Title: White Matter and Alzheimer's Disease: A bidirectional Mendelian Randomization Study

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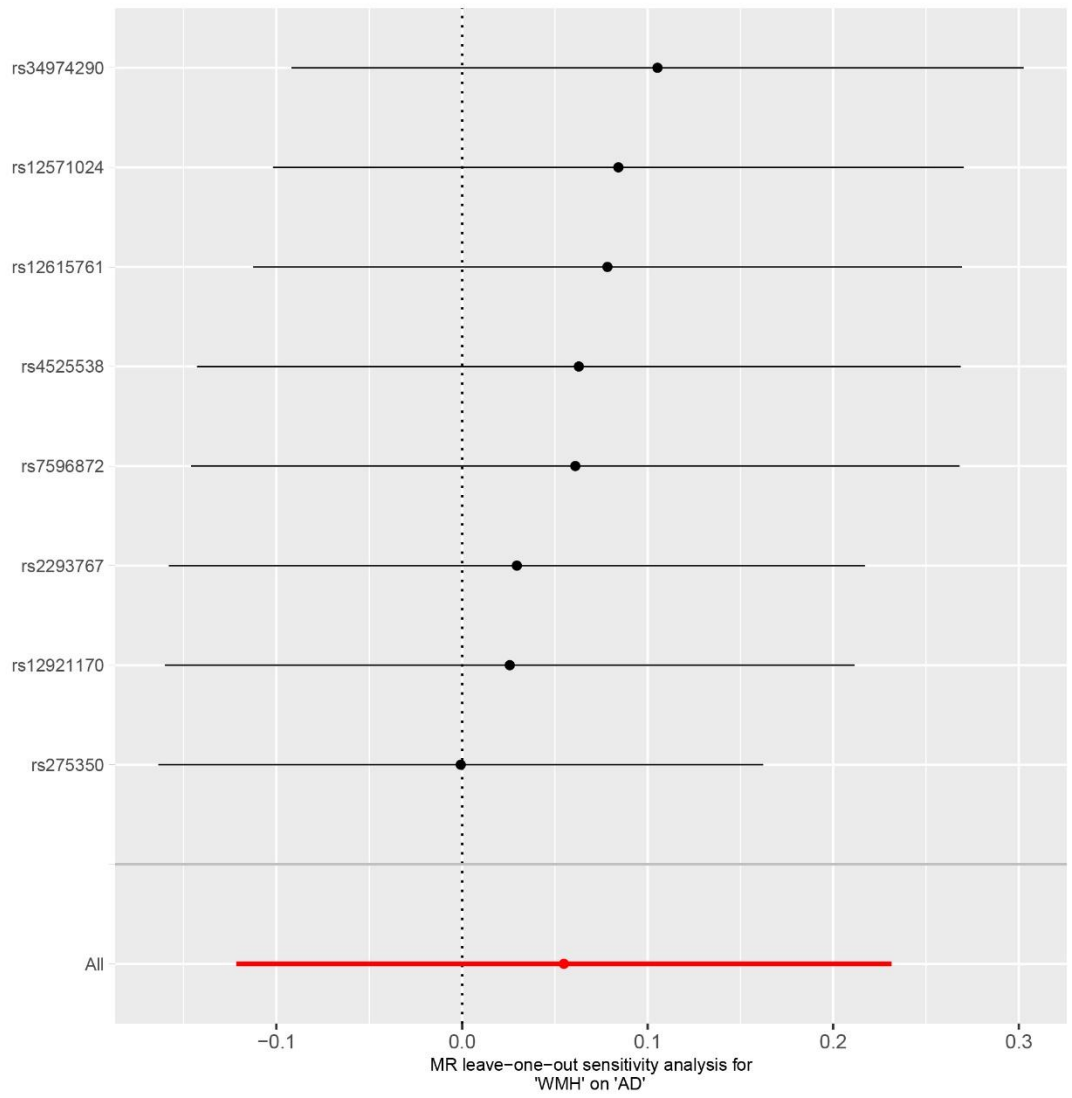
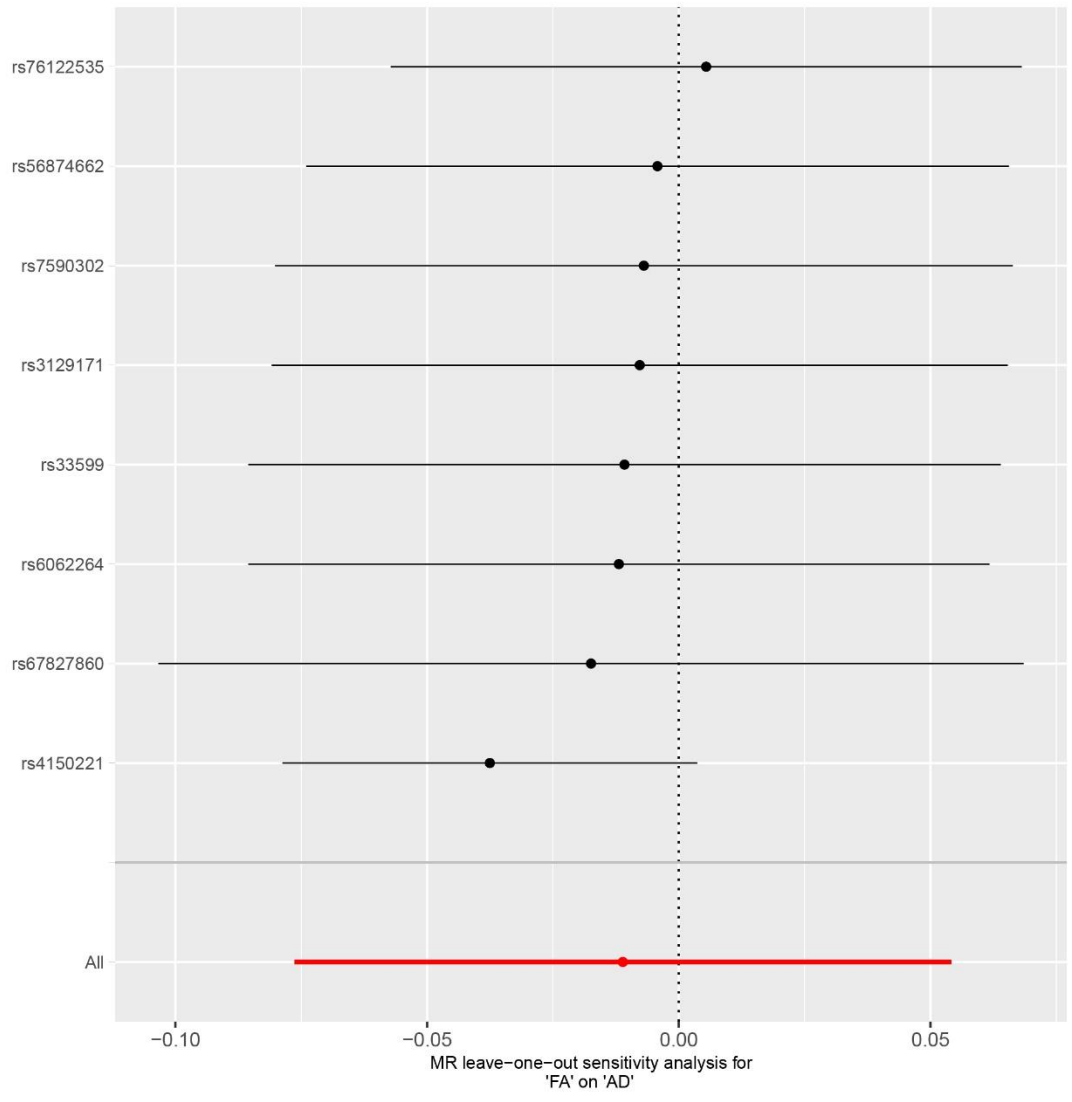


