Systemic inflammation and risk of Alzheimer's disease: a bi-directional Mendelian Randomization Study

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Background

Previous observational studies have shown evidence in the association between systemic inflammation and Alzheimer's disease. However, whether systemic inflammation is the cause or downstream factor is still unknown.

To answer the question, we have utilized Mendelian Randomization to assess the direction of association between level of systemic inflammatory regulators with risk of Alzheimer's disease.

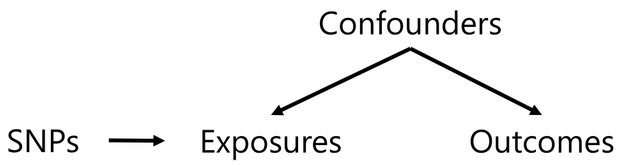
Methods

Mendelian Randomization (MR) is a type of instrumental variable analysis using genetic variation (SNPs) as instrument to predict the exposure for obtaining an unbiased estimate of the association between exposure and outcome under below assumptions.

1.The SNPs is strongly associated with the exposure

2.The SNPs is independent of the confounding factors that confound the association between exposure and outcome

3.Every unblocked path connecting SNPs and outcome must contain an arrow pointing into the exposure

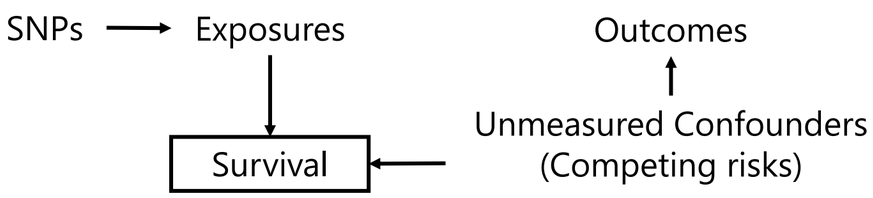


- Confounding and reverse causality are less likely to influence the estimates in MR as the allocation of gene generally not affected by the confounders nor the outcomes.

Statistical analysis:

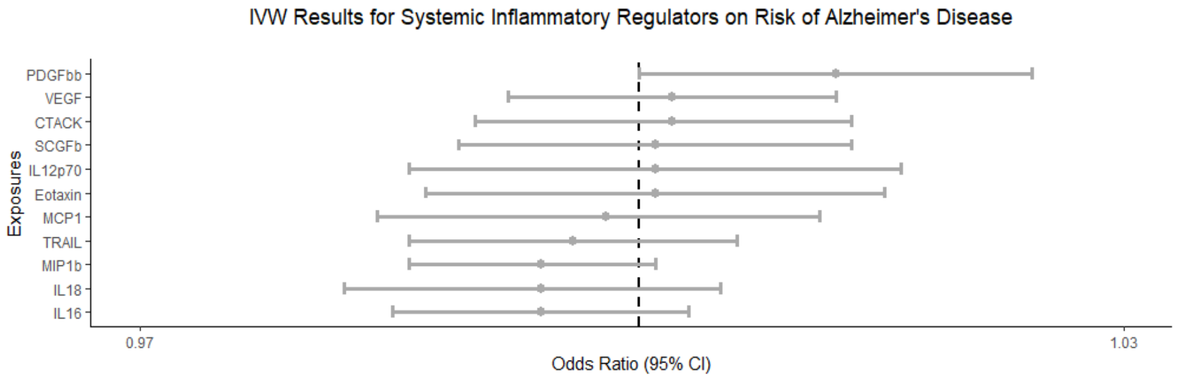
- Association between SNPs with systemic inflammatory regulators and Alzheimer's disease were obtained from the most updated genome-wide association studies (GWAS).
- We extracted the SNPs strongly and independently ($R^2 < 0.001$) predicted the exposure reaching genome-wide significance (5×10^{-8}).
- Inverse variance weighting (IVW) was presented as the main analysis; MR-Egger, Weighted Median and MR-PRESSO as sensitivity analysis.

