

## Supplementary Material

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**Supplementary Table 1.** Brief description of source datasets utilized in this study

Traits	Sample size	Cases	Controls	Ancestry	Access Link
Low back pain	177,860	13,178	164,682	European	<a href="https://r5.finngen.fi/">https://r5.finngen.fi/</a>
Alzheimer's disease	63,926	21,982	41,944	European	<a href="https://www.niagads.org/datasets/ng00075">https://www.niagads.org/datasets/ng00075</a>
Parkinson's disease	482,730	33,674	449,056	European	<a href="https://pdgenetics.org/resources">https://pdgenetics.org/resources</a>
Amyotrophic lateral sclerosis	80,610	20,806	59,804	European	<a href="http://als.umassmed.edu/">http://als.umassmed.edu/</a>

**Supplementary Table 2.** Summary statistics utilized in the Mendelian randomization analysis of low back pain on neurodegenerative diseases

Trait	SNP	Coordinate (GRCh37)	EA	OA	EAF	$R^2$	$F$	Association with LBP			Association with outcome trait		
								Beta	SE	$P$ -value	Beta	SE	$P$ -value
AD	rs6426282	1:246310585	C	T	0.196	0.002	22.3	-0.080	0.017	$2.27 \times 10^{-6}$	0.006	0.021	0.783
AD	rs56091004	6:3744847	T	C	0.061	0.002	23.9	0.140	0.029	$1.05 \times 10^{-6}$	-0.039	0.028	0.171
AD	rs9469835	6:34611001	G	A	0.330	0.002	25.3	0.073	0.015	$4.83 \times 10^{-7}$	-0.005	0.015	0.759
AD	rs112412403	6:129060572	A	G	0.038	0.002	21.7	0.169	0.036	$3.15 \times 10^{-6}$	-0.041	0.070	0.555
AD	rs147356029	7:4042724	A	G	0.018	0.002	21.5	0.238	0.051	$3.46 \times 10^{-6}$	-0.040	0.045	0.376
AD	rs143783757	7:79133344	G	A	0.021	0.002	21.2	-0.220	0.048	$4.06 \times 10^{-6}$	-0.023	0.068	0.732
AD	rs1481789	8:72040468	A	G	0.159	0.002	24.1	0.091	0.019	$9.94 \times 10^{-7}$	0.008	0.017	0.661
AD	rs4284332	10:73733952	C	T	0.557	0.002	22.6	0.065	0.014	$2.10 \times 10^{-6}$	0.006	0.015	0.690
AD	rs231908	11:2751660	G	A	0.755	0.003	27.8	-0.083	0.016	$1.42 \times 10^{-7}$	-0.024	0.018	0.179
AD	rs60127327	12:54627857	G	A	0.481	0.002	22.4	-0.064	0.014	$2.42 \times 10^{-6}$	-0.031	0.015	0.034
AD	rs941157	12:90776124	T	C	0.412	0.002	22.1	-0.064	0.014	$2.76 \times 10^{-6}$	-0.006	0.014	0.692

