Mendelian Randomization Analysis of Circulating Adipokines and C-reactive Protein on Breast Cancer Risk

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Supplementary Table 1. Estimates of sample overlap across exposure and BCAC datasets

Instrument	Overlapping Cohort	Sample size after QC in BCAC	As a percentage of total BCAC population (228,951)
Adiponectin	NHS	3,392	1.5
C-reactive protein	EPIC	7,057	3.1
	WHI	9,521	4.2
Interleukin-6	EPIC	7,057	3.1
	WHI	9,521	4.2

QC= Quality control, BCAC= Breast Cancer Association Consortium, NHS = Nurses Health Study, EPIC = European Prospective Investigation into Cancer and Nutrition, WHI = Women's Health Initiative

Supplementary Table 2. Summary genetic association data used across each adipokine and C-reactive protein

Trait	rsid	Effect allele	Non-effect allele	Effect allele frequency	Beta	SE
Adiponectin	rs3001032	T	C	0.70	-0.02	0.004
	rs1108842	C	A	0.50	0.03	0.004
	rs6810075	T	C	0.60	0.06	0.004
	rs998584	C	A	0.50	0.03	0.005
	rs2980879	T	A	0.70	0.03	0.005
	rs7955516	C	A	0.40	0.02	0.004
	rs601339	G	A	0.20	0.03	0.005
	rs2925979	T	C	0.30	-0.04	0.005
	rs12922394	T	C	0.10	-0.08	0.01
	rs731839	G	A	0.35	-0.03	0.004
C-reactive Protein	rs1051338	G	T	0.31	0.024	0.004
	rs10832027	G	A	0.33	-0.026	0.004
	rs10838687	G	T	0.22	-0.031	0.004
	rs112635299	T	G	0.02	-0.107	0.017
	rs12202641	T	C	0.39	-0.023	0.004
	rs12960928	C	T	0.27	0.024	0.004
	rs12995480	T	C	0.17	-0.031	0.005
	rs1441169	G	A	0.53	-0.025	0.004
	rs1490384	T	C	0.51	-0.025	0.004
	rs1514895	A	G	0.71	-0.027	0.004
	rs1558902	A	T	0.41	0.034	0.004
	rs1582763	A	G	0.37	-0.022	0.004
	rs17658229	C	T	0.05	0.056	0.010
	rs178810	T	C	0.56	0.020	0.004
	rs1880241	G	A	0.48	-0.028	0.004
	rs2239222	G	A	0.36	0.035	0.004
	rs2315008	T	G	0.31	-0.023	0.004
	rs2352975	C	T	0.3	0.025	0.004
	rs2710804	C	T	0.37	0.021	0.004
	rs2836878	G	A	0.27	0.043	0.004
	rs2891677	C	T	0.46	-0.020	0.004
	rs4092465	A	G	0.35	-0.027	0.004
	rs4246598	A	C	0.46	0.022	0.004
	rs469772	T	C	0.19	-0.031	0.005
	rs4774590	A	G	0.35	-0.022	0.004
	rs6001193	G	A	0.35	-0.028	0.004
	rs7121935	A	G	0.38	-0.022	0.004
	rs75460349	A	C	0.97	0.086	0.014
	rs9271608	G	A	0.22	0.042	0.005
	rs9284725	C	A	0.24	0.027	0.004
	rs9385532	T	C	0.33	-0.026	0.004
	rs2293476	C	G	0.23	0.030	0.004
	rs1805096	G	A	0.39	0.104	0.004
	rs4129267	C	T	0.39	0.088	0.004
	rs2794520	C	T	0.33	0.182	0.004
	rs10925027	T	C	0.4	0.036	0.004
	rs1260326	T	C	0.39	0.073	0.004
	rs13409371	A	G	0.43	0.048	0.004

	rs13233571	C	T	0.12	0.057	0.005
	rs4841132	G	A	0.09	0.065	0.006
	rs340005	A	G	0.38	0.03	0.004
	rs10521222	C	T	0.05	0.104	0.011
	rs2852151	A	G	0.40	0.025	0.004
	rs4420638	A	G	0.18	0.229	0.006
	rs1800961	C	T	0.03	0.112	0.011
HGF	rs5745695	A	G	0.76	0.19	0.03
Interleukin 6	rs7529229	T	C	0.55	0.086	0.012
	rs4845371	T	C	0.43	0.062	0.013
	rs12740969	T	G	0.49	0.078	0.013
Leptin receptor	rs3790438	A	T	0.18	-1.37	0.02
PAI-I	rs2227631	A	G	0.59	0.073	0.007
	rs6486122	T	C	0.69	0.046	0.007
	rs6976053	T	C	0.48	0.048	0.007
Resistin	rs34124816	C	A	0.04	-0.61	0.06

SE= Standard error, HGF= Hepatocyte growth factor, PAI-1= Plasminogen activator inhibitor-1. Effect estimates and standard errors are scaled as follows: natural log-transformed adiponectin, C-reactive protein, interleukin-6, and plasminogen activator inhibitor-1 and standardised hepatocyte growth factor, leptin receptor, and resistin.

Supplementary Table 3. Posterior probabilities under differing hypotheses relating the associations between hepatocyte growth factor and oestrogen receptor-negative breast cancer risk

Configuration	H_0	H_1	H_2	H_3	H_4
	7.25×10^{-7}	0.93	1.47×10^{-8}	1.90×10^{-2}	5.50×10^{-2}

H_0 = neither hepatocyte growth factor nor oestrogen receptor-negative breast cancer has a genetic association in the region, H_1 = only hepatocyte growth factor has a genetic association in the region, H_2 = only oestrogen receptor-negative breast cancer has a genetic association in the region, H_3 = both hepatocyte growth factor and oestrogen receptor-negative breast cancer are associated but have different causal variants, H_4= both hepatocyte growth factor and oestrogen receptor-negative breast cancer are associated and share a single causal variant

Supplementary Table 4. Effect estimates per unit increase in adiponectin, C-reactive protein, and plasminogen activator inhibitor-1 on overall and oestrogen receptor stratified breast cancer risk using conservative (*cis*-SNP) instruments*

Risk factor	Overall breast cancer	ER+ breast cancer	ER- breast cancer
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Adiponectin	0.97 (0.92-1.02)	0.98 (0.92-1.05)	0.98 (0.89-1.09)
C-reactive protein	1.01 (0.95-1.07)	1.02 (0.96-1.10)	1.04 (0.94-1.16)
PAI-1	1.10 (0.93-1.30)	1.16 (0.94-1.42)	1.13 (0.83-1.53)

SNP = single-nucleotide polymorphism, OR = Odds Ratio, 95% CI = 95% Confidence Interval, PAI-1 = Plasminogen activator inhibitor-1.

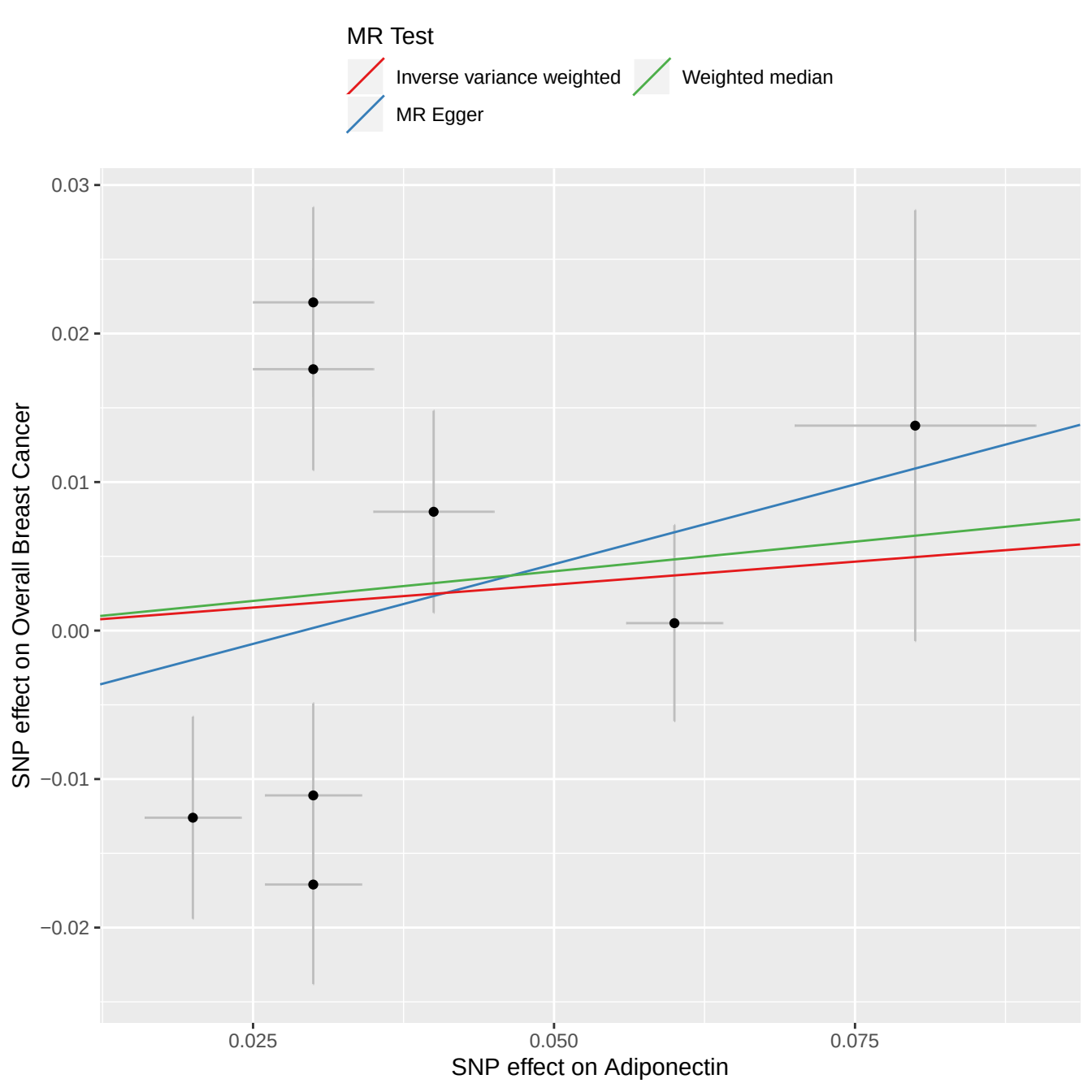
**Cis*-SNP instruments were constructed as follows: adiponectin was instrumented using four variants within *ADIPOQ* (rs6810075, rs16861209, rs17366568, rs3774261), C-reactive protein was instrumented using four variants within *CRP* (rs3093077, rs1205, rs1130864, rs1800947), and plasminogen activator inhibitor-1 was instrumented using one variant within *SERPINE* (rs2227631).

