Two Sample Mendelian Randomization: Total Cholesterol and Alzheimer's Disease

This study aims to estimate the causal effect of total cholesterol (TC) levels on Alzheimer's disease (AD) using MR Egger, weighted median estimators, fixed effects inverse variance weighted analysis, and weighted mode estimators, using the TwoSampleMR R package.

Exposure: Total Cholesterol (TC)

The exposure in this two sample Mendelian randomization is total cholesterol (TC) (Willer et al., 2013).

Outcome: Alzheimer's Disease (AD)

The outcome of interest in this two sample Mendelian randomization is Alzheimer's disease (AD) (Kunkle et al., 2019).

Mendelian Randomization

Outcome	Exposure	Method	NSNP	B	SE	P-Value
AD	TC	MR Egger	105	0.6174671	0.1635801	0.0002681
AD	TC	Weighted median	105	0.0513137	0.0640419	0.4229863
AD	TC	Inverse variance weighted (fixed effects)	105	0.3075600	0.0339910	0.0000000
AD	TC	Weighted mode	105	-0.0480759	0.0686928	0.4855720

Table 1. Summary of Mendelian randomization estimates for the causal effect of TC on AD.

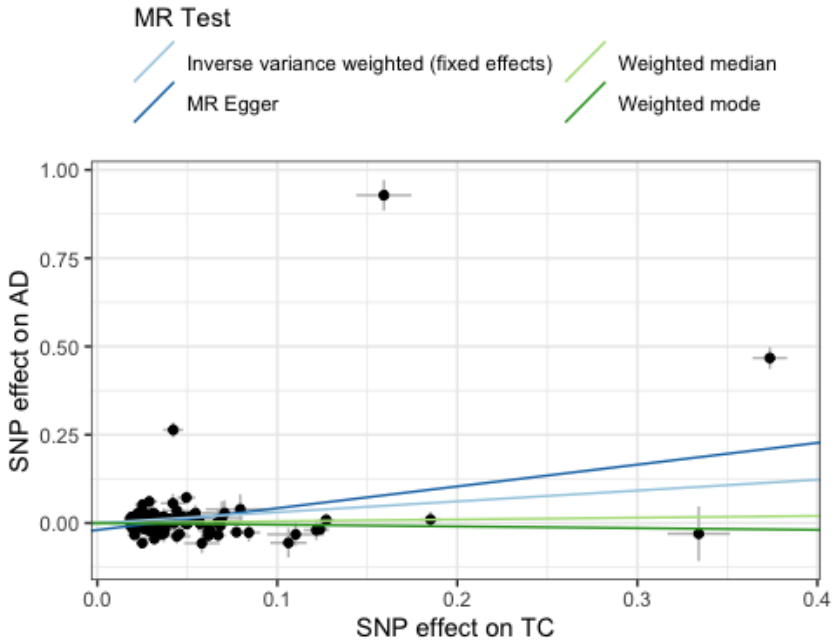

Figure 1. Scatter plot of Mendelian randomization estimates for the causal effect of TC on AD.

Sensitivity Analysis

Heterogeneity Statistics

Outcome	Exposure	Method	Q	Q (DF)	Q P-Value
AD	TC	MR Egger	890.8061	103	0
AD	TC	Inverse variance weighted	940.3490	104	0

Table 2. Heterogeneity statistics for Mendelian randomization analysis exploring the causal effect of TC on AD.

Horizontal Pleiotropy

Outcome	Exposure	Egger Intercept	SE	P-Value
AD	TC	-0.019667	0.0082172	0.0185026

Table 3. Results of the MR-Egger regression intercept test for horizontal pleiotropy in the causal relationship between TC and AD.