AD	rs225880	14:30481804	C	T	0.786	0.002	22.7	0.078	0.016	$1.94 \times 10^{-6}$	-0.017	0.019	0.375
AD	rs2022845	14:66343168	T	G	0.309	0.002	22.5	-0.069	0.015	$2.21 \times 10^{-6}$	-0.011	0.015	0.448
AD	rs72726942	15:31876216	T	G	0.026	0.002	21.7	0.202	0.043	$3.17 \times 10^{-6}$	0.008	0.041	0.841
AD	rs56807215	16:87951030	A	T	0.099	0.002	21.2	-0.106	0.023	$4.22 \times 10^{-6}$	-0.022	0.033	0.504
AD	rs62097992	18:50835863	C	T	0.412	0.002	23.5	0.067	0.014	$1.17 \times 10^{-6}$	-0.015	0.014	0.298
AD	rs113679764	19:17486898	A	G	0.096	0.002	21.9	0.108	0.023	$2.99 \times 10^{-6}$	0.042	0.032	0.195
PD	rs6426282	1:246310585	C	T	0.196	0.002	22.3	-0.080	0.017	$2.27 \times 10^{-6}$	0.035	0.032	0.274
PD	rs56091004	6:3744847	T	C	0.061	0.002	23.9	0.140	0.029	$1.05 \times 10^{-6}$	0.040	0.038	0.289
PD	rs9469835	6:34611001	G	A	0.330	0.002	25.3	0.073	0.015	$4.83 \times 10^{-7}$	-0.012	0.018	0.504
PD	rs112412403	6:129060572	A	G	0.038	0.002	21.7	0.169	0.036	$3.15 \times 10^{-6}$	-0.006	0.075	0.932
PD	rs147356029	7:4042724	A	G	0.018	0.002	21.5	0.238	0.051	$3.46 \times 10^{-6}$	0.015	0.068	0.825
PD	rs143783757	7:79133344	G	A	0.021	0.002	21.2	-0.220	0.048	$4.06 \times 10^{-6}$	0.022	0.085	0.797
PD	rs1481789	8:72040468	A	G	0.159	0.002	24.1	0.091	0.019	$9.94 \times 10^{-7}$	0.030	0.029	0.301
PD	rs4284332	10:73733952	C	T	0.557	0.002	22.6	0.065	0.014	$2.10 \times 10^{-6}$	-0.015	0.023	0.506
PD	rs231908	11:2751660	G	A	0.755	0.003	27.8	-0.083	0.016	$1.42 \times 10^{-7}$	-0.026	0.028	0.345
PD	rs60127327	12:54627857	G	A	0.481	0.002	22.4	-0.064	0.014	$2.42 \times 10^{-6}$	-0.005	0.020	0.808
PD	rs941157	12:90776124	T	C	0.412	0.002	22.1	-0.064	0.014	$2.76 \times 10^{-6}$	-0.042	0.022	0.062

PD	rs225880	14:30481804	C	T	0.786	0.002	22.7	0.078	0.016	$1.94 \times 10^{-6}$	-0.019	0.029	0.520
PD	rs2022845	14:66343168	T	G	0.309	0.002	22.5	-0.069	0.015	$2.21 \times 10^{-6}$	-0.001	0.023	0.981
PD	rs72726942	15:31876216	T	G	0.026	0.002	21.7	0.202	0.043	$3.17 \times 10^{-6}$	-0.097	0.062	0.118
PD	rs56807215	16:87951030	A	T	0.099	0.002	21.2	-0.106	0.023	$4.22 \times 10^{-6}$	0.089	0.037	0.017
PD	rs62097992	18:50835863	C	T	0.412	0.002	23.5	0.067	0.014	$1.17 \times 10^{-6}$	0.028	0.020	0.155
PD	rs113679764	19:17486898	A	G	0.096	0.002	21.9	0.108	0.023	$2.99 \times 10^{-6}$	0.005	0.042	0.914
ALS	rs6426282	1:246310585	C	T	0.196	0.002	22.3	-0.080	0.017	$2.27 \times 10^{-6}$	0.024	0.019	0.209
ALS	rs56091004	6:3744847	T	C	0.061	0.002	23.9	0.140	0.029	$1.05 \times 10^{-6}$	0.003	0.024	0.894
ALS	rs9469835	6:34611001	G	A	0.330	0.002	25.3	0.073	0.015	$4.83 \times 10^{-7}$	-0.006	0.014	0.663
ALS	rs112412403	6:129060572	A	G	0.038	0.002	21.7	0.169	0.036	$3.15 \times 10^{-6}$	-0.051	0.053	0.344
ALS	rs147356029	7:4042724	A	G	0.018	0.002	21.5	0.238	0.051	$3.46 \times 10^{-6}$	-0.089	0.045	0.045
ALS	rs143783757	7:79133344	G	A	0.021	0.002	21.2	-0.220	0.048	$4.06 \times 10^{-6}$	0.008	0.064	0.904
ALS	rs1481789	8:72040468	A	G	0.159	0.002	24.1	0.091	0.019	$9.94 \times 10^{-7}$	-0.007	0.016	0.676
ALS	rs4284332	10:73733952	C	T	0.557	0.002	22.6	0.065	0.014	$2.10 \times 10^{-6}$	-0.006	0.014	0.667
ALS	rs231908	11:2751660	G	A	0.755	0.003	27.8	-0.083	0.016	$1.42 \times 10^{-7}$	-0.006	0.017	0.707
ALS	rs60127327	12:54627857	G	A	0.481	0.002	22.4	-0.064	0.014	$2.42 \times 10^{-6}$	0.001	0.014	0.956
ALS	rs941157	12:90776124	T	C	0.412	0.002	22.1	-0.064	0.014	$2.76 \times 10^{-6}$	-0.005	0.014	0.746