Effect estimates represent the effect of a one unit increase in: natural log-transformed adiponectin, C-reactive protein, and plasminogen activator inhibitor-1.

Supplementary Table 5. Sensitivity analyses for adiponectin, C-reactive protein, and plasminogen activator inhibitor-1 using MR-Egger and weighted median estimates

Trait	Model	Overall Breast cancer OR (95% CI); *P*	ER+ Breast cancer OR (95% CI); *P*	ER- Breast cancer OR (95% CI); *P*
Adiponectin	MR-Egger regression	1.04 (0.91-1.20); 0.53	1.07 (0.93-1.23); 0.33	1.03 (0.86-1.23); 0.77
	MR-Egger intercept parameter	1.00 (0.99-1.01); 0.83	1.00 (0.99-1.01); 0.58	1.00 (0.99-1.01); 0.72
	Weighted median estimate	1.03 (0.97-1.09); 0.35	1.06 (1.00-1.14); 0.06	1.07 (0.97-1.18); 0.16
C-reactive protein	MR-Egger regression	1.24 (0.55-2.78); 0.62	1.27 (0.50-3.24); 0.63	0.95 (0.45-1.99); 0.89
	MR-Egger intercept parameter	0.99 (0.96-1.02); 0.70	0.99 (0.95-1.03); 0.58	1.01 (0.98-1.04); 0.54
	Weighted median estimate	1.08 (0.91-1.29); 0.37	1.02 (0.84-1.25); 0.84	0.98 (0.72-1.34); 0.92
PAI-1	MR-Egger regression	0.58 (0.17-2.02); 0.55	0.54 (0.22-1.32); 0.40	0.50 (0.03-7.71); 0.71
	MR-Egger intercept parameter	1.03 (0.96-1.11); 0.53	1.04 (0.98-1.09); 0.41	1.04 (0.89-1.22); 0.69
	Weighted median estimate	0.94 (0.81-1.10); 0.46	0.94 (0.78-1.13); 0.49	0.90 (0.69-1.18); 0.46

