Unraveling the role of alanine on mental disorders: A Mendelian Randomization Study

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Background

Alanine, commonly found in meaty foods and popular as a sports supplement, has interactions with neurotransmitters and brain energy supply [1]. However, it remains unclear whether alanine is a friend or foe in mental health.

Exiting studies found that d-alanine improved the positive and cognitive symptoms of patients with schizophrenia, suggesting a therapeutic role for alanine in psychosis [2,3]. But contradictory evidence showed alanine was higher in patients with bipolar disorder, ADHD and positively correlated with the severity of depression [4,5], raising safety concerns.

Mendelian randomization (MR), which uses genetic variants as instruments for predicting exposure, can minimize confounding and offer a promising method for studying the causal associations without the need for harmful interventions [6].

Objectives

This two-sample Mendelian Randomization (MR) study aimed to investigate causal associations of plasma alanine with major mental disorders—depression, bipolar disorder, schizophrenia, anxiety, and attention deficit hyperactivity disorder (ADHD), and to further explore sex-specific associations using available data considering potential sex disparity.

Methods

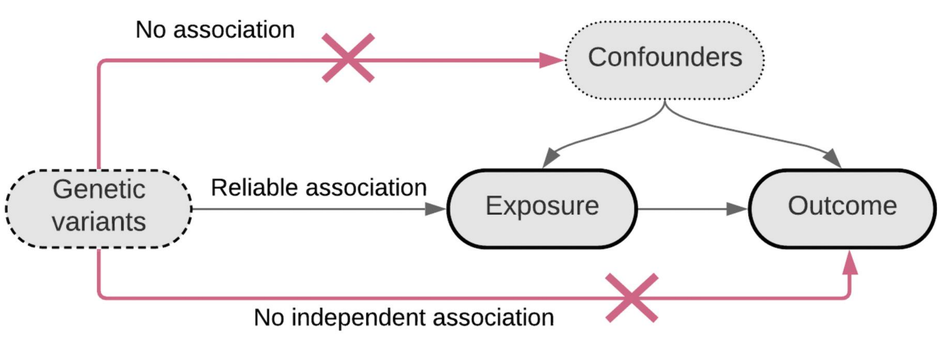


Figure 1. Directed acyclic graph of MR study design

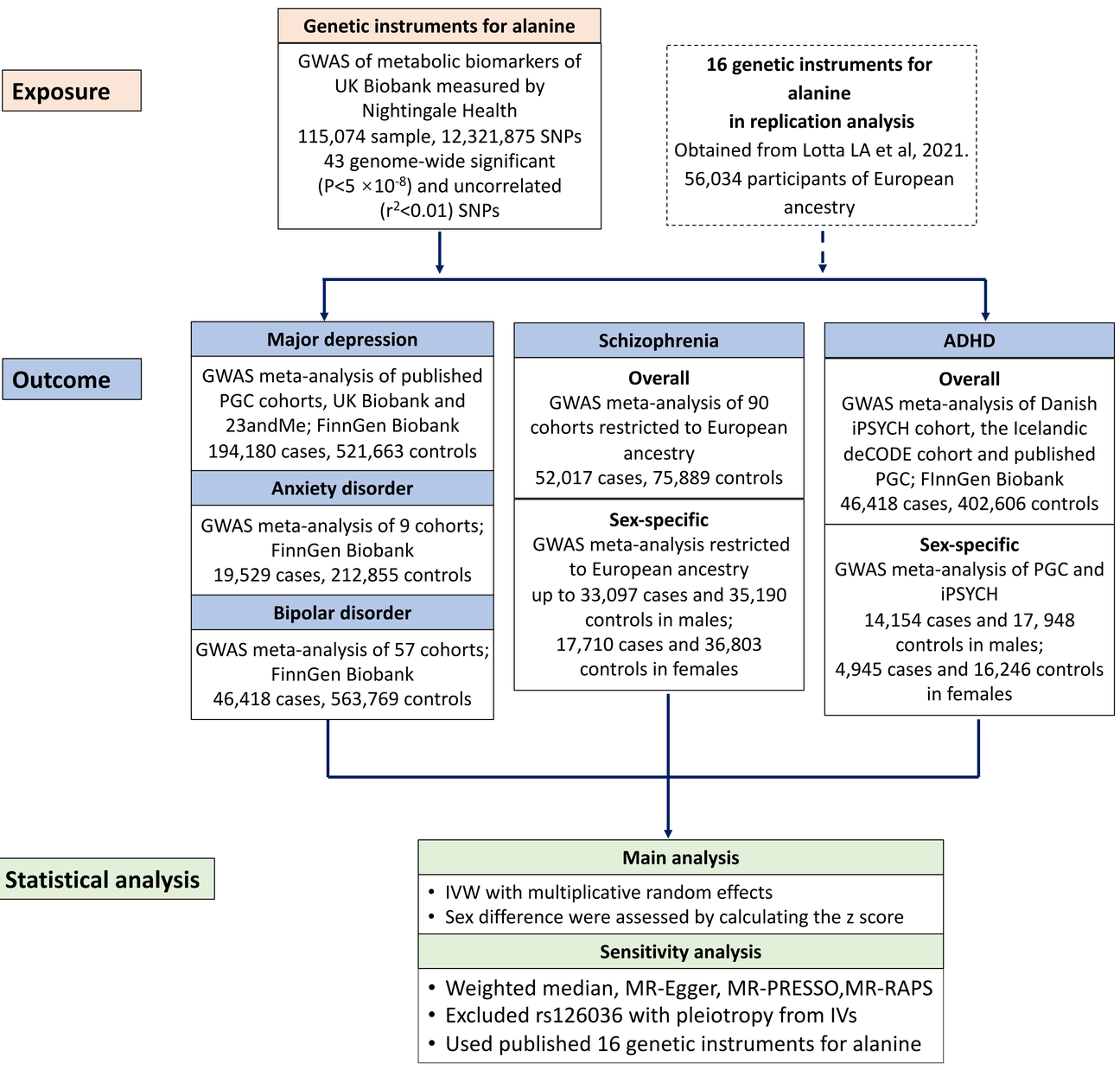
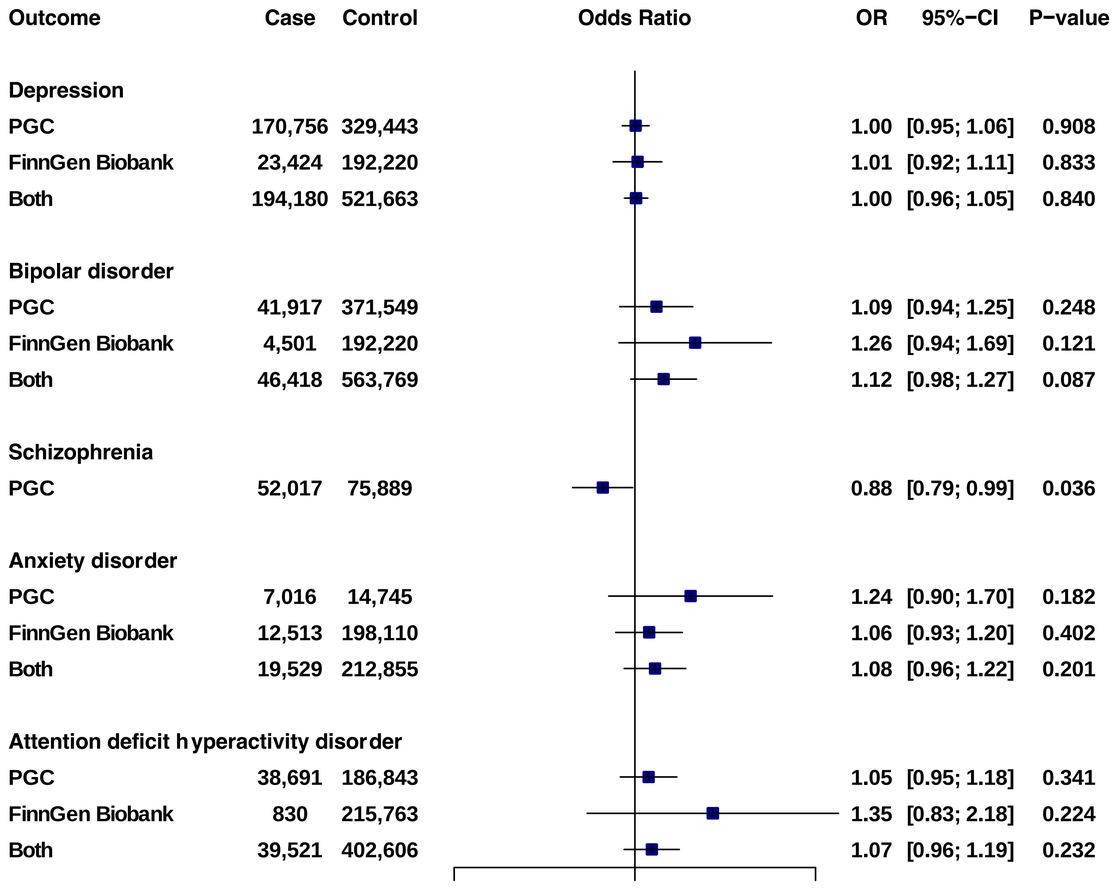