ALS	rs225880	14:30481804	C	T	0.786	0.002	22.7	0.078	0.016	$1.94 \times 10^{-6}$	-0.021	0.018	0.242
ALS	rs2022845	14:66343168	T	G	0.309	0.002	22.5	-0.069	0.015	$2.21 \times 10^{-6}$	-0.016	0.014	0.257
ALS	rs72726942	15:31876216	T	G	0.026	0.002	21.7	0.202	0.043	$3.17 \times 10^{-6}$	0.013	0.038	0.743
ALS	rs56807215	16:87951030	A	T	0.099	0.002	21.2	-0.106	0.023	$4.22 \times 10^{-6}$	0.043	0.028	0.122
ALS	rs62097992	18:50835863	C	T	0.412	0.002	23.5	0.067	0.014	$1.17 \times 10^{-6}$	0.006	0.014	0.655
ALS	rs113679764	19:17486898	A	G	0.096	0.002	21.9	0.108	0.023	$2.99 \times 10^{-6}$	-0.008	0.032	0.816

Note: As for instrumental SNPs for the exposure, proportion of variance explained was calculated using formula:  $R^2 = 2 \times \text{EAF} \times (1-\text{EAF}) \times \text{Beta}^2$ . Strength of individual SNP was approximated by the formula:  $F\text{-statistic} = (\text{Beta}/\text{SE})^2$ , where  $F < 10$  was seen as a weak instrument.

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; EA, effect allele; EAF, effect allele frequency of instrumental SNP associated with the exposure; LBP, low back pain; SE, standard error; OA, other allele; PD, Parkinson's disease; SNP, single nucleotide polymorphism.

**Supplementary Table 3.** Summary statistics utilized in the Mendelian randomization analysis of neurodegenerative diseases on low back pain

Trait	SNP	Coordinate (GRCh37)	EA	OA	EAF	$R^2$	F	Association with exposure trait			Association with LBP		
								Beta	SE	$P$ -value	Beta	SE	$P$ -value
AD	rs679515	1:207750568	C	T	0.828	0.006	70.4	-0.151	0.018	$1.55 \times 10^{-16}$	-0.005	0.017	0.777
AD	rs6733839	2:127892810	T	C	0.380	0.014	126.9	0.169	0.015	$4.02 \times 10^{-28}$	-0.006	0.014	0.700
AD	rs114812713	6:41034000	C	G	0.028	0.005	48.0	0.298	0.043	$4.47 \times 10^{-12}$	0.188	0.068	0.006
AD	rs9381563	6:47432637	T	C	0.322	0.003	29.9	-0.082	0.015	$2.93 \times 10^{-8}$	-0.013	0.016	0.420
AD	rs11767557	7:143109139	C	T	0.218	0.004	32.7	-0.103	0.018	$1.56 \times 10^{-8}$	-0.025	0.018	0.176
AD	rs73223431	8:27219987	T	C	0.346	0.004	39.3	0.094	0.015	$8.34 \times 10^{-10}$	-0.021	0.014	0.142
AD	rs867230	8:27468503	A	C	0.598	0.009	69.1	0.133	0.016	$3.49 \times 10^{-17}$	-0.013	0.014	0.340
AD	rs11257242	10:11721119	G	C	0.651	0.003	31.4	0.084	0.015	$4.64 \times 10^{-8}$	-0.010	0.014	0.459
AD	rs3740688	11:47380340	T	G	0.543	0.004	45.1	0.094	0.014	$9.70 \times 10^{-11}$	0.006	0.015	0.704
AD	rs1582763	11:60021948	A	G	0.363	0.007	67.2	-0.123	0.015	$1.19 \times 10^{-16}$	0.009	0.015	0.548
AD	rs3851179	11:85868640	C	T	0.629	0.007	64.0	0.120	0.015	$5.81 \times 10^{-16}$	0.018	0.014	0.197
AD	rs12590654	14:92938855	A	G	0.337	0.004	32.3	-0.091	0.016	$8.73 \times 10^{-9}$	0.008	0.015	0.601