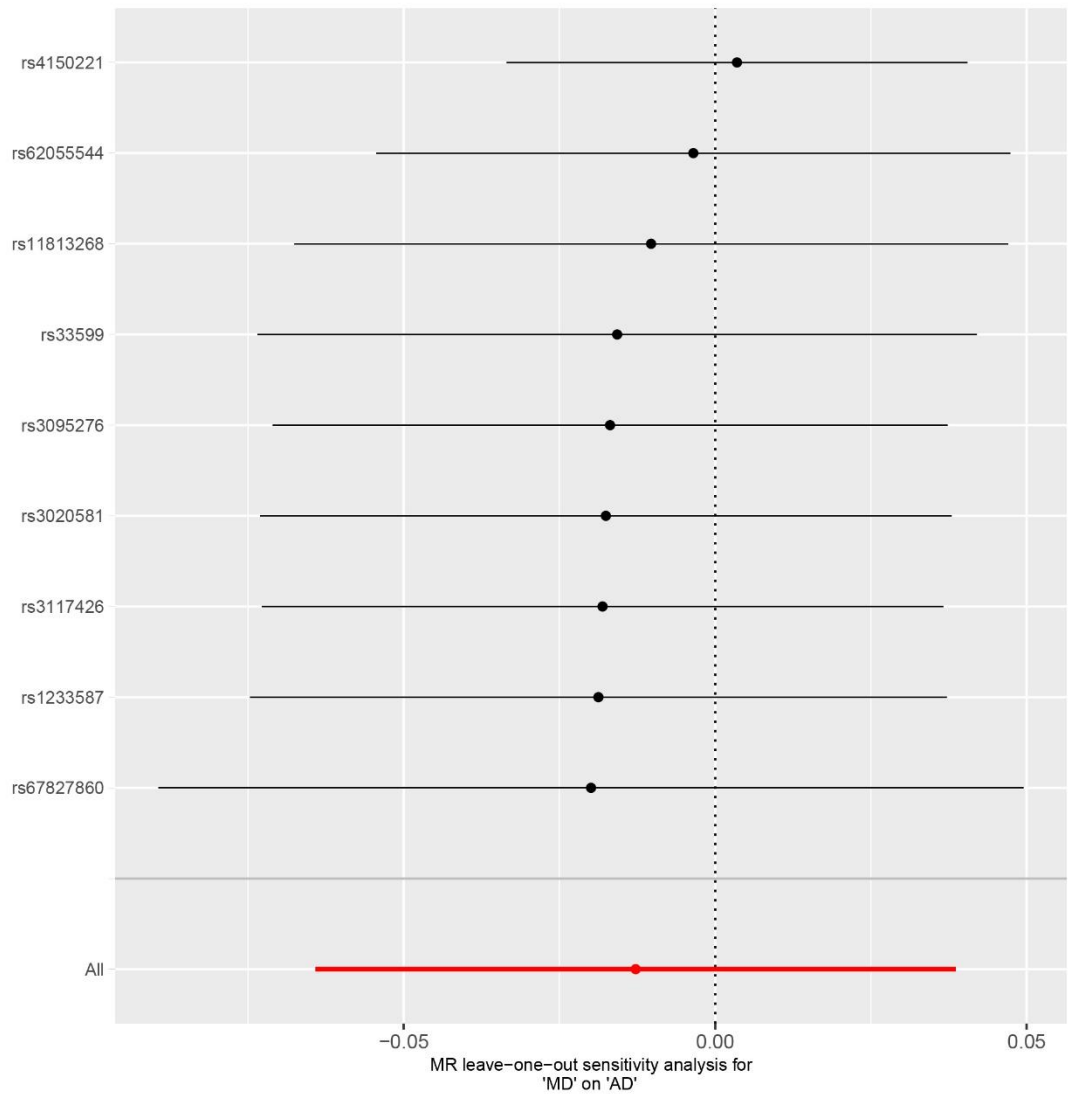
FigureS1 MR leave-one-out sensitivity analysis for WMH on AD