ER+ = Oestrogen-receptor positive, ER- = Oestrogen-receptor negative, 95% CI = 95% Confidence Interval, PAI-1 = Plasminogen activator inhibitor-1.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MR Egger
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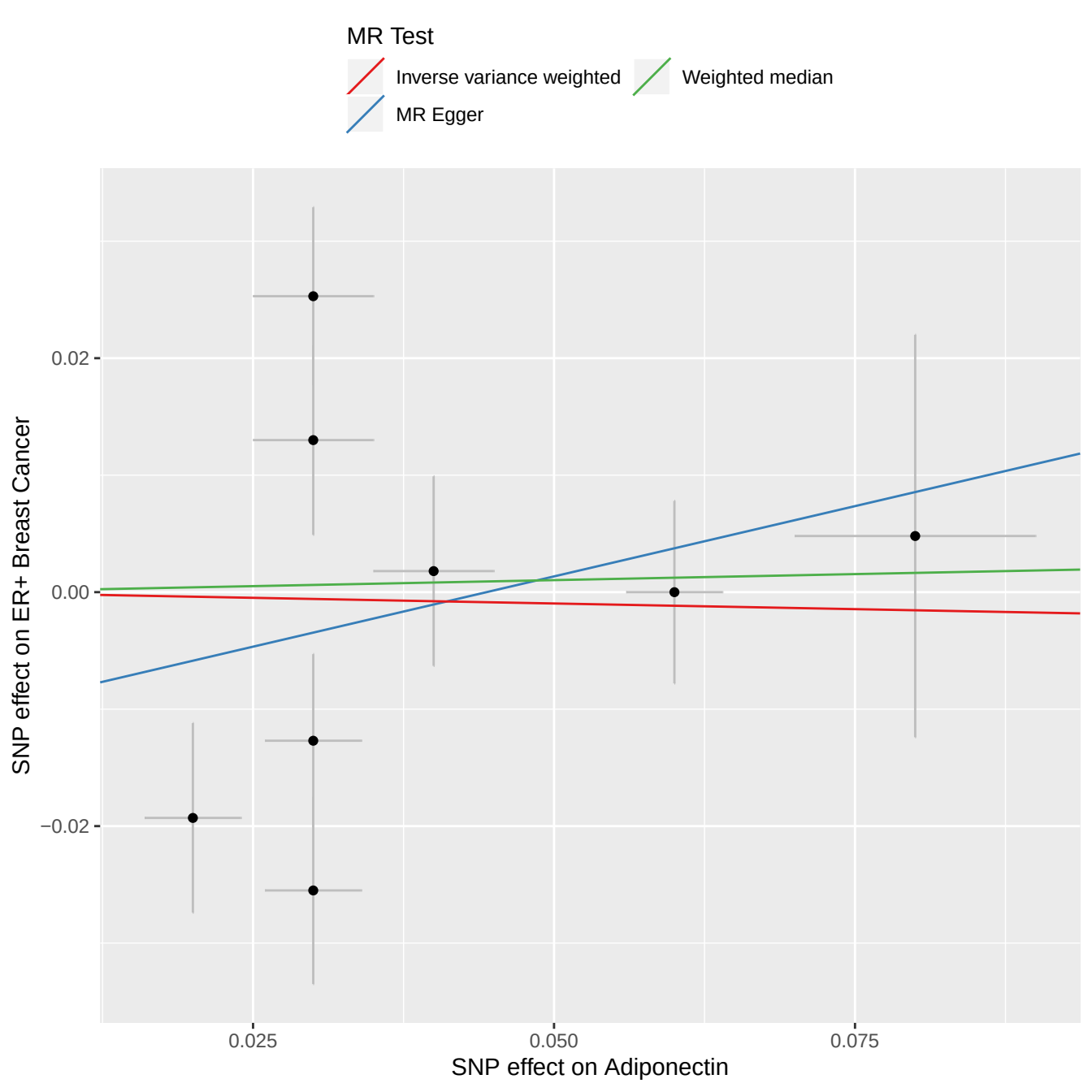
SNP effect on Adiponectin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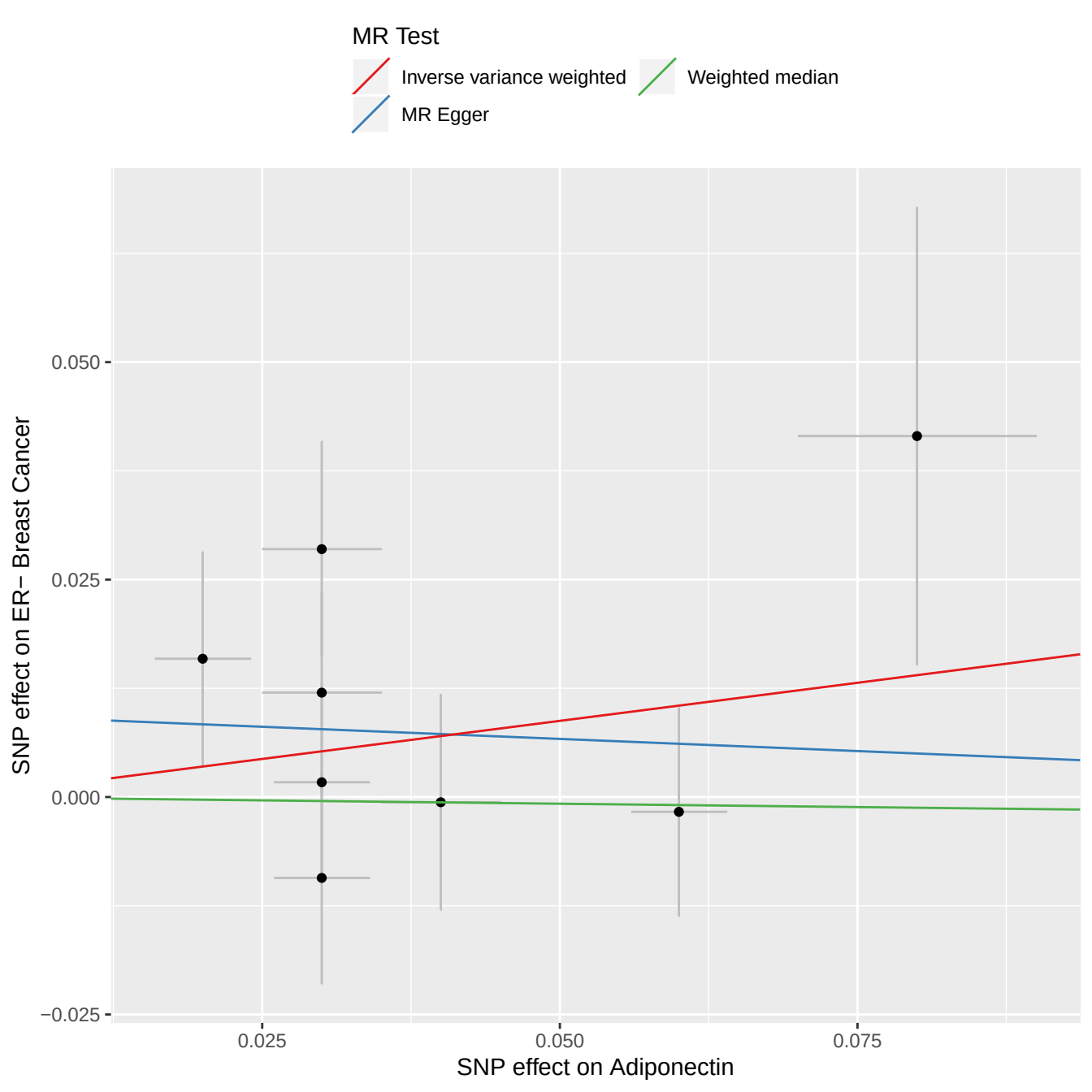