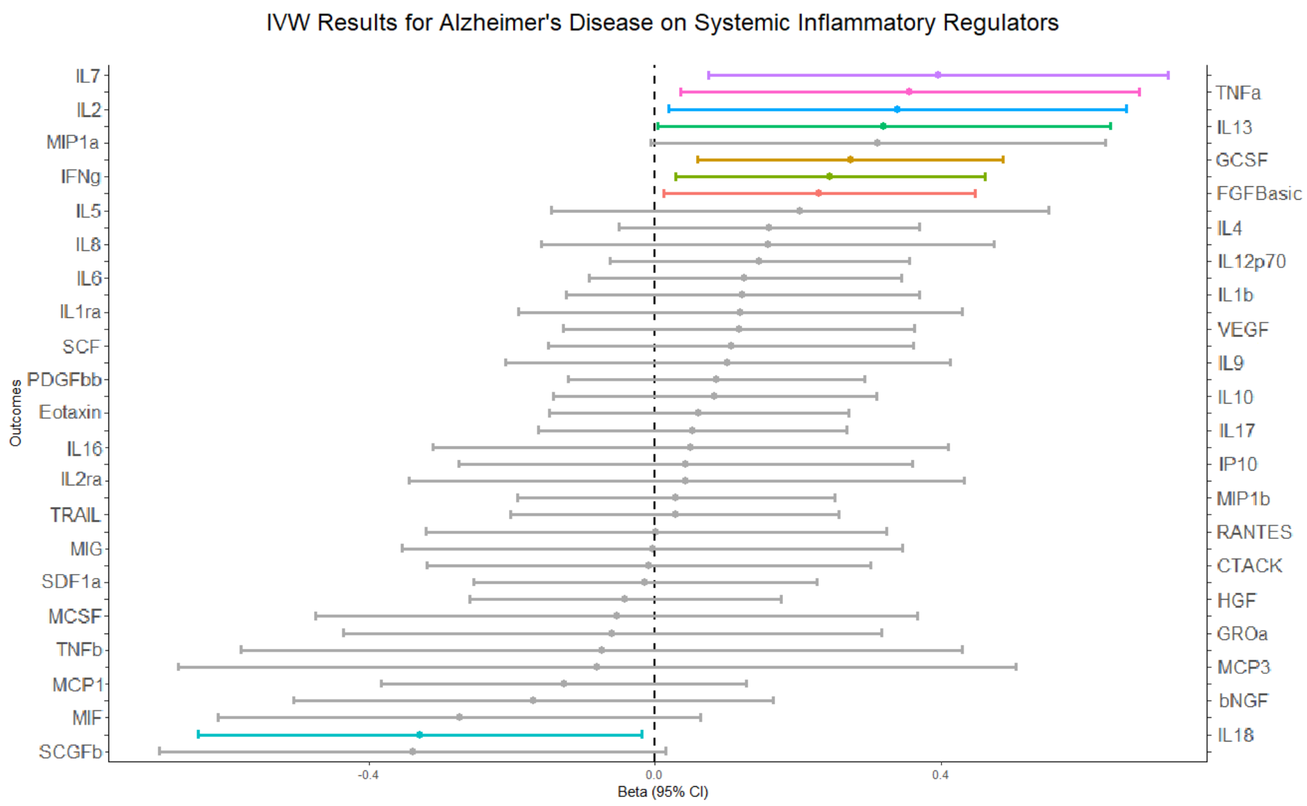
Considering selection bias by death as shown in the DAG below may violate the 3rd assumption, we also considered whether the exposures affect survival and selection for recruitment. We found no evidence suggests cytokines affect survival.



Results

Out of the 41 systemic inflammatory regulators assessed in the GWAS, 11 have more than 3 SNPs to include in our analysis. Conversely, 27 SNPs were obtained to predict the risk of Alzheimer's disease.





Conclusion

Our results did not support the hypothesis that systemic inflammatory regulators may affect the risk of Alzheimer's disease. Conversely, Alzheimer's disease was found to be associated with the level of certain systemic inflammatory regulators. These results suggest systemic inflammation may be a downstream factors rather than the cause of Alzheimer's disease.

References

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