Single SNP Analysis

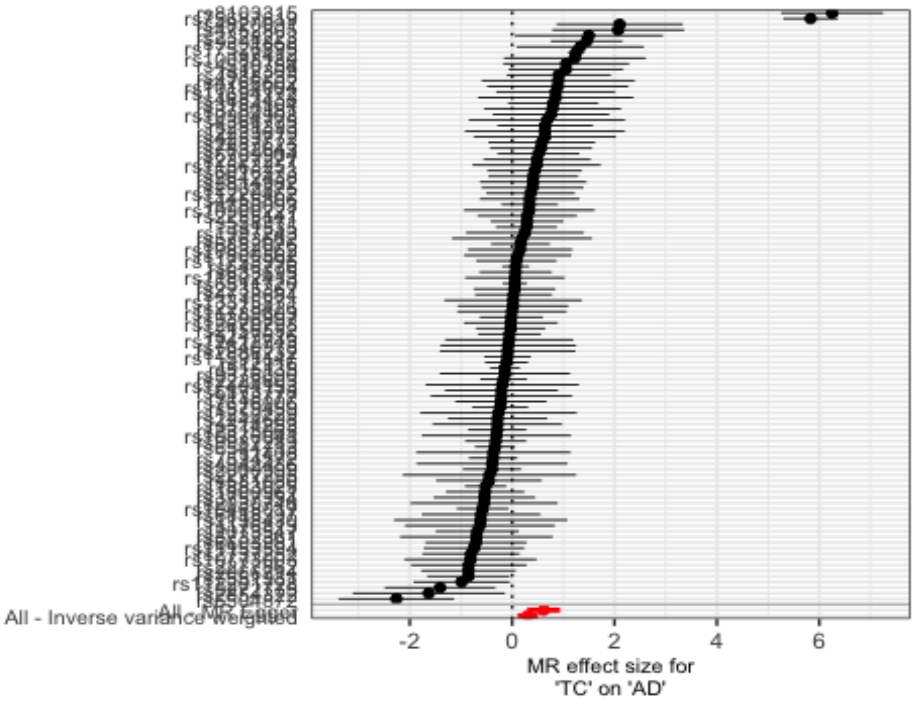

Figure 2. Forest plot of single SNP Mendelian randomization for the causal effect of TC on AD.

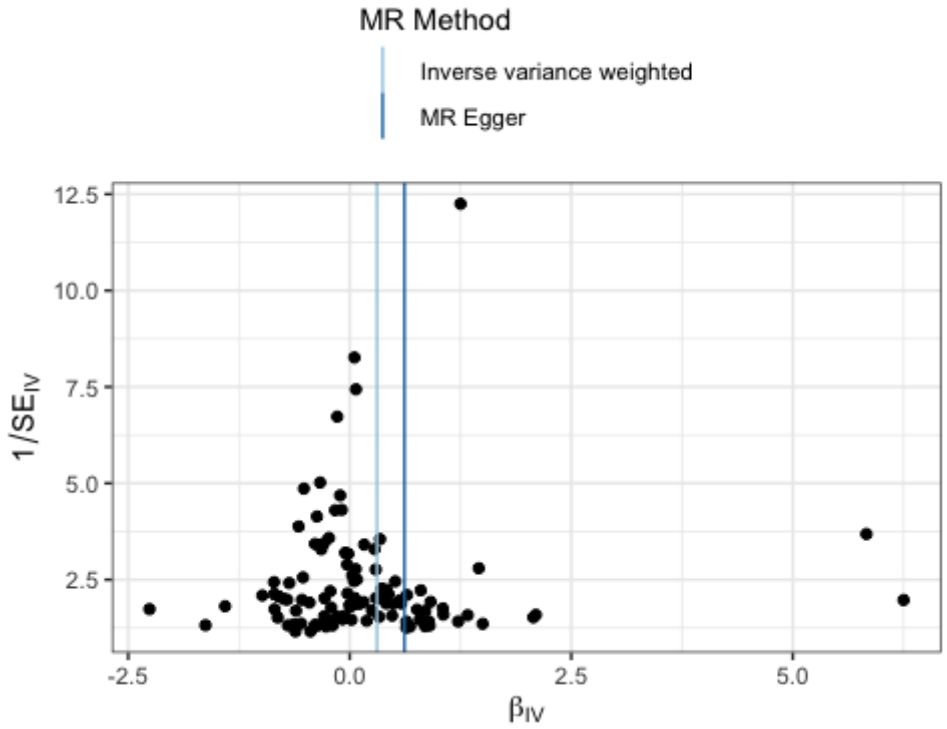

Figure 3. Funnel plot of single SNP Mendelian randomization analysis for the causal effect of TC on AD.