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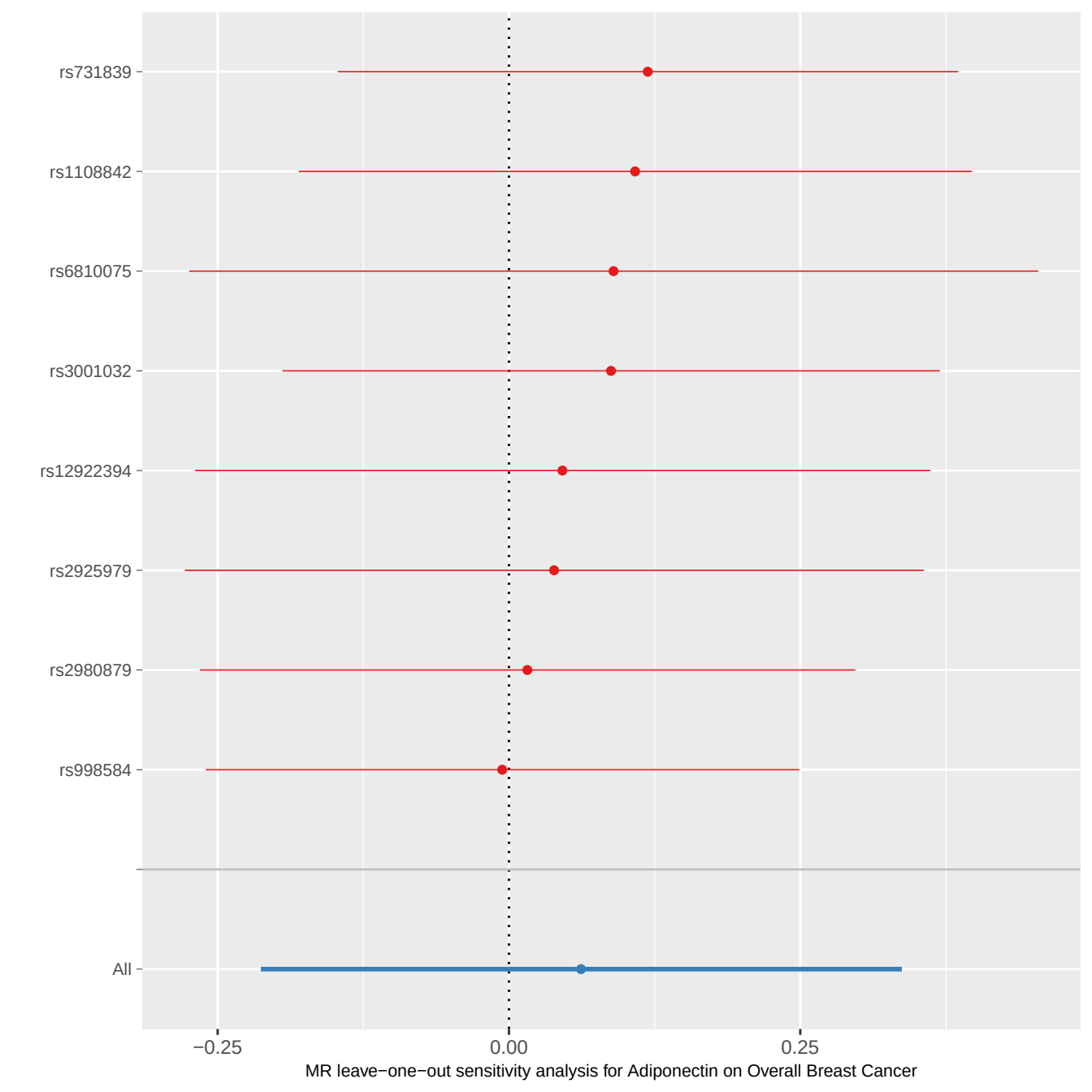
SNP effect on Adiponectin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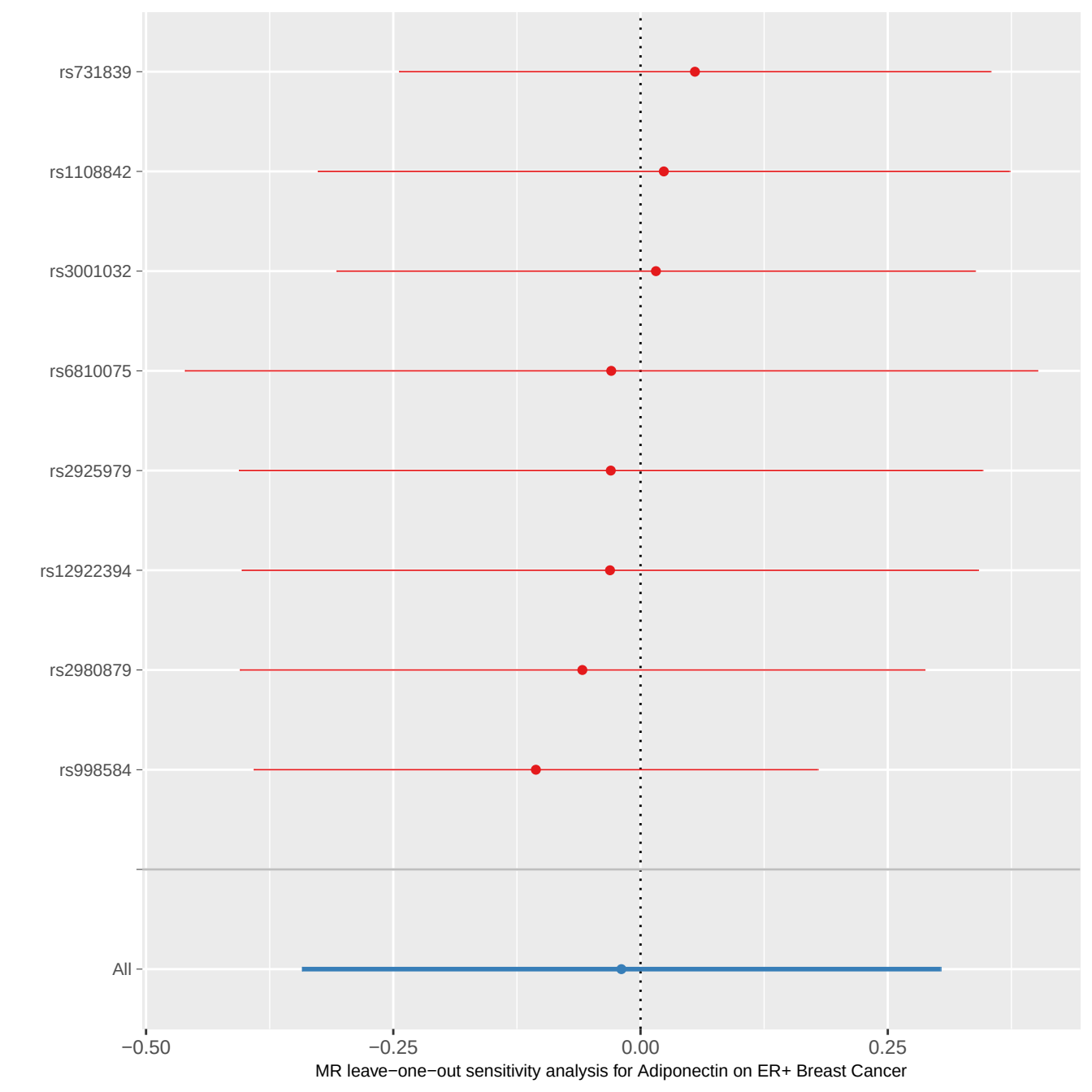
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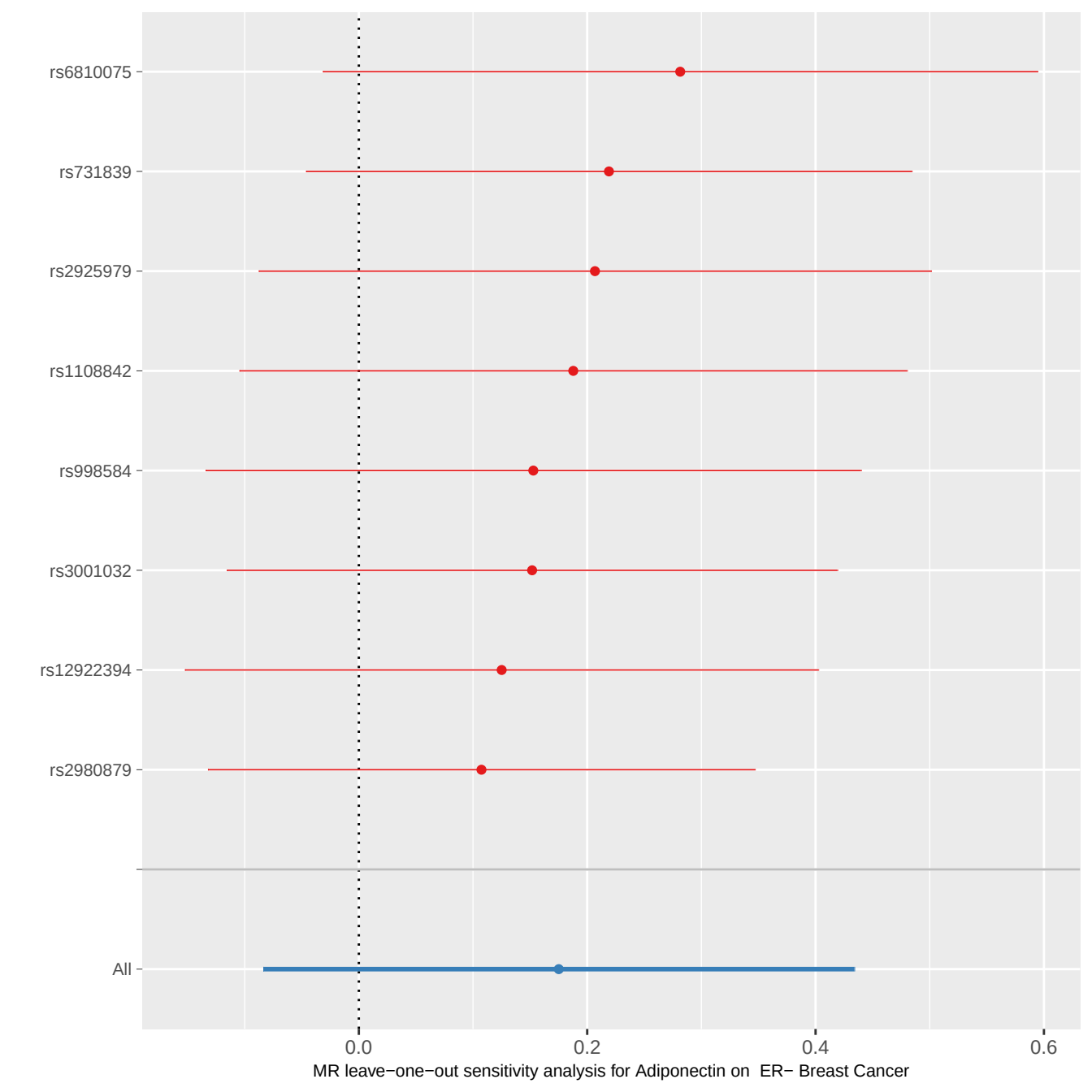
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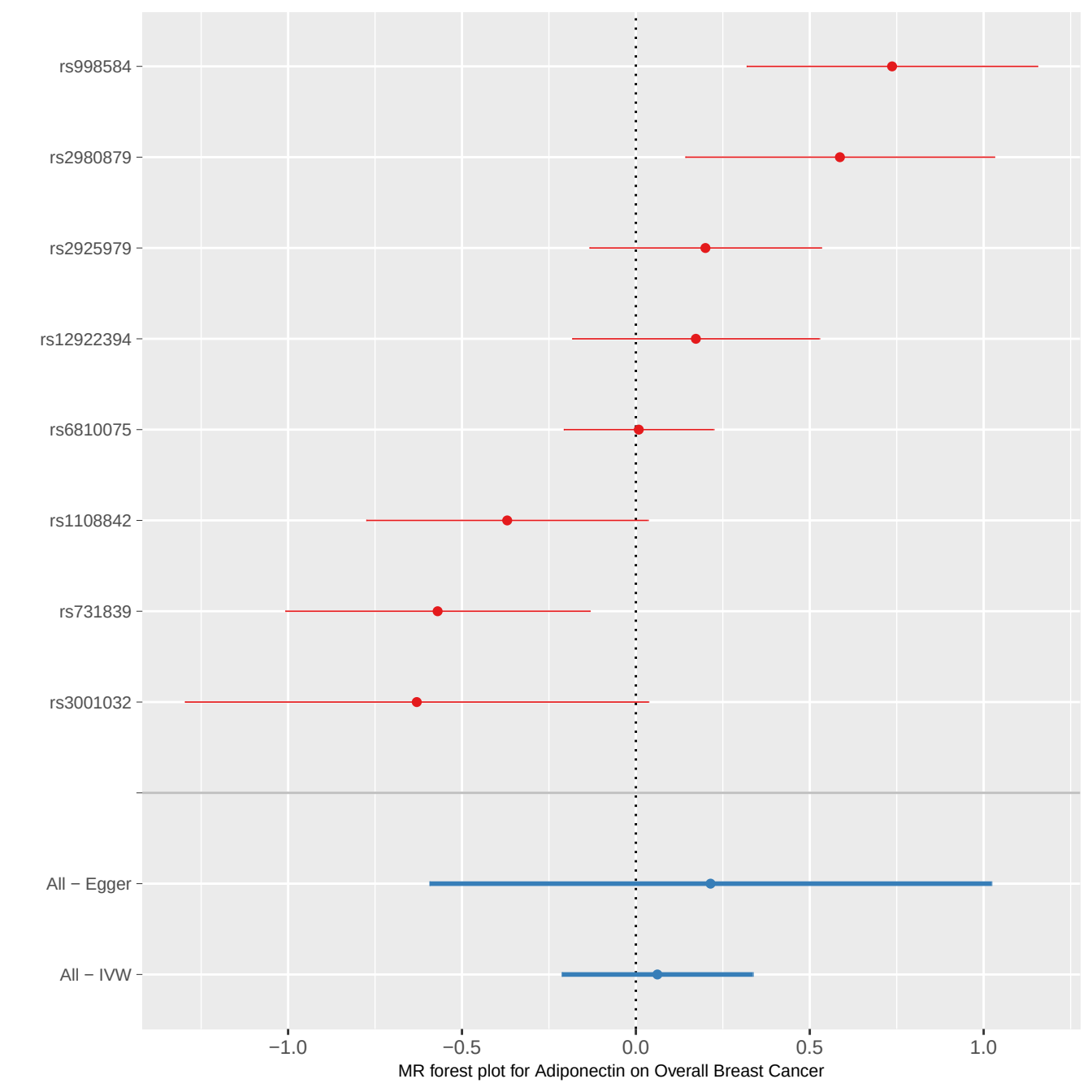
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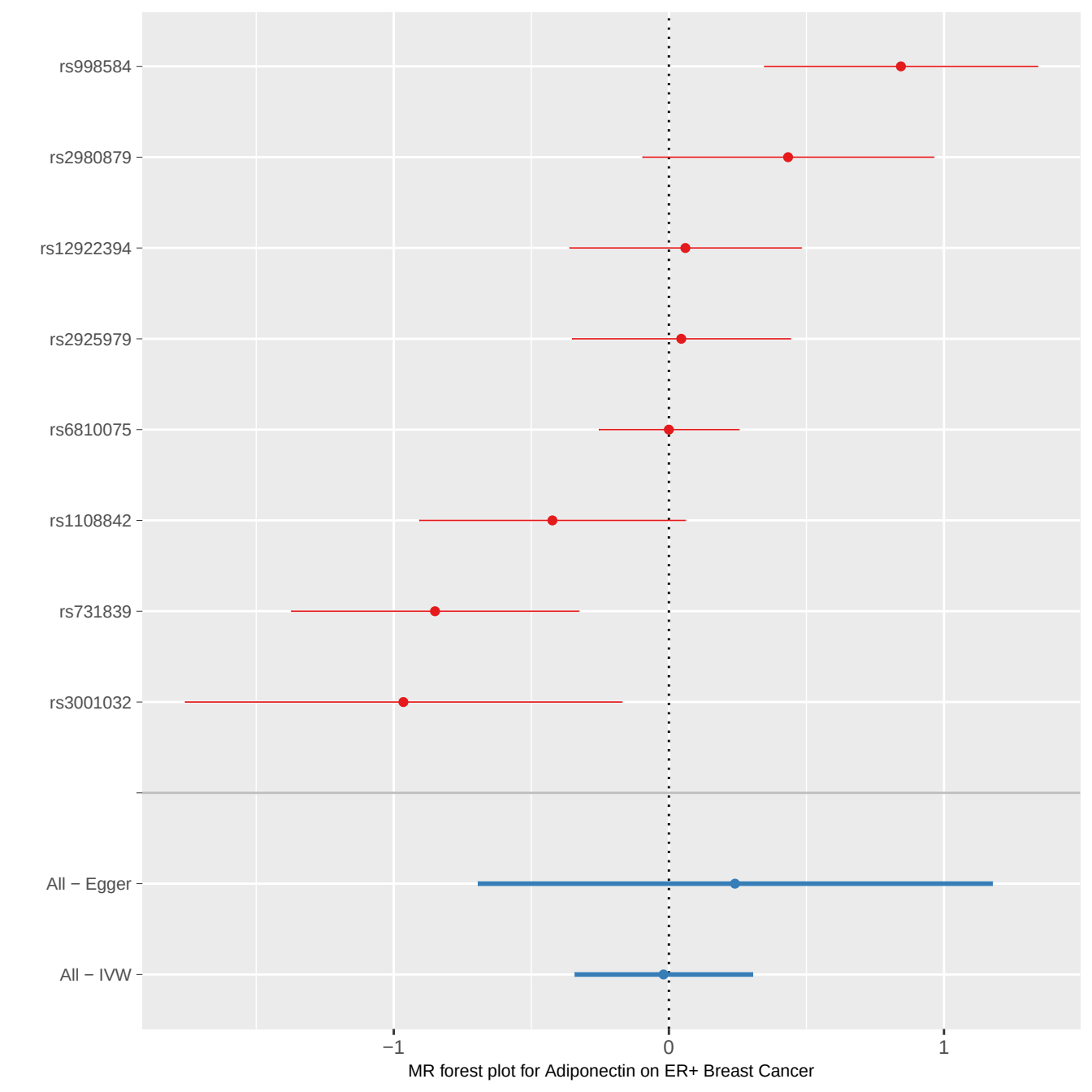