AD	rs12151021	19:1050874	G	A	0.662	0.005	39.6	-0.107	0.017	$2.56 \times 10^{-10}$	-0.012	0.015	0.431
AD	rs111278137	19:45215081	A	G	0.014	0.006	44.6	-0.474	0.071	$3.20 \times 10^{-11}$	0.070	0.068	0.305
AD	rs147711004	19:45337918	A	G	0.029	0.072	941.0	1.135	0.037	$1.00 \times 10^{-200}$	-0.071	0.034	0.036
AD	rs7412	19:45412079	T	C	0.063	0.026	226.9	-0.467	0.031	$6.40 \times 10^{-53}$	0.037	0.030	0.219
AD	rs1081105	19:45412955	C	A	0.031	0.053	458.3	0.942	0.044	$1.51 \times 10^{-103}$	-0.071	0.048	0.142
AD	rs72654445	19:45417200	A	G	0.011	0.006	44.9	-0.543	0.081	$2.27 \times 10^{-11}$	-0.073	0.066	0.273
AD	rs139136389	19:45427136	T	C	0.026	0.012	33.8	-0.494	0.085	$6.43 \times 10^{-9}$	0.121	0.110	0.272
AD	rs150685845	19:45675180	G	A	0.013	0.008	73.2	0.556	0.065	$6.62 \times 10^{-18}$	0.043	0.050	0.388
PD	rs35749011*	1:155135036	A	G	0.019	0.021	129.5	0.751	0.066	$5.02 \times 10^{-30}$	-0.052	0.033	0.111
PD	rs823106	1:205656453	C	G	0.849	0.006	38.5	-0.149	0.024	$4.10 \times 10^{-10}$	0.011	0.019	0.557
PD	rs6741007	2:135537119	G	T	0.451	0.008	46.7	-0.123	0.018	$2.09 \times 10^{-12}$	0.006	0.014	0.657
PD	rs4613239	2:169119609	G	C	0.133	0.007	50.7	0.178	0.025	$6.21 \times 10^{-13}$	0.029	0.022	0.194
PD	rs4488803	3:58218352	A	G	0.375	0.006	32.5	-0.114	0.020	$1.08 \times 10^{-8}$	0.002	0.014	0.882
PD	rs10513789	3:182760073	G	T	0.183	0.008	52.9	-0.160	0.022	$3.18 \times 10^{-13}$	-0.019	0.017	0.272
PD	rs34311866	4:951947	C	T	0.196	0.016	97.4	0.227	0.023	$7.97 \times 10^{-23}$	-0.020	0.017	0.225
PD	rs4698412	4:15737348	A	G	0.553	0.008	54.9	0.126	0.017	$7.05 \times 10^{-14}$	-0.018	0.014	0.193
PD	rs7695720	4:77183300	C	A	0.209	0.005	36.0	-0.126	0.021	$1.53 \times 10^{-9}$	0.015	0.016	0.365



PD	rs356203	4:90666041	T	C	0.617	0.027	177.8	-0.240	0.018	$3.01 \times 10^{-41}$	-0.006	0.014	0.696
PD	rs75646569	5:60345424	G	T	0.112	0.007	50.6	0.192	0.027	$5.62 \times 10^{-13}$	0.024	0.023	0.286
PD	rs35265698	6:32561334	G	C	0.155	0.010	44.4	-0.200	0.030	$3.93 \times 10^{-11}$	0.010	0.019	0.581
PD	rs858295	7:23245569	G	A	0.395	0.005	33.4	-0.104	0.018	$3.83 \times 10^{-9}$	0.015	0.014	0.291
PD	rs620490	8:16697579	G	T	0.276	0.006	37.9	-0.117	0.019	$6.46 \times 10^{-10}$	-0.004	0.014	0.762
PD	rs144814361	10:121410917	T	C	0.017	0.007	42.1	0.441	0.068	$9.07 \times 10^{-11}$	-0.013	0.088	0.884
PD	rs329647	11:133764666	C	G	0.666	0.006	39.4	-0.113	0.018	$1.94 \times 10^{-10}$	0.013	0.018	0.461
PD	rs75505347	12:40885549	T	C	0.020	0.006	34.2	0.392	0.067	$6.12 \times 10^{-9}$	-0.061	0.057	0.289
PD	rs10847864	12:123326598	T	G	0.363	0.008	49.8	0.127	0.018	$9.81 \times 10^{-13}$	0.006	0.014	0.698
PD	rs4774417	15:61993702	A	G	0.740	0.004	30.5	0.105	0.019	$4.63 \times 10^{-8}$	-0.019	0.015	0.202
PD	rs12934900	16:30923602	T	A	0.657	0.007	45.9	0.122	0.018	$4.33 \times 10^{-11}$	0.007	0.014	0.619
PD	rs10451230	17:16035225	T	A	0.565	0.005	28.4	-0.096	0.018	$4.42 \times 10^{-8}$	0.013	0.014	0.347
PD	rs58879558*	17:44095467	C	T	0.223	0.020	90.6	-0.238	0.025	$1.36 \times 10^{-21}$	0.035	0.021	0.096
PD	rs4588066	18:40672964	A	G	0.326	0.005	34.0	0.105	0.018	$4.45 \times 10^{-9}$	0.001	0.014	0.962
ALS	rs10463311	5:150410835	T	C	0.744	0.003	28.2	-0.085	0.016	$4.00 \times 10^{-8}$	0.011	0.015	0.492
ALS	rs3849943	9:27543382	T	C	0.752	0.012	121.0	-0.176	0.016	$3.77 \times 10^{-30}$	-0.003	0.018	0.885
ALS	rs142321490	12:58676132	C	G	0.018	0.004	38.6	0.317	0.051	$6.15 \times 10^{-10}$	0.016	0.042	0.704