Leave-One-Out Analysis

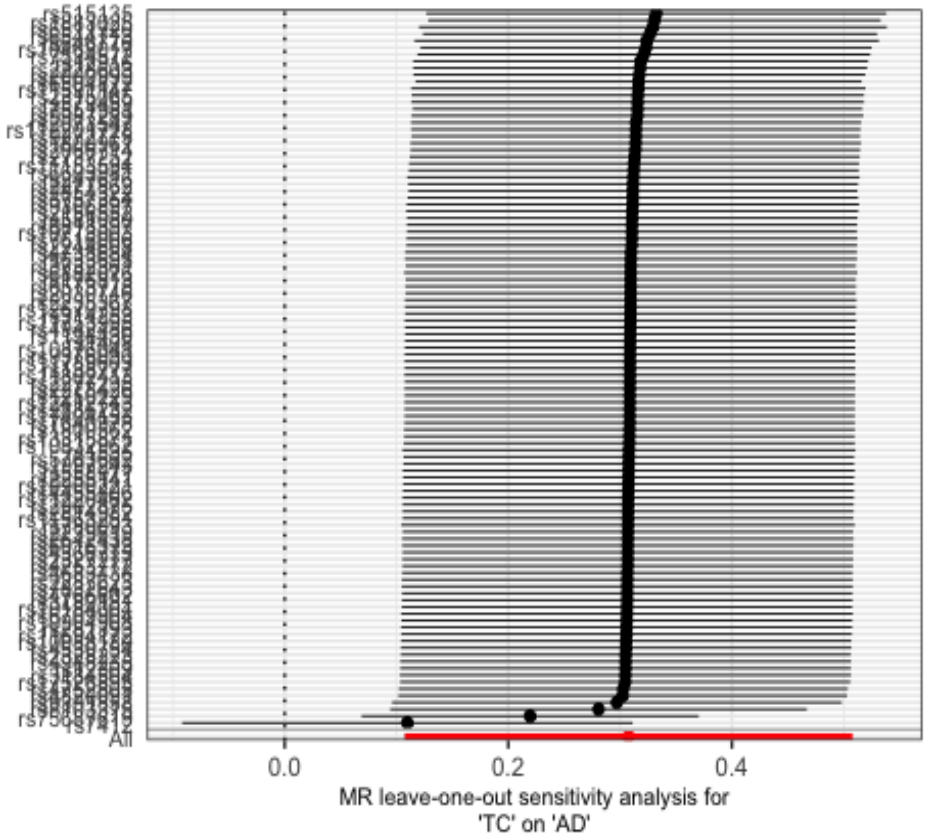

Figure 4. Leave-one-out plot representing robustness of the Mendelian randomization analysis for the causal effect of TC on AD.

Radial Mendelian Randomization

Eight SNPs were identified as outliers.

Radial IVW Outlier SNPs

Outlier SNPs	Q Statistic	P-Value
rs1883025	15.91118	6.64e-05
rs6504872	19.74802	8.80e-06
rs7412	132.46377	0.00e+00
rs75687619	409.57867	0.00e+00
rs8103315	136.55388	0.00e+00

Table 4. Summary of SNPs identified as outliers in Radial IVW analysis for the causal effect of TC on AD.

Radial Egger Outlier SNPs

Outlier SNPs	Q Statistic	P-Value
rs10468017	12.25917	0.0004630
rs1883025	18.39221	0.0000180
rs515135	14.32852	0.0001535
rs6504872	15.99085	0.0000636
rs6544713	12.70046	0.0003656
rs7412	85.77454	0.0000000
rs75687619	396.88426	0.0000000
rs8103315	143.11804	0.0000000

Table 5. Summary of SNPs identified as outliers in Radial Egger analysis for the causal effect of TC on AD.

Radial IVW and Egger Plots

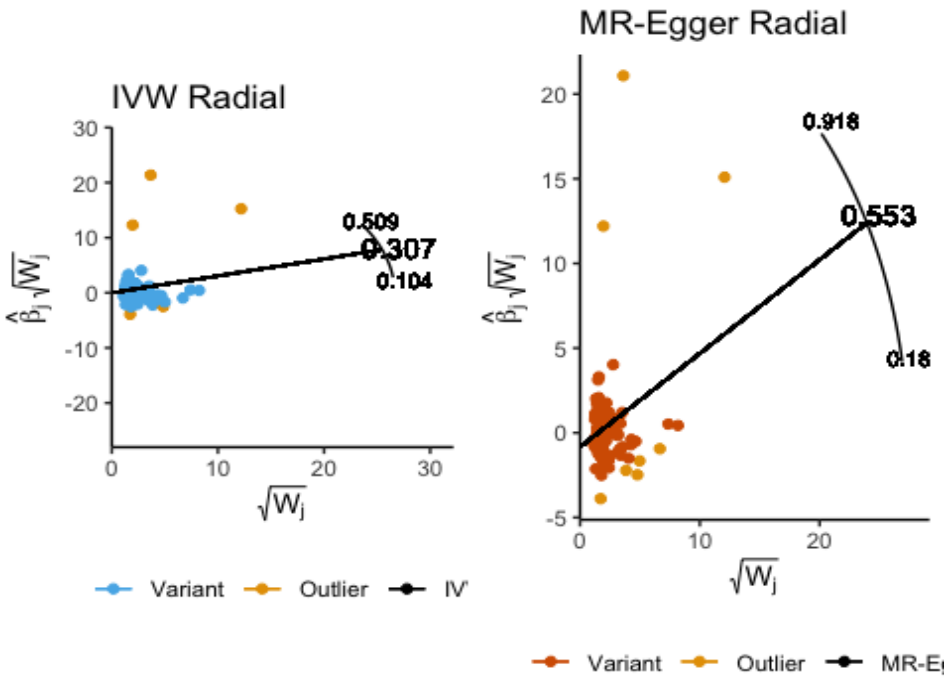

Figure 5. Radial IVW and Radial Egger plots for the causal effect of TC on AD.