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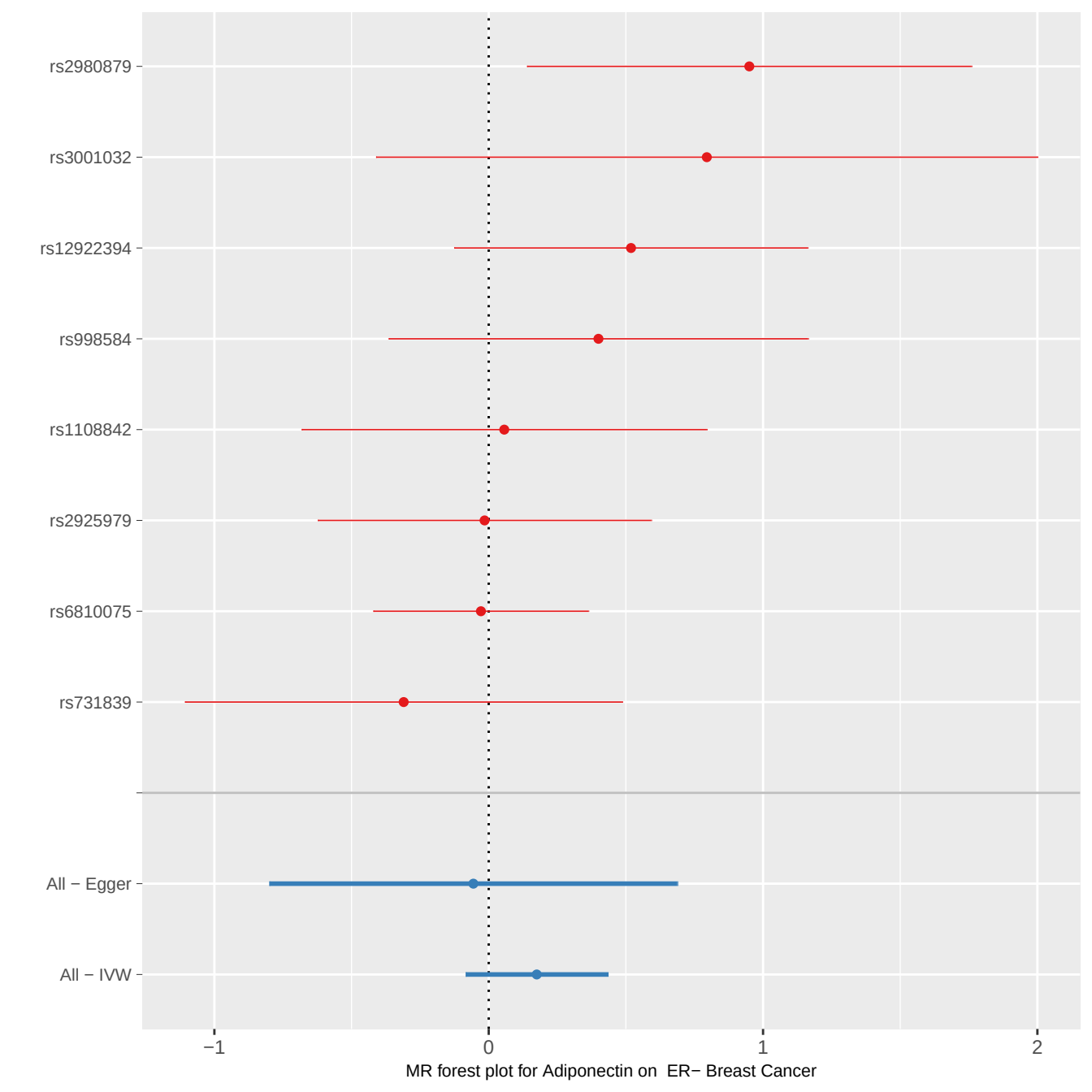
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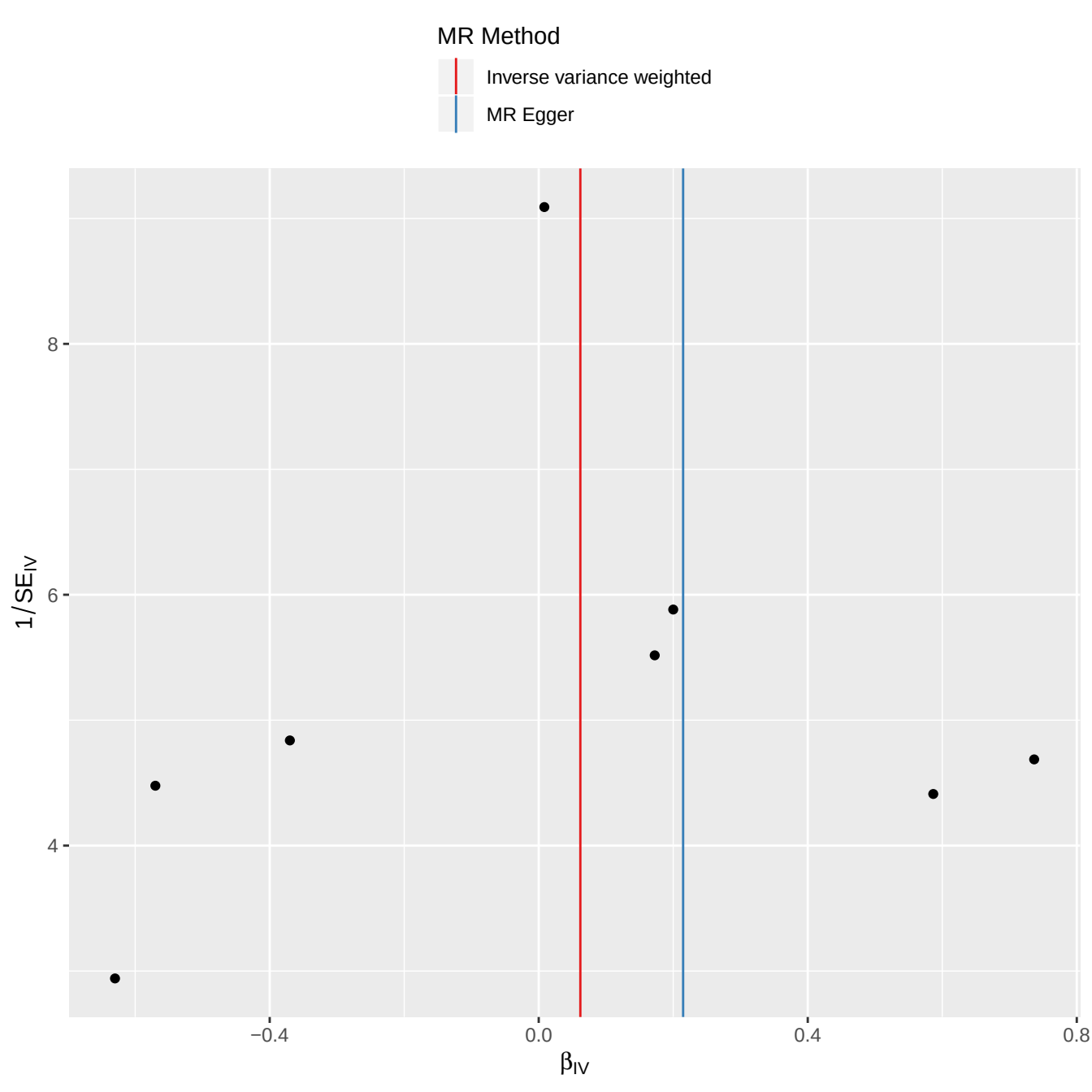
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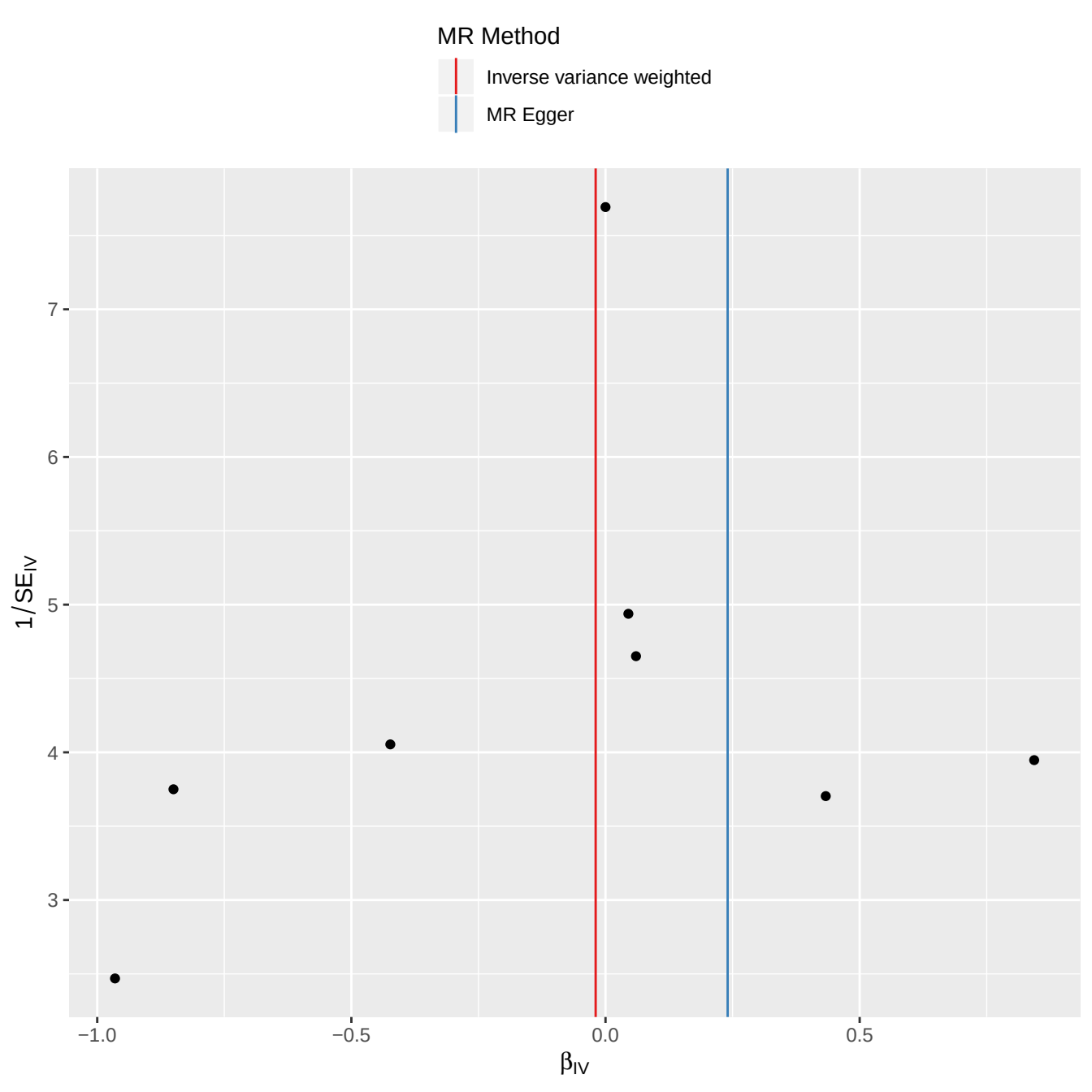
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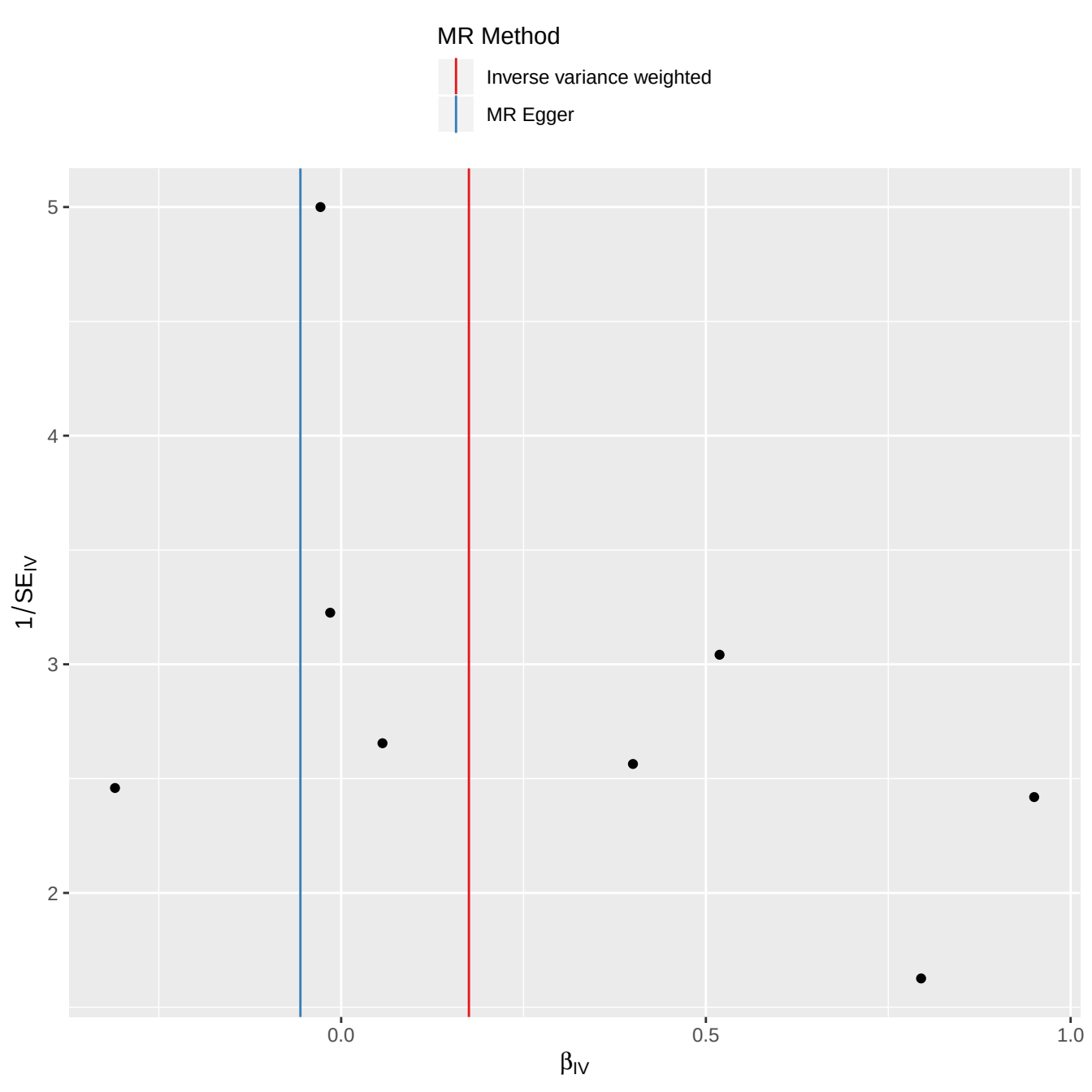
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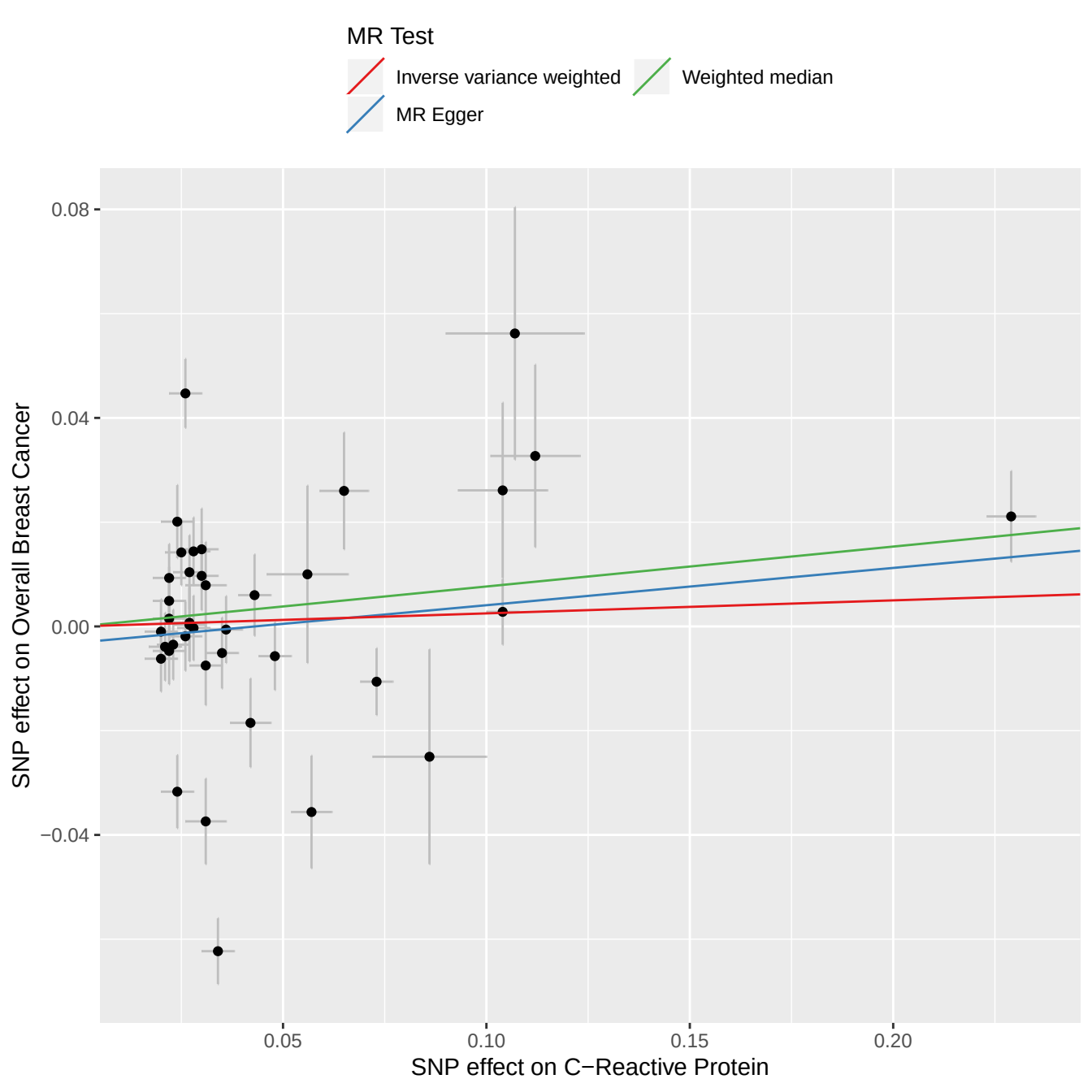
