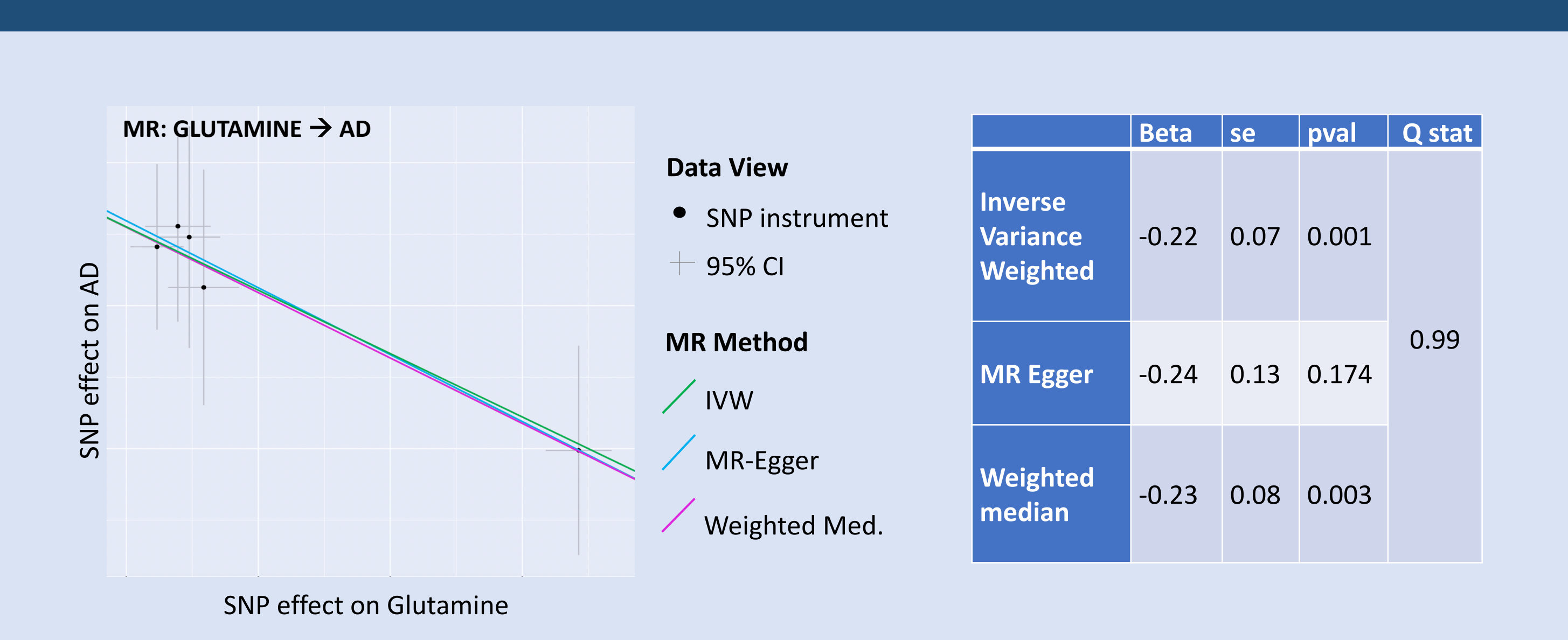
3. Investigate Mediating Relationships using Multivariable MR

- One metabolite at a time: following tested:
 - Schooling years data added to MR model to test direct impact of each metabolite (exposure) on AD holding schooling (mediator) constant, and vice versa.
 - Diastolic blood pressure and systolic blood pressure added to MR model to test impact of each metabolite on AD holding blood pressure constant, and vice versa