Mendelian Randomization Post-Outlier SNP Removal

Mendelian randomization analysis was again performed after removing eight outlier SNPs identified in Radial IVW and Radial Egger analysis. None of the Mendelian randomization methods employed found a significant causal effect of TC on AD. The Egger estimate returned a p-value of 0.3695. The weighted median estimate returned a p-value of 0.4617. The inverse variance weighted with fixed effects estimate returned a p-value of 0.4681. The weighted mode estimate returned a p-value of 0.9302. The heterogeneity test of the Egger estimate returned a p-value of 0.0019. The heterogeneity test of inverse weighted variance estimate returned a p-value of 0.001384. The test for horizontal pleiotropy returned a p-value of 0.1585.

Outcome	Exposure	Method	NSNP	B	SE	P-Value
AD	TC	MR Egger.	97	-0.0867634	0.0962241	0.3695070
AD	TC	Weighted median	97	0.0496502	0.0697248	0.4764099
AD	TC	Inverse variance weighted (fixed effects)	97	0.0299748	0.0413161	0.4681460
AD	TC	Weighted mode	97	0.0062299	0.0764436	0.9352169

Table 6. Summary of Mendelian randomization estimates for the causal effect of TC on AD.

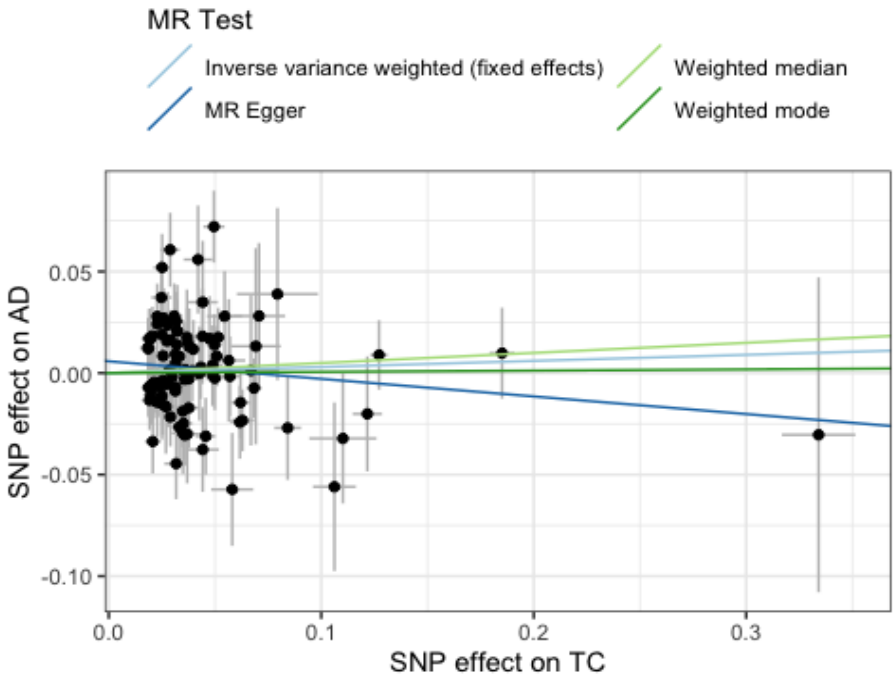

Figure 6. Scatter plot of Mendelian randomization estimates for the causal effect of TC on AD.

Outcome	Exposure	Method	Q	Q (DF)	Q P-Value
AD	TC	MR Egger	139.8264	95	0.0019023
AD	TC	Inverse variance weighted	142.7995	96	0.0013841

Table 7. Heterogeneity statistics for Mendelian randomization analysis exploring the causal effect of TC on AD.

Outcome	Exposure	Egger Intercept	SE	P-Value
AD	TC	0.0058698	0.00413	0.1585184

Table 8. Results of the MR-Egger regression intercept test for horizontal pleiotropy in the causal relationship between TC and AD.

References

1. Hemani G, Zheng J, Elsworth B, Wade KH, Baird D, Haberland V, Laurin C, Burgess S, Bowden J, Langdon R, Tan VY, Yarmolinsky J, Shihab HA, Timpson NJ, Evans DM, Relton C, Martin RM, Davey Smith G, Gaunt TR, Haycock PC, The MR-Base Collaboration. The MR-Base platform supports systematic causal inference across the human phenome. eLife 2018;7:e34408. https://doi.org/10.7554/eLife.34408

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