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SNP effect on Overall Breast Cancer
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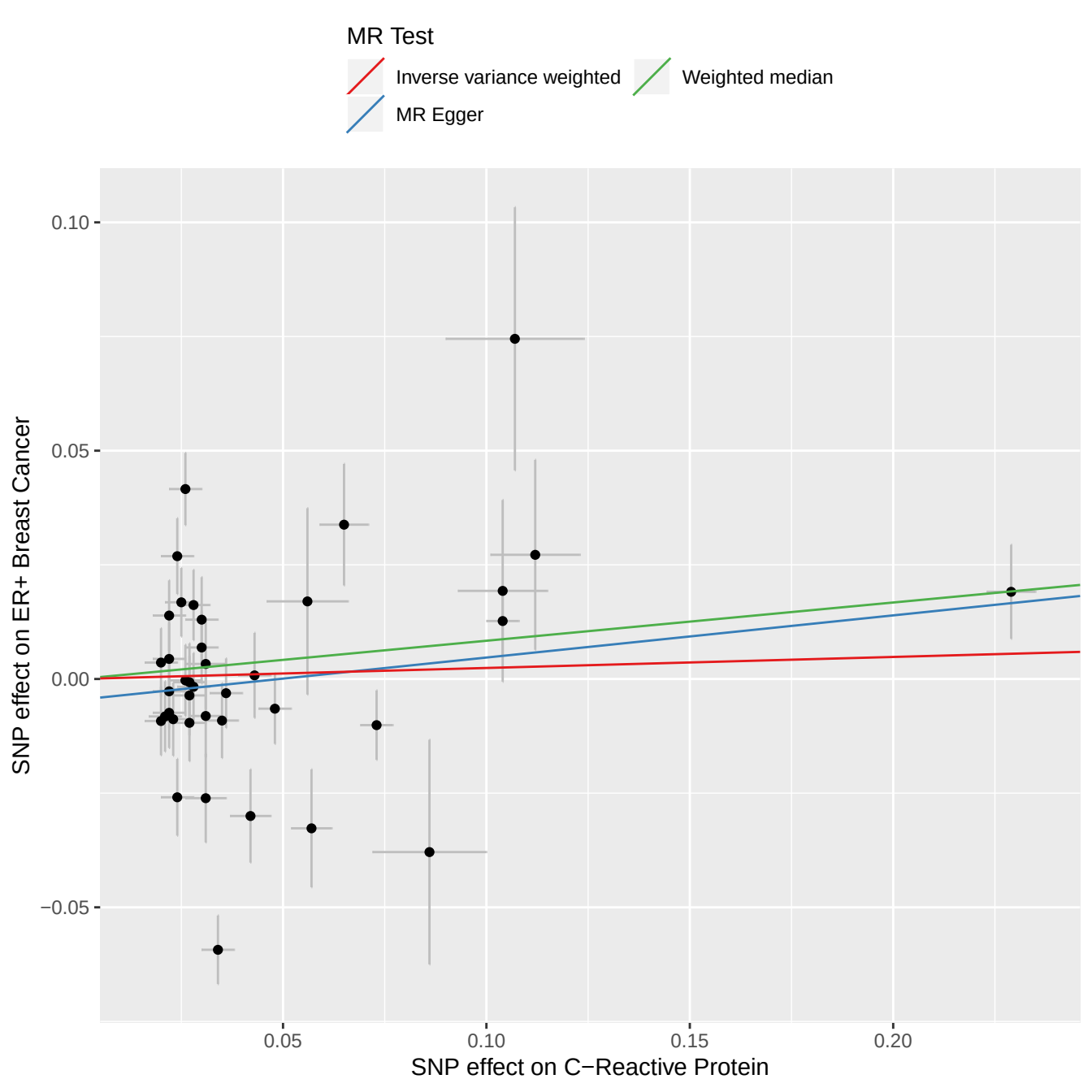
SNP effect on C−Reactive Protein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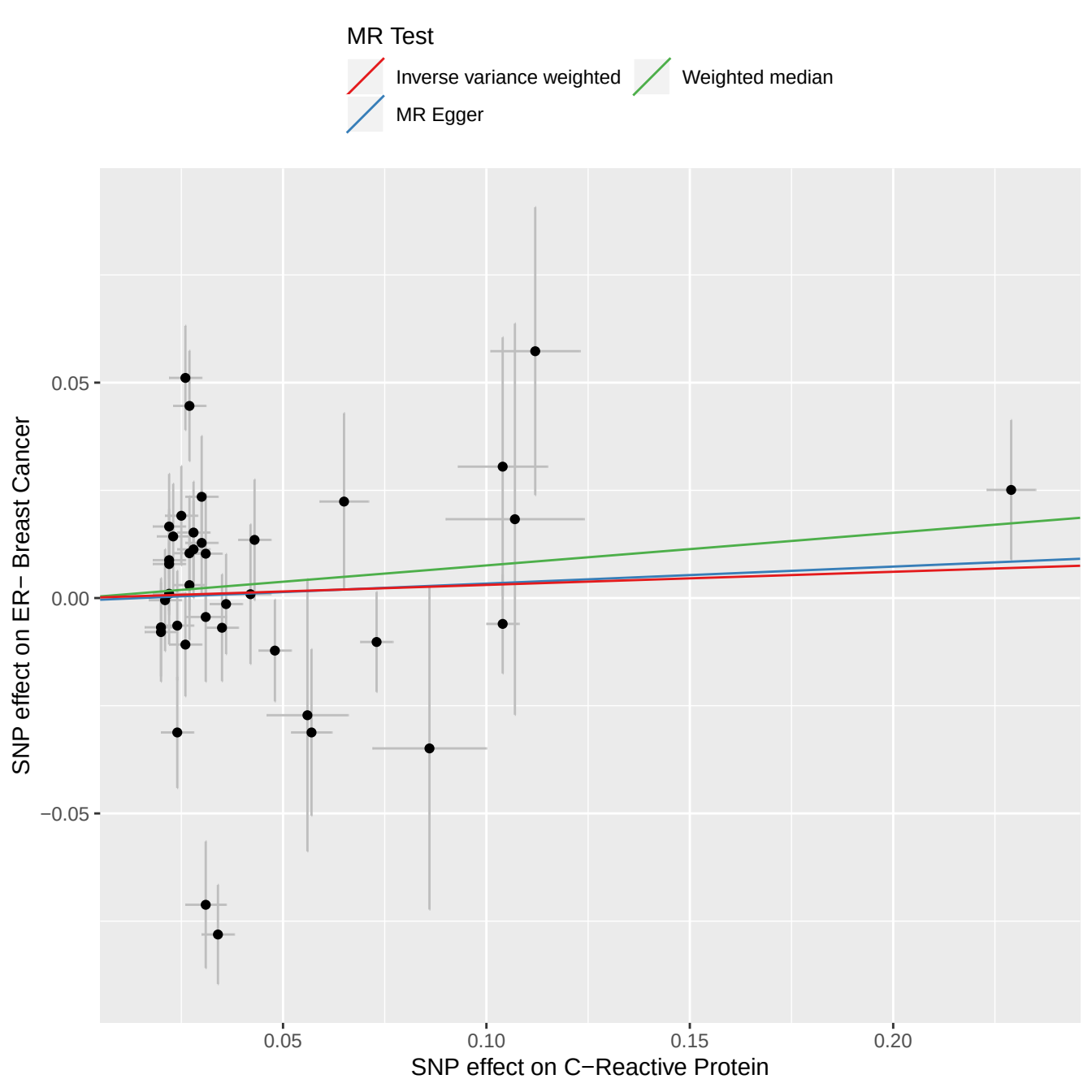
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Weighted median
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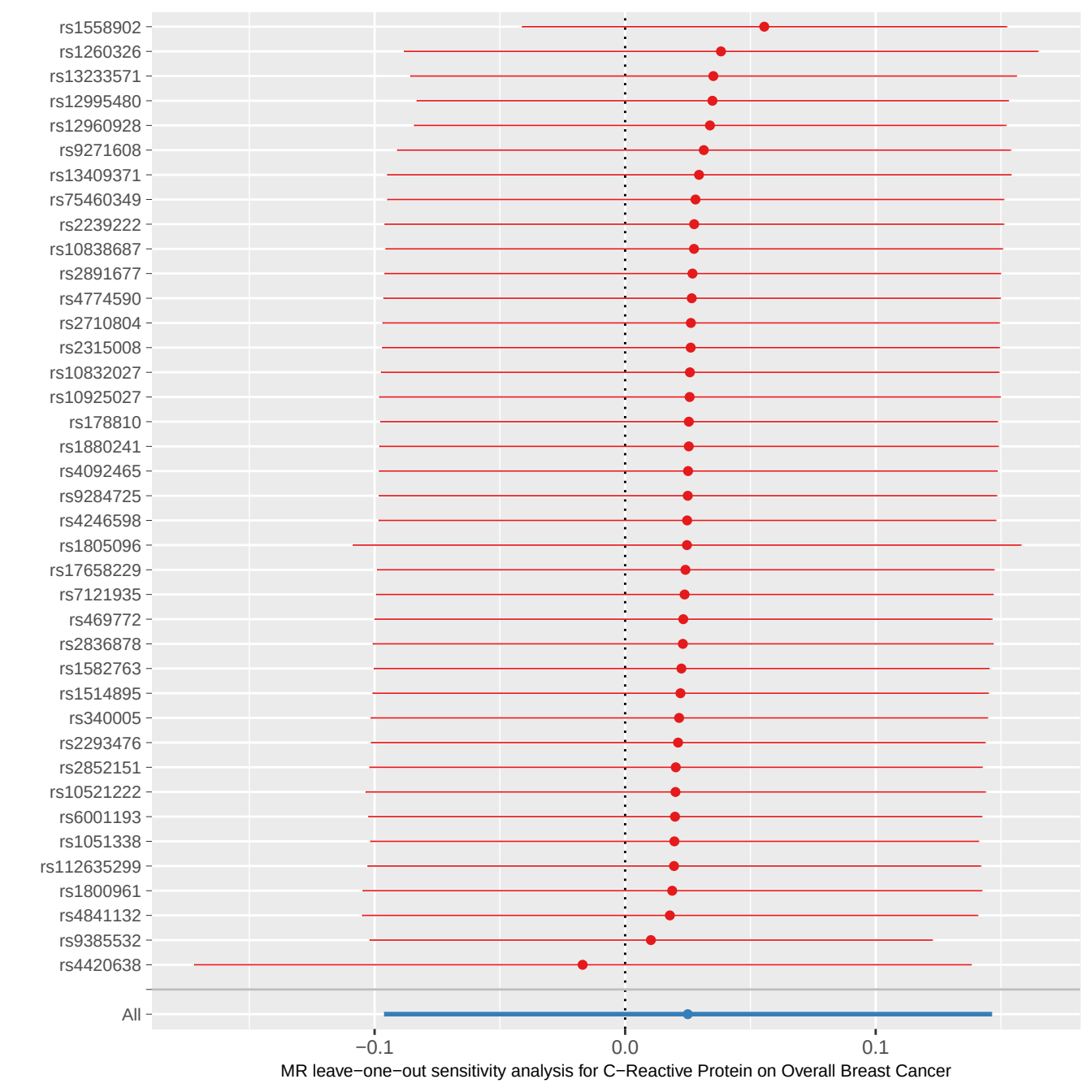