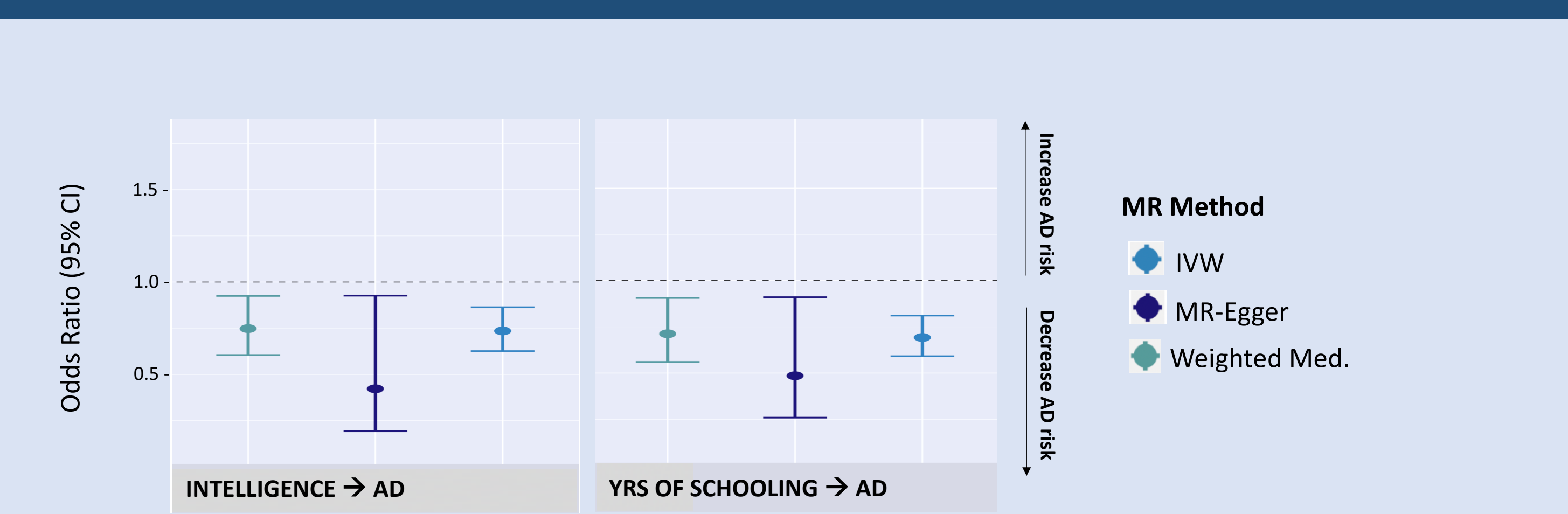
1. A number of METABOLITES demonstrate POLYGENIC OVERLAP with Alzheimer’s Disease.



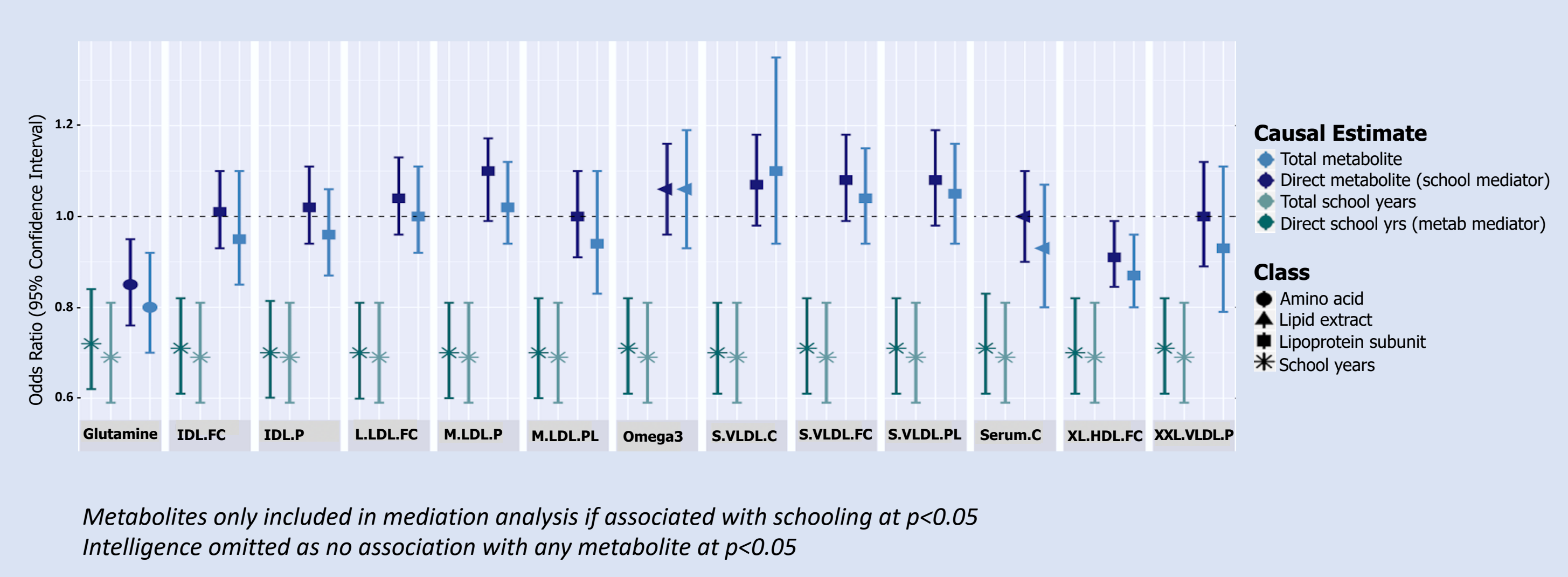
2. Of these, higher GLUTAMINE levels may be PROTECTIVE against ALZHEIMER’S DISEASE risk.