ALS	rs74654358	12:64881967	A	G	0.047	0.004	33.9	0.198	0.034	$4.66 \times 10^{-9}$	0.008	0.035	0.826
ALS	rs12973192	19:17753239	G	C	0.325	0.006	65.1	0.121	0.015	$3.92 \times 10^{-15}$	0.008	0.014	0.588
ALS	rs75087725	21:45753117	A	C	0.015	0.008	59.1	0.515	0.067	$1.85 \times 10^{-14}$	0.025	0.047	0.590

Note: As for instrumental SNPs for the exposure, proportion of variance explained was calculated using the formula:  $R^2 = 2 \times \text{EAF} \times (1 - \text{EAF}) \times \text{Beta}^2$ . Strength of individual SNP was approximated by the formula:  $F\text{-statistic} = (\text{Beta}/\text{SE})^2$ , where  $F < 10$  was seen as a weak instrument. Effect allele frequency for instrumental variable of AD was not available in the original GWAS, and hence was retrieved by searching LDlink in the EUR sub-population (1000 Genomes Phase 3).

\* In the summary statistics of low back pain two proxy SNPs were utilized for rs35749011 (rs35682329, chr1:155121143,  $r^2 = 1$ ) and rs58879558 (rs62062271, chr17: 44091988,  $r^2 = 0.99$ ).

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; EA, effect allele; EAF, effect allele frequency of instrumental SNP associated with the exposure; LBP, low back pain; SE, standard error; OA, other allele; PD, Parkinson's disease; SNP, single nucleotide polymorphism.

**Supplementary Table 4.** Mendelian randomization analysis power estimation

Exposure	No. of SNPs	PVE	Outcome	Outcome sample size	<i>K</i>	OR detected with adequate power (>80%)
LBP	17	0.036	AD	63,926	0.344	$\leq 0.882$ , or $\geq 1.129$
LBP	17	0.036	PD	482,730	0.070	$\leq 0.917$ , or $\geq 1.084$
LBP	17	0.036	ALS	80,610	0.258	$\leq 0.885$ , or $\geq 1.122$
AD	20	0.262	LBP	177,860	0.074	$\leq 0.951$ , or $\geq 1.050$
PD	23	0.206	LBP	177,860	0.074	$\leq 0.944$ , or $\geq 1.056$
ALS	6	0.036	LBP	177,860	0.074	$\leq 0.867$ , or $\geq 1.136$

Note: Assuming a power of 80% and an alpha of 5%, we calculated the minimum detectable OR using the web application, mRnd (<https://shiny.cnsgenomics.com/mRnd/>) with input parameters: (1) PVE, proportion of variance explained for the association between instrumental SNPs with the exposure; (2) the outcome sample size; and (3) *K*, proportion of cases in the association study of the outcome of interest.

Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; LBP, low back pain; PD, Parkinson's disease; SNP, Single-nucleotide polymorphism.