Abbreviations: WMH, white matter hyperintensities; AD, Alzheimer's disease



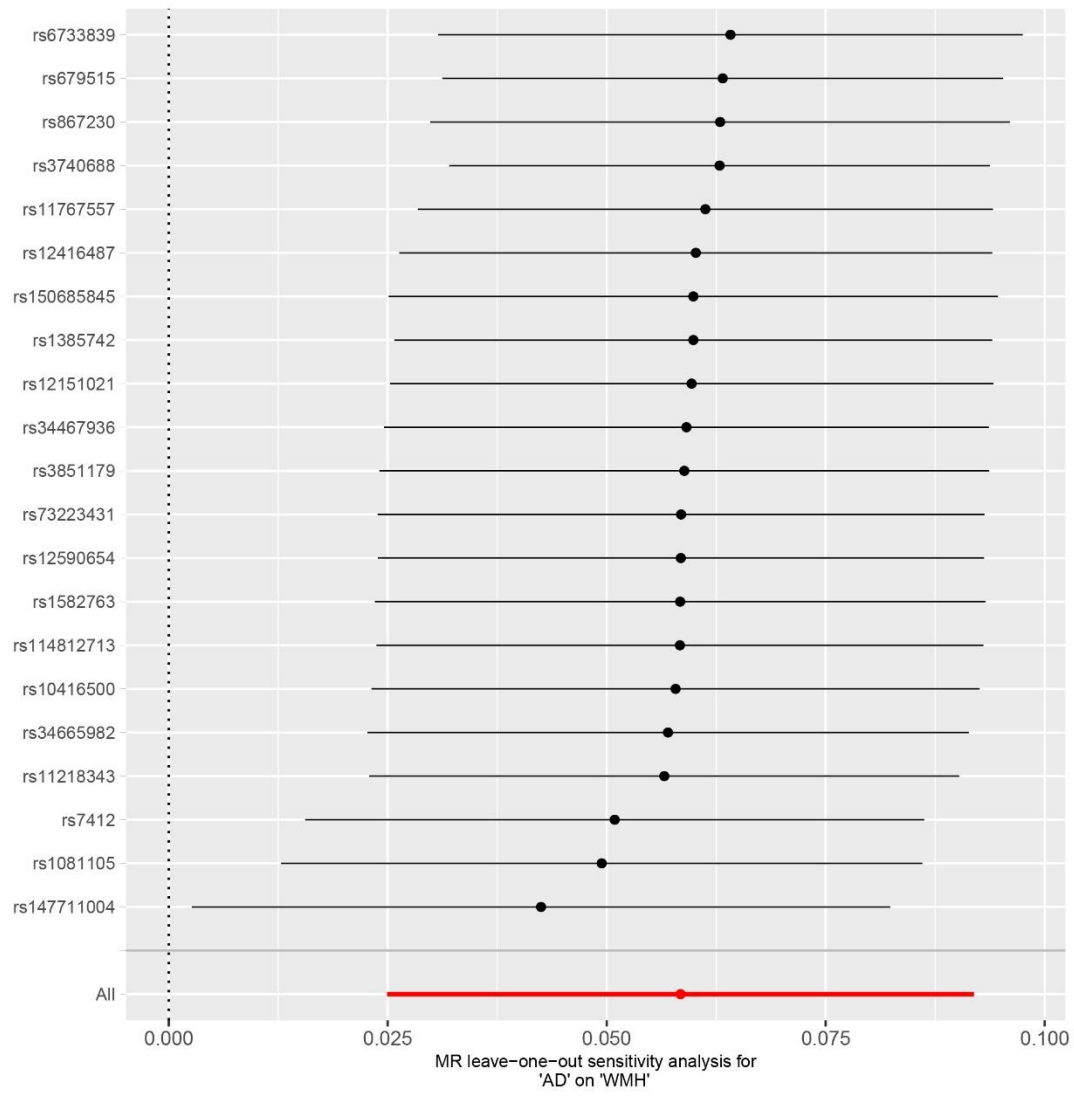
FigureS2 MR leave-one-out sensitivity analysis for FA on AD

