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.
- Factors like years of schooling & intelligence show (protective) 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 an accessible source to track disease progression and monitor efficacy of intervention strategies. But **ONLY if they are causally linked to AD**.

AIMS:

1. Harness use of polygenic risk scores to identify metabolites which genetically predict AD case/control status.
2. Disentangle causal relationships between these metabolites and AD.
3. Identify any causal association between metabolites and:
   a. Years of schooling b. Intelligence
4. Investigate whether associations found between metabolites and a or b influence:
   i. Casual associations between metabolite levels and AD.
   ii. Casual associations between a/b and AD.

WORKFLOW:

<u>1. Assess Genetic Overlap using Cross-Trait Polygenic Risk Scoring</u>

- 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**:
  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 greatest genetic overlap with AD → MR

<u>2. Disentangle Causality using Univariable Mendelian Randomization</u>

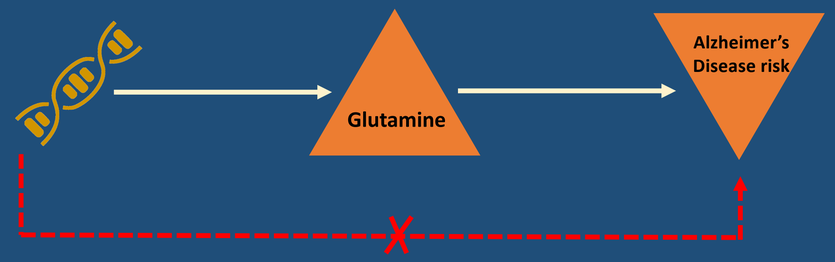
- 2-sample inverse variance weighted MR (excl. ApoE) for:
  metab ←→ AD | metab ←→ yrs of schooling | metab ←→ Intelligence | years of schooling ←→ AD | Intelligence ←→ AD.
- Robust methods: MR egger | weighted median.
- Sensitivity analyses: leave-one-out | MR-PRESSO | Cochran's Q.
- Metabs showing causal assoc with schooling/intelligence → MV-MR

<u>3. Investigate Mediating Relationships using Multivariable MR</u>

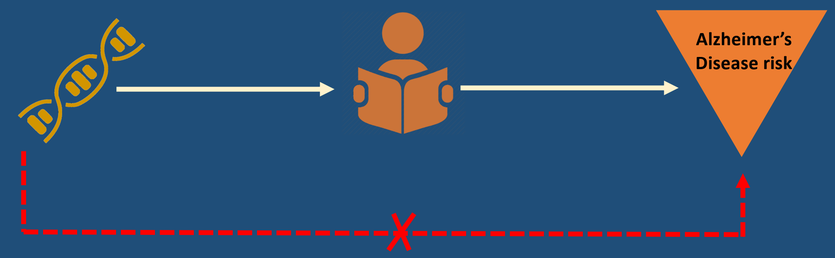
- One metabolite at a time, schooling years data added to MR model to test direct impact of each metabolite (exposure) on AD holding schooling (mediator) constant, and vice versa.

MR Datasets	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

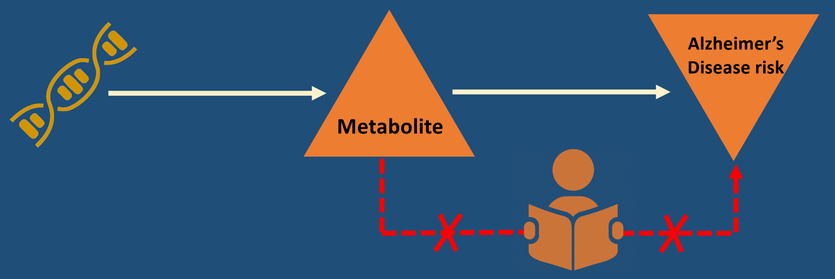
1. **HIGHER** levels of **GLUTAMINE** may be **PROTECTIVE** against **ALZHEIMER'S DISEASE** risk.



2. Greater number of **SCHOOL YEARS** and **HIGHER INTELLIGENCE** may also be **PROTECTIVE** against **ALZHEIMER'S DISEASE** risk.



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



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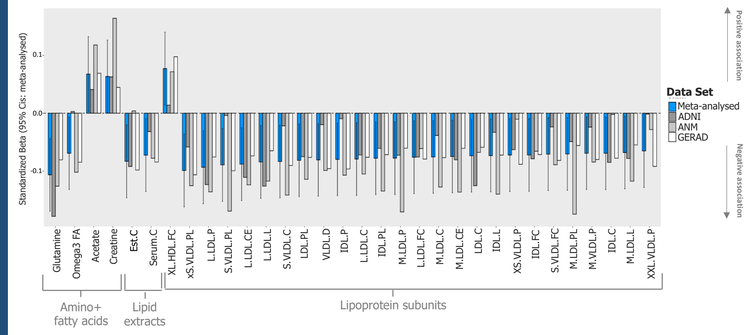
RESULTS:

<u>Cross-Trait Polygenic Risk Scores (ApoE excluded)</u>

- 34 metabolite-AD genetic associations at p<0.05 (**plot 1 below**).
- Majority of nominal associations = lipoprotein subunits.
- No association reached multiple test significance (*p*<0.0001).
- Glutamine = most sig. genetic assoc. with AD (*β*=-0.11, *se*=0.03, *p*=0.0009).



<u>Mendelian Randomization</u>

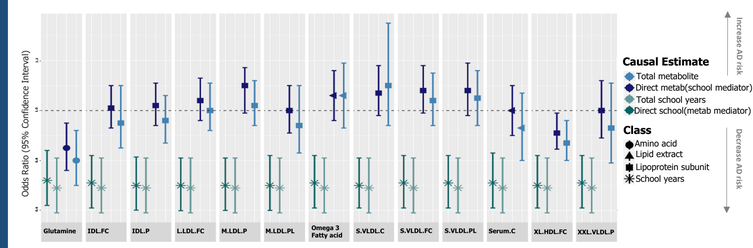
Univariable:

- All exposure -> AD sig associations:
- No sig AD → exposure assoc.

Factor	Exposure	*β*eta	*p*-val
Metabolite	Glutamine	-0.22	0.001
Cognitive	School yrs	-0.37	$10^{*}5^{-06}$
Cognitive	Intelligence	-0.35	$10.^{*}2^{-05}$

Multivariable:

- 0 metab ←→ intelligence assoc. So intel. dropped from MV-MR.
- 13 metab ←→ schooling assoc taken forward to MV-MR.
- No sig change on metab → AD when school = mediator (**blue below**).
- No sig change on school → AD when any metab = mediator (**green below**).



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.
- How cognitive factors influence biology to impact AD risk still elusive.
- 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.

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<u>References</u>

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