0.20
SNP effect on C−Reactive Protein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rs1051338
rs112635299
rs1800961
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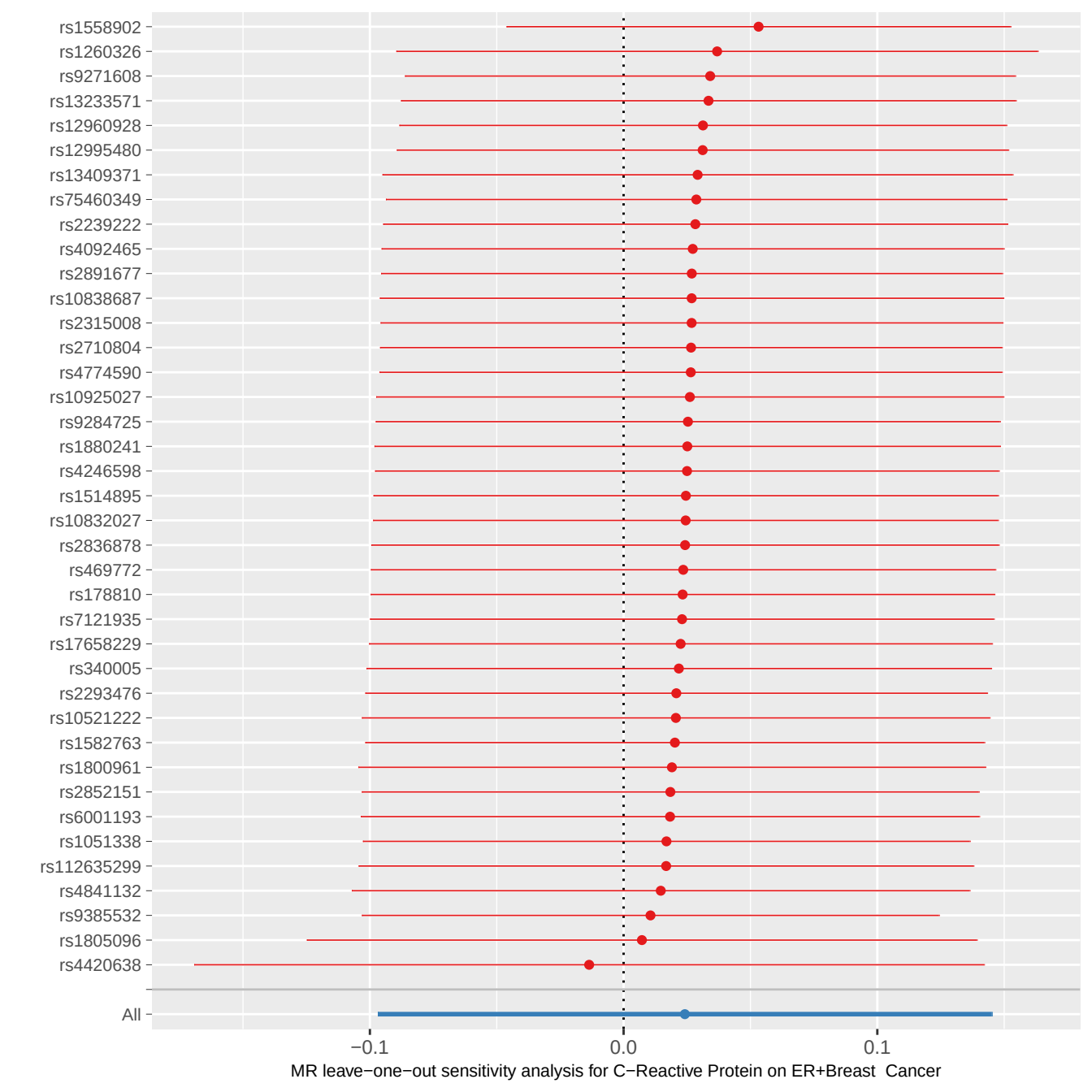
rs4420638
All
−0.1
0.0
0.1
MR leave−one−out sensitivity analysis for C−Reactive Protein on Overall Breast Cancer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rs1582763
rs1800961
rs2852151
rs6001193
rs1051338
rs112635299