Abbreviations: FA, fractional anisotropy; AD, Alzheimer's disease



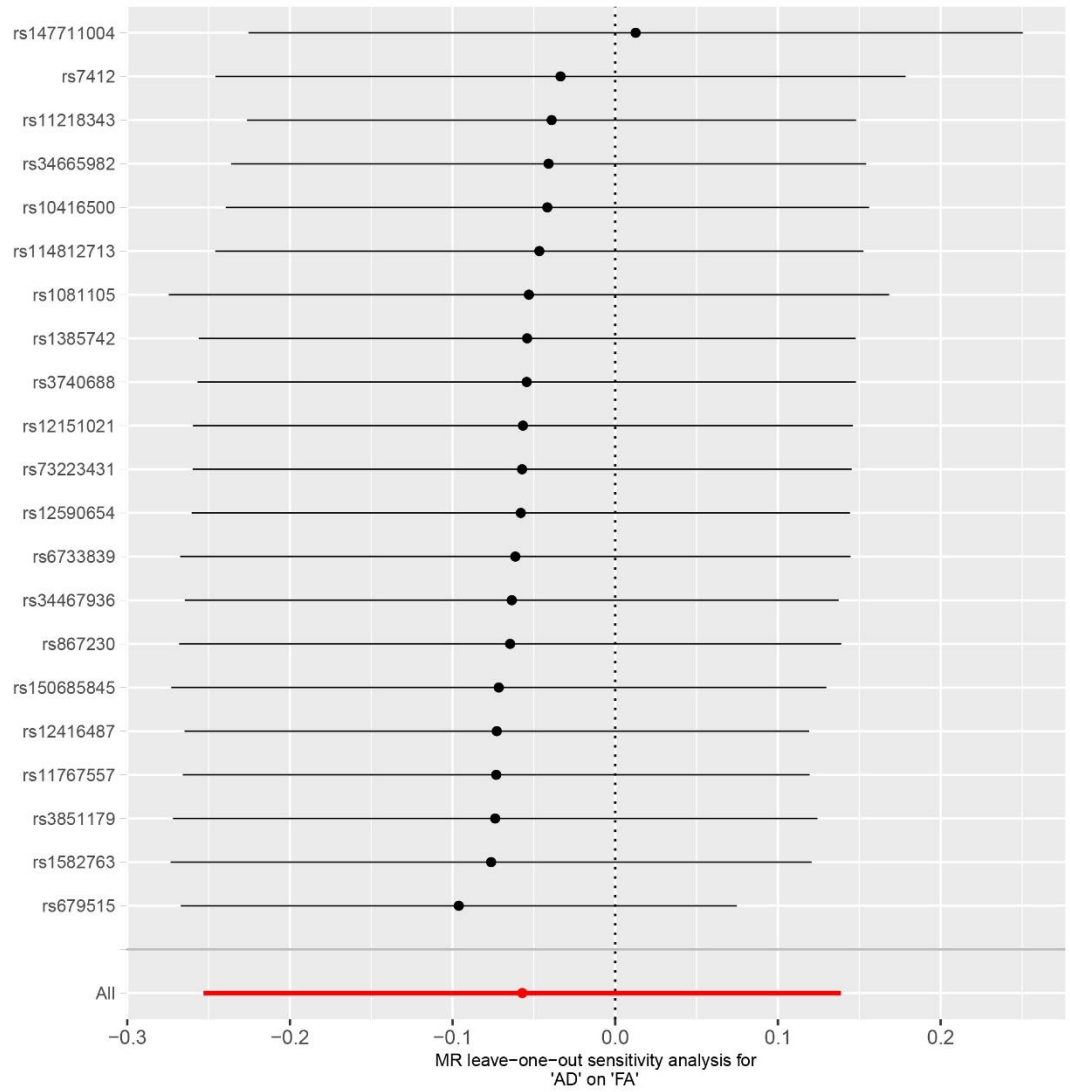
FigureS3 MR leave-one-out sensitivity analysis for MD on AD