**Supplementary Table 5.** MR-Egger regression intercepts examining unbalanced horizontal pleiotropy

Exposures and outcomes	Number of SNPs	MR-Egger regression		
		Intercept	Standard error	<i>P</i> -value
LBP on AD	17	0.017	0.014	0.246
LBP on PD	17	0.021	0.022	0.357
LBP on ALS	17	0.015	0.013	0.273
AD on LBP	20	0.007	0.007	0.307
PD on LBP	23	0.002	0.007	0.792
ALS on LBP	6	-0.010	0.017	0.598

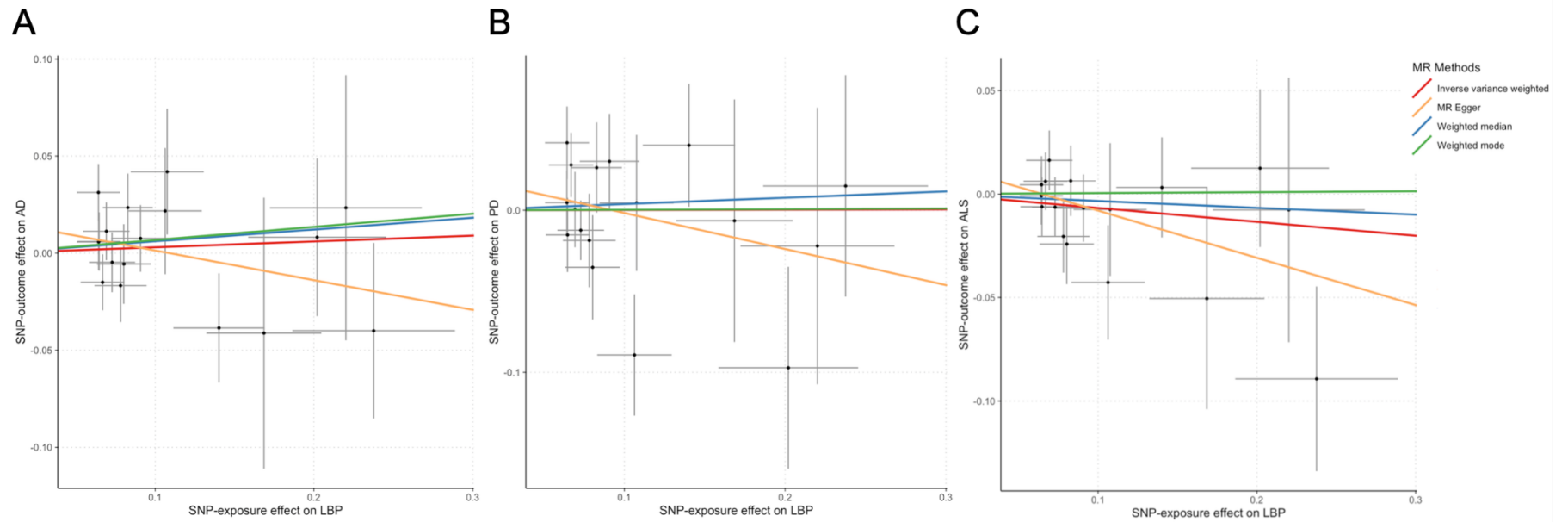
Abbreviations: AD, Alzheimer’s disease; ALS, amyotrophic lateral sclerosis; LBP, low back pain; PD, Parkinson’s disease; SNP, Single-nucleotide polymorphism.