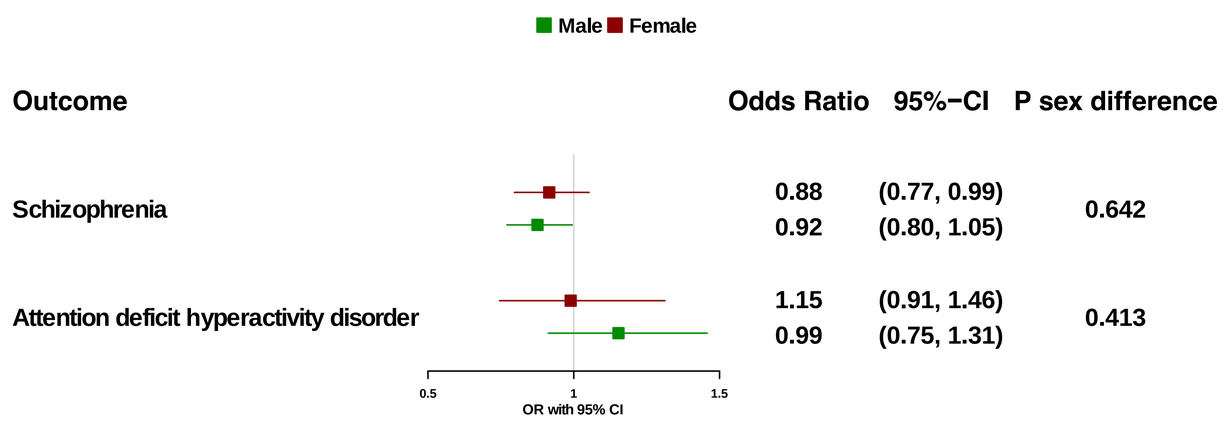
Figure 2. Flowchart of overall study design

Results

Genetically predicted plasma alanine was nominally associated with a lower risk of schizophrenia when using IVW method. Weighted median, MR-Egger, MR-PRESSO and MR-RAPS gave directionally similar estimates. Null associations were observed between plasma alanine and major depression, bipolar disorder, anxiety disorder and ADHD.



The negative associations of plasma alanine with the risk of schizophrenia were only nominally significant in males but not in females, although the sex difference was not statistically significant



Discussion and Conclusion

- Our study did not support a causal effect of plasma alanine on major depression, bipolar disorder, anxiety, and ADHD, but suggested a potentially beneficial effect on schizophrenia, especially for males.
- Caution is needed when considering alanine as an adjunctive treatment for schizophrenia due to modest effect size and potential side effects.
- Limitations: ((1) potential violations of MR assumptions due to directional pleiotropy (excluded potentially pleiotropic SNPs; multiple MR methods) (2) genetic only capture a small proportion of variance (large GWAS and meta-analysis) (3) limited external validity (only data of European ancestry); (4) lack of GWAS data on cerebrospinal fluid alanine levels.

References

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Acknowledgements

We would like to thank PGC and FinnGen Biobank for sharing the data.