Abbreviations: MD, mean diffusivity; AD, Alzheimer's disease



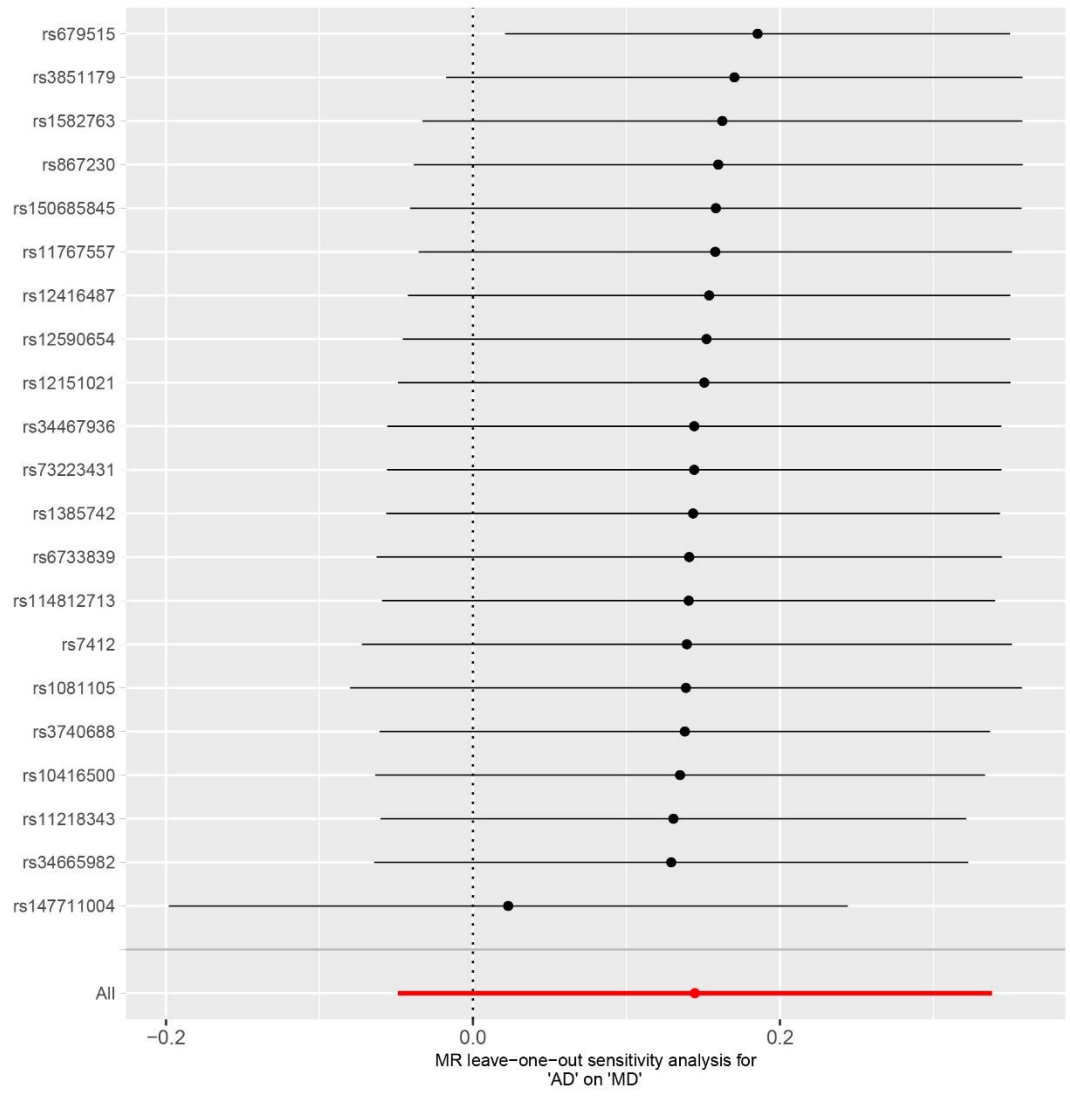
FigureS4 MR leave-one-out sensitivity analysis for AD on WMH