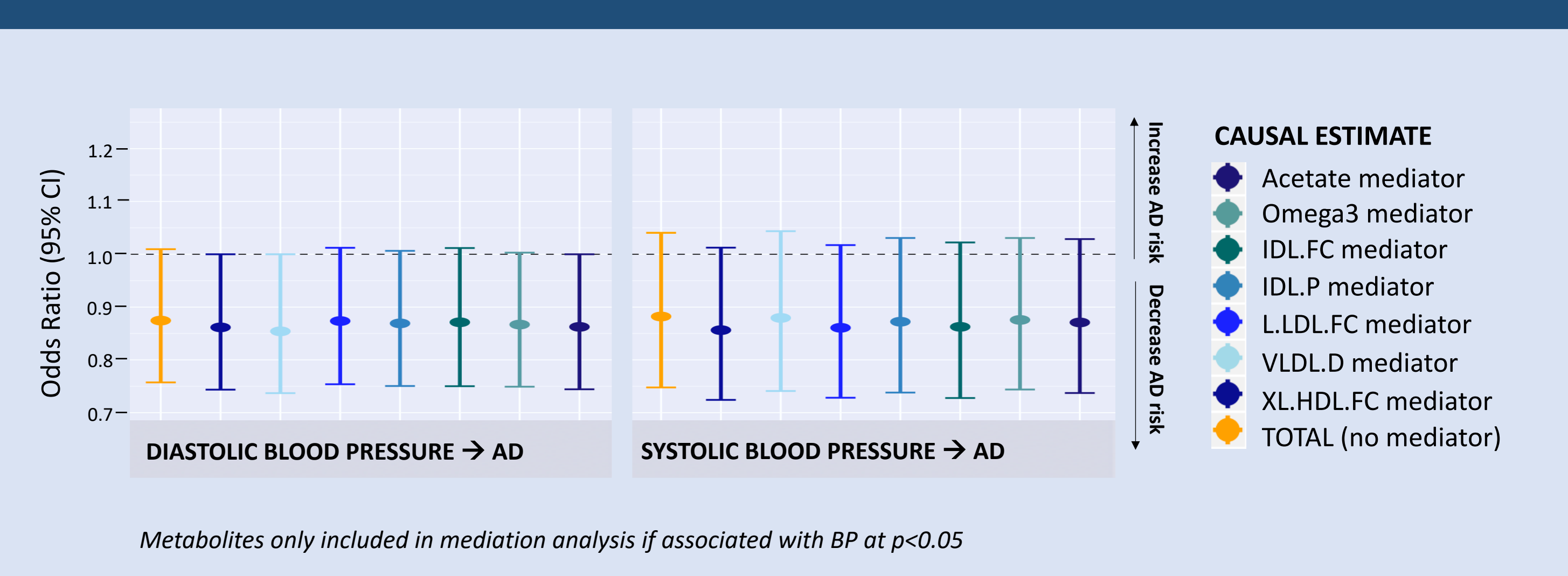
3. Greater number of SCHOOL YEARS and HIGHER INTELLIGENCE may also be PROTECTIVE against ALZHEIMER’S DISEASE risk.