**Supplementary Table 6.** Heterogeneity assessment by Cochran's Q statistics

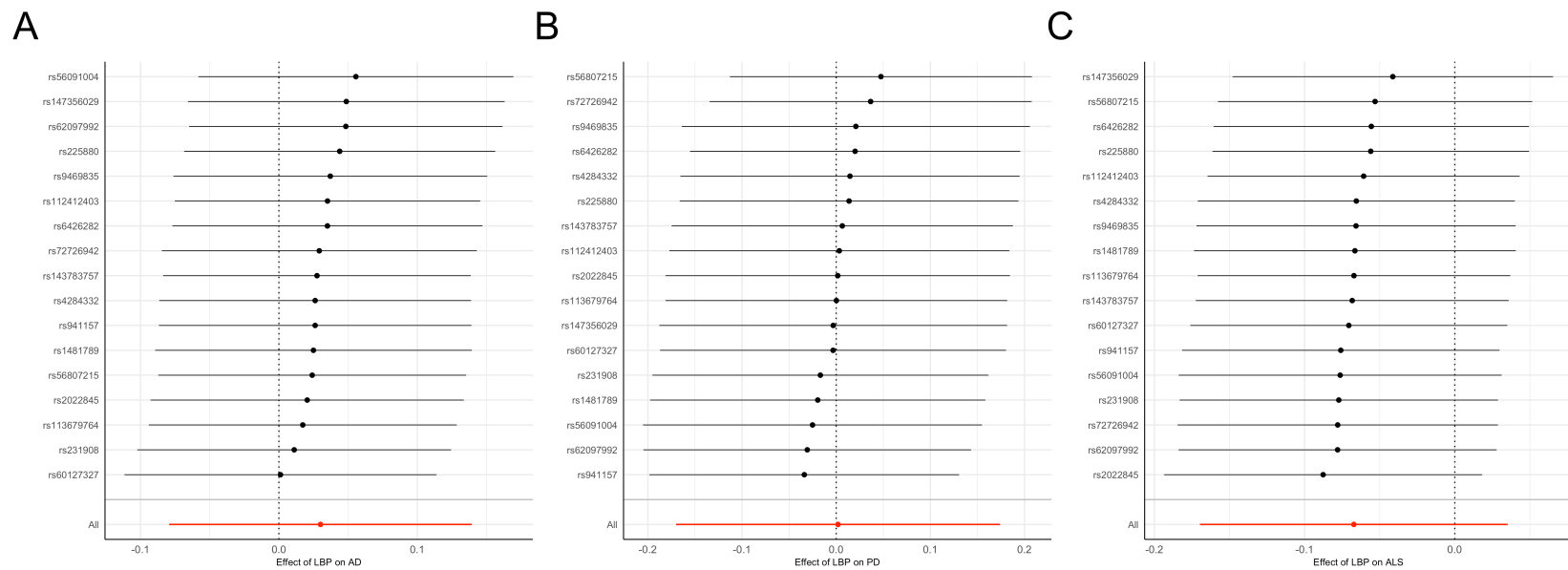
Exposures and outcomes	Number of SNPs	Cochran's <i>Q</i> test		
		<i>Q</i> -statistic	<i>I</i> <sup>2</sup>	<i>P</i> -value
LBP on AD	17	14.5	0	0.564
LBP on PD	17	19.4	17.6%	0.248
LBP on ALS	17	11.1	0	0.805
AD on LBP	20	25.5	25.5%	0.144
PD on LBP	23	16.3	0	0.801
ALS on LBP	6	0.9	0	0.970

Note: *I*<sup>2</sup> statistic measured the percentage of variation across instrumental variants that is due to heterogeneity,  $I^2 = (Q-df)/Q \times 100\%$ , where  $df = N-1$ ,  $df$  was degree of freedom,  $N$  was number of instrumental SNPs.

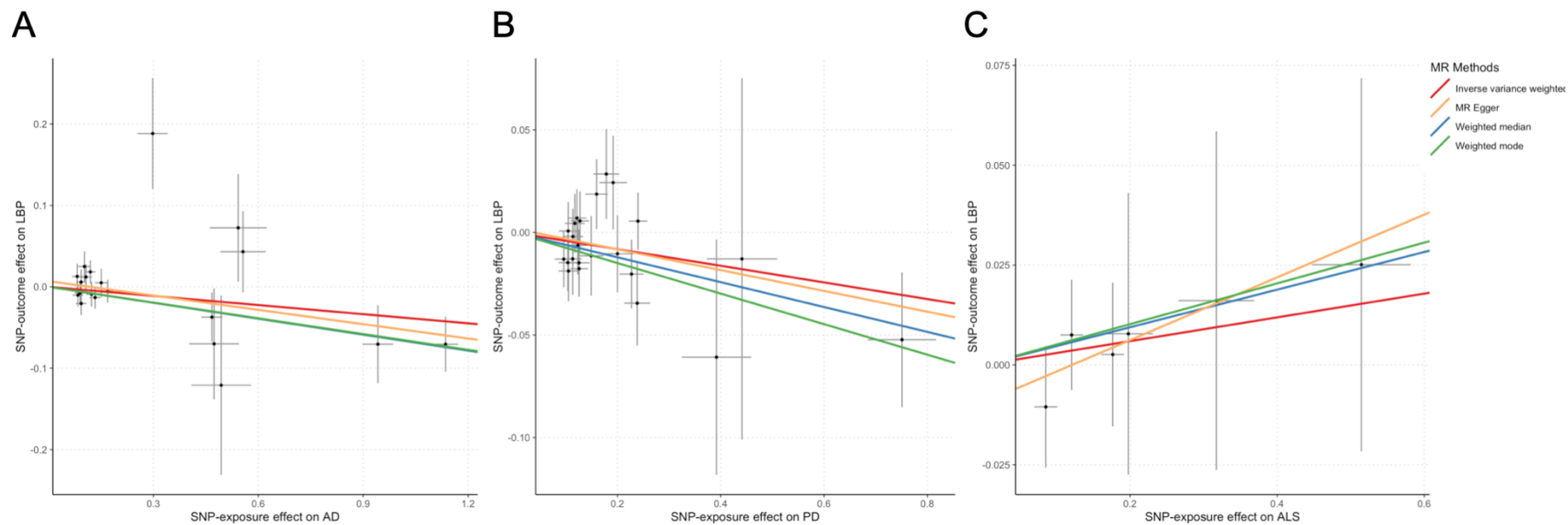
Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; LBP, low back pain; PD, Parkinson's disease; SNP, Single-nucleotide polymorphism.