Abbreviations: WMH, white matter hyperintensities; AD, Alzheimer's disease



FigureS5 MR leave-one-out sensitivity analysis for AD on FA

Abbreviations: FA, fractional anisotropy; AD, Alzheimer's disease



FigureS6 MR leave-one-out sensitivity analysis for AD on MD

Abbreviations: MD, mean diffusivity; AD, Alzheimer's disease

Table S1 Data sources and the instrumental variable used for exposure included in the MR analyses

Exposure	Sample size	Cases	Population	SNPs	R^2	F-statistic
The effect of WH on AD						
WMH	18,381	NA	European	8	0.0035	64.832
FA	17,673	NA	European	8	0.0032	57.581
MD	17,467	NA	European	9	0.0039	67.782
The effect of AD on WM						
AD	63,926	21,982	European	21	0.0037	234.876

Note

R^2, calculated the 90th percentile of variance estimations;

F-statistic, calculated the 90th percentile strength of the instrument based on the formula: $F=R^2\times(N-2)/(1-R^2)$

Abbreviations: MR, Mendelian randomization; SNP, single nucleotide polymorphism; WM, white matter; AD, Alzheimer's disease; WMH, white matter hyperintensities; FA, fractional anisotropy; MD, mean diffusivity

TableS2 Pleiotropy, heterogeneity analyses, and power for MR analysis

Phenotype	IVW-Phet		MR Egger-Phet		MR Egger-Ppltr		MR PRESSO-Ppltr	Power
	Cochran Q	P_value	Cochran Q	P_value	Intercept	P_value		
The effect of WM on AD								
WMH								
Total	9.17	0.24	6.67	0.35	0.03	0.18	0.25	1.00
FA								
Total	21.75	<0.01	21.66	<0.01	0.01	0.88	0.01	1.00
MD								
Total	19.72	0.01	18.79	0.01	-0.02	0.58	0.03	1.00
The effect of AD on WM								
WMH								
Total	33.22	0.03	19.63	0.42	-0.01	<0.01	<0.01	0.60
Without *APOE*	16.88	0.33	16.67	0.27	0.00	0.68	0.33	0.09
FA								
Total	52.54	<0.01	59.32	<0.01	0.04	0.13	<0.01	0.92
Without *APOE*	23.25	0.04	22.37	0.03	0.04	0.50	<0.01	0.16
MD								
Total	55.47	<0.01	46.34	<0.01	-0.05	0.07	<0.01	1.00
Without *APOE*	26.65	0.02	25.52	0.02	-0.05	0.46	<0.01	0.12

Note

Power for MR analyses, calculated using an online calculator(https://sb452.shinyapps.io/power);

Phet, P-value for heterogeneity between instrumental SNP causal estimates;

Ppltr, P-value for horizontal pleiotropy from MR-Egger intercept test or MR-PRESSO global test;

IVW, inverse variance weighted; MR-PRESSO, Pleiotropy Residual Sum and Outlier

Table S3 Summary statistics for the genetic instruments used to assess the effect of WM on AD

Exposure	SNPs	BETA	SE	P-value
WMH	rs12571024	-0.22	0.25	0.39
	rs12615761	-0.17	0.26	0.51
	rs12921170	0.33	0.25	0.19
	rs2293767	0.32	0.27	0.23
	rs275350	0.53	0.24	0.03
	rs34974290	-0.13	0.17	0.45
	rs4525538	0.01	0.21	0.97
	rs7596872	0.02	0.20	0.92
FA	rs3129171	-0.05	0.06	0.47
	rs33599	-0.01	0.06	0.81
	rs4150221	0.19	0.06	0.00
	rs56874662	-0.11	0.07	0.14
	rs6062264	0.00	0.06	0.97
	rs67827860	0.00	0.03	0.96
	rs7590302	-0.05	0.06	0.41
	rs76122535	-0.15	0.06	0.01
MD	rs11813268	-0.04	0.06	0.50
	rs1233587	0.04	0.05	0.41
	rs3020581	0.05	0.06	0.43
	rs3095276	0.08	0.08	0.32
	rs3117426	0.06	0.07	0.33
	rs33599	0.01	0.05	0.81
	rs4150221	-0.21	0.06	0.00
	rs62055544	-0.13	0.06	0.03
	rs67827860	0.00	0.03	0.96