4. The CAUSAL EFFECT of metabolite levels on Alzheimer’s does NOT appear to be MEDIATED by school years or intelligence and vice versa. This suggests their effect on Alzheimer’s are via INDEPENDENT causal pathways.



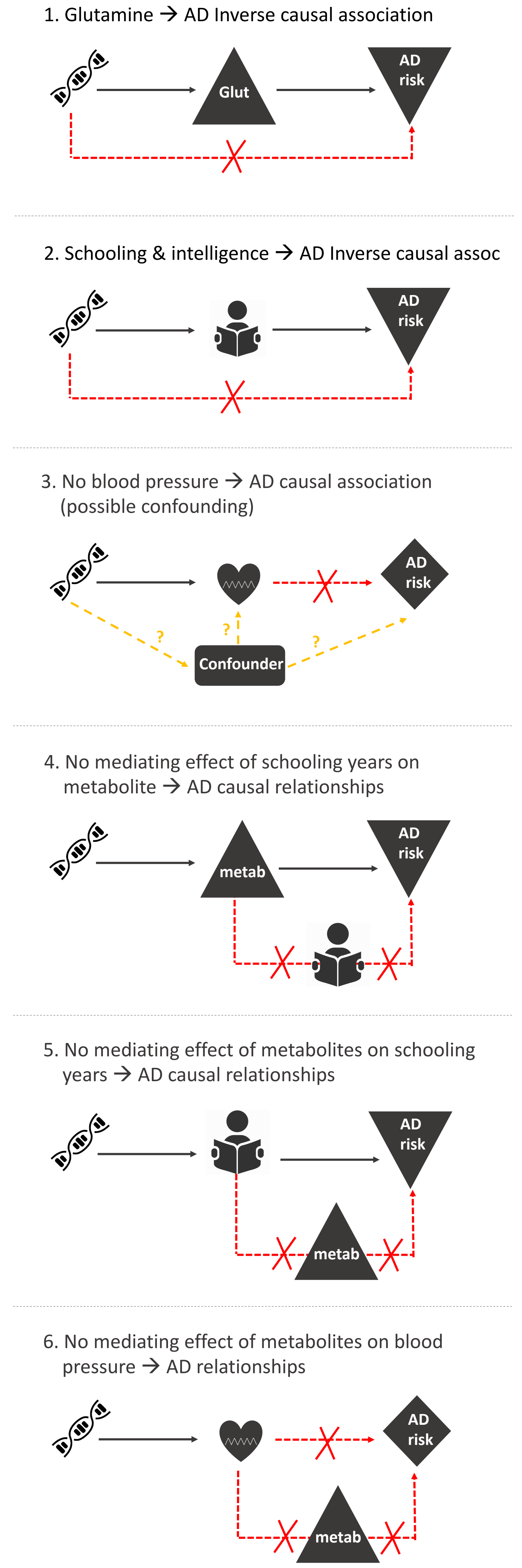
5. BLOOD PRESSURE does NOT appear to be CAUSALLY ASSOCIATED with Alzheimer’s risk; not directly, nor via metabolites.



ADDITIONAL INFORMATION

MR Samples	Phenotype	Sample N
Kettunen et al. (2016)	Metabolites	24,925
Kunkle et al. (2019)	Alzheimer’s	94,437
Lee et al. (2018)	School yrs	1.1 mill
Savage et al. (2018)	Intelligence	269,867
Neale lab (2017)	Diastolic BP	317,756
Neale lab (2017)	Systolic BP	317,754

MR Models: Illustrated Results



SUMMARY & IMPLICATIONS

- Glutamine & schooling both show a causally protective effect on AD but the effect of one does not mitigate or exacerbate the effect of the other.
- No evidence from our data of a causal association between blood pressure and AD.
- Glutamine = abundant in brain & crucial for neurotransmission so offers efficacy as direct AD treatment target, but more research needed.
- How cognitive factors influence biology to impact AD risk still elusive.
- Signal for other metabolites likely attenuated by removal of ApoE – future studies should seek to incorporate into models.

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