**Supplementary Figure 1.** Scatter plots in the Mendelian randomization analyses of low back pain on neurodegenerative diseases

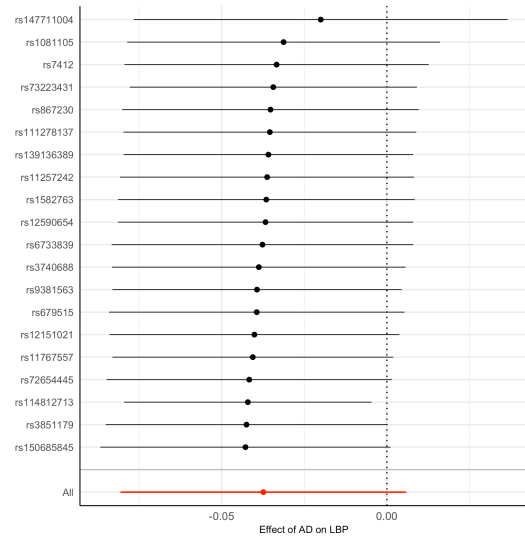
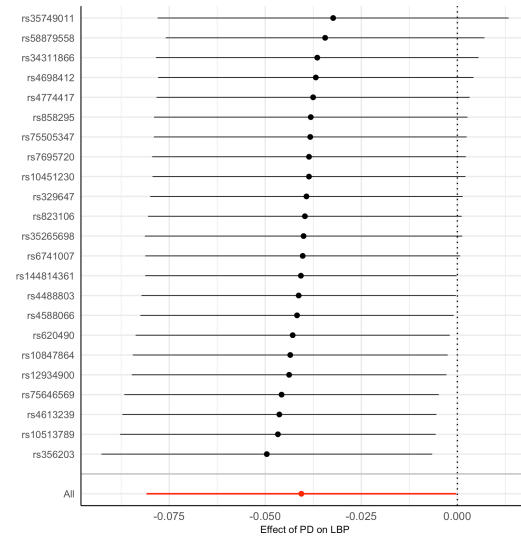
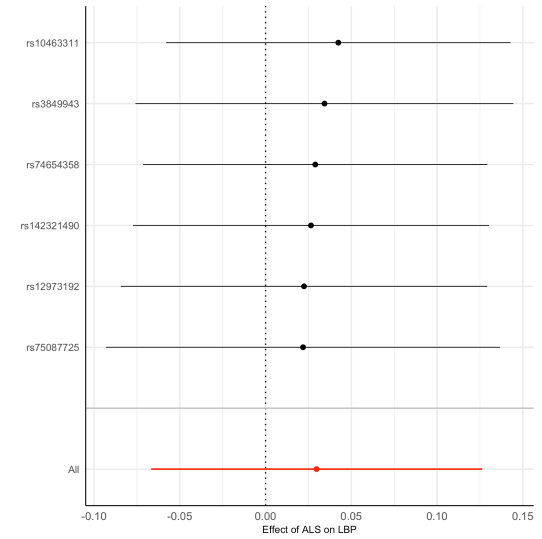


**Supplementary Figure 2.** Leave-one-out plots in the Mendelian randomization analyses of low back pain on neurodegenerative diseases



**Supplementary Figure 3.** Scatter plots in the Mendelian randomization analyses of neurodegenerative diseases on low back pain



**A****B****C**

**Supplementary Figure 4.** Leave-one-out plots in the Mendelian randomization analyses of neurodegenerative diseases on low back pain