Note

Abbreviations: SNP, single nucleotide polymorphism; WM, white matter; AD, Alzheimer’s disease; WMH, white matter hyperintensities; FA, fractional anisotropy; MD, mean diffusivity

TableS4 Summary statistics for the genetic instruments used to assess the effect of AD on WM

Outcome	SNPs	BETA	SE	P-value
WMH	rs10416500	0.08	0.09	0.35
	rs1081105	0.10	0.03	0.00
	rs11218343	0.22	0.12	0.08
	rs114812713	0.06	0.10	0.55
	rs11767557	-0.15	0.11	0.19
	rs12151021	-0.01	0.10	0.93
	rs12416487	-0.08	0.12	0.49
	rs12590654	0.06	0.11	0.62
	rs1385742	-0.05	0.12	0.65
	rs147711004	0.09	0.02	0.00
	rs150685845	0.02	0.07	0.82
	rs1582763	0.06	0.08	0.46
	rs34467936	0.01	0.11	0.92
	rs34665982	0.14	0.10	0.17
	rs3740688	-0.21	0.10	0.04
	rs3851179	0.04	0.08	0.61
	rs6733839	-0.05	0.06	0.41
	rs679515	-0.13	0.08	0.13
	rs73223431	0.05	0.11	0.61
	rs7412	0.11	0.04	0.00
	rs867230	-0.08	0.07	0.30
FA	rs10416500	-0.74	0.39	0.06
	rs1081105	-0.08	0.14	0.58
	rs11218343	-1.62	0.54	0.00
	rs114812713	-0.69	0.45	0.13
	rs11767557	1.11	0.50	0.03
	rs12151021	-0.08	0.43	0.85
	rs12416487	1.21	0.52	0.02
	rs12590654	0.01	0.49	0.99
	rs1385742	-0.29	0.51	0.57
	rs147711004	-0.20	0.10	0.05
	rs150685845	0.36	0.32	0.26
	rs1582763	0.63	0.35	0.07
	rs34467936	0.39	0.49	0.43
	rs34665982	-0.96	0.44	0.03
	rs3740688	-0.22	0.46	0.63
	rs3851179	0.58	0.36	0.11
	rs6733839	0.02	0.26	0.93
	rs679515	1.45	0.37	0.00
	rs73223431	-0.05	0.46	0.91
	rs7412	-0.23	0.17	0.17
	rs867230	0.16	0.32	0.61

MD	rs10416500	0.57	0.40	0.15
	rs1081105	0.17	0.14	0.22
	rs11218343	1.36	0.55	0.01
	rs114812713	0.39	0.46	0.41
	rs11767557	-0.82	0.51	0.11
	rs12151021	-0.18	0.44	0.68
	rs12416487	-0.60	0.54	0.26
	rs12590654	-0.40	0.50	0.43
	rs1385742	0.23	0.52	0.65
	rs147711004	0.40	0.10	0.00
	rs150685845	-0.25	0.32	0.44
	rs1582763	-0.49	0.36	0.17
	rs34467936	0.17	0.50	0.73
	rs34665982	1.00	0.45	0.02
	rs3740688	0.54	0.47	0.25
	rs3851179	-0.84	0.37	0.02
	rs6733839	0.21	0.26	0.42
	rs679515	-1.43	0.37	0.00
	rs73223431	0.17	0.47	0.72
	rs7412	0.18	0.17	0.28
	rs867230	-0.31	0.33	0.35

Note

Abbreviations: SNP, single nucleotide polymorphism; WM, white matter; AD, Alzheimer’s disease; WMH, white matter hyperintensities; FA, fractional anisotropy; MD, mean diffusivity