rs4841132
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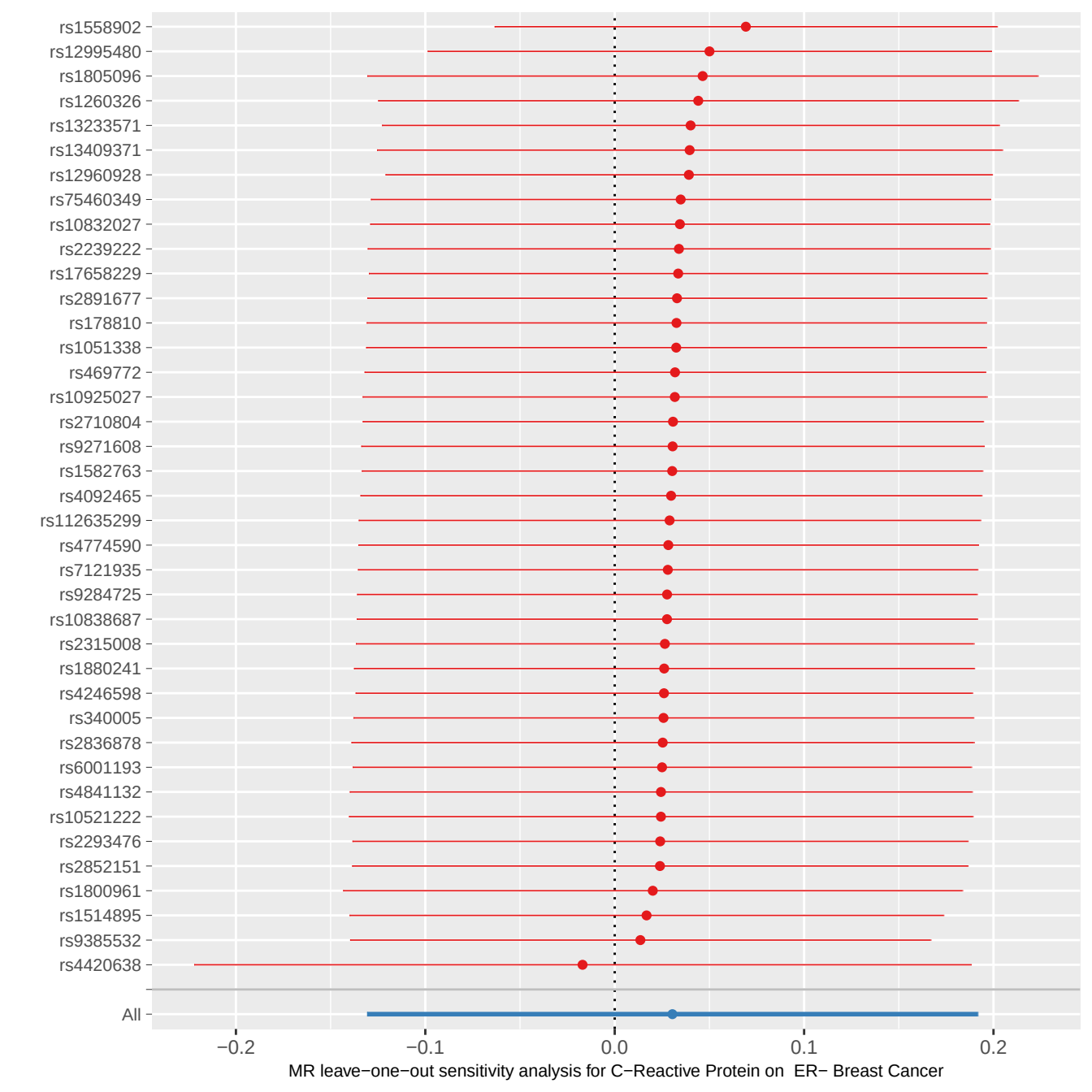
rs1805096
rs4420638
All
−0.1
0.0
0.1
MR leave−one−out sensitivity analysis for C−Reactive Protein on ER+Breast Cancer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rs2836878
rs6001193
rs4841132
rs10521222
rs2293476
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rs1800961
rs1514895
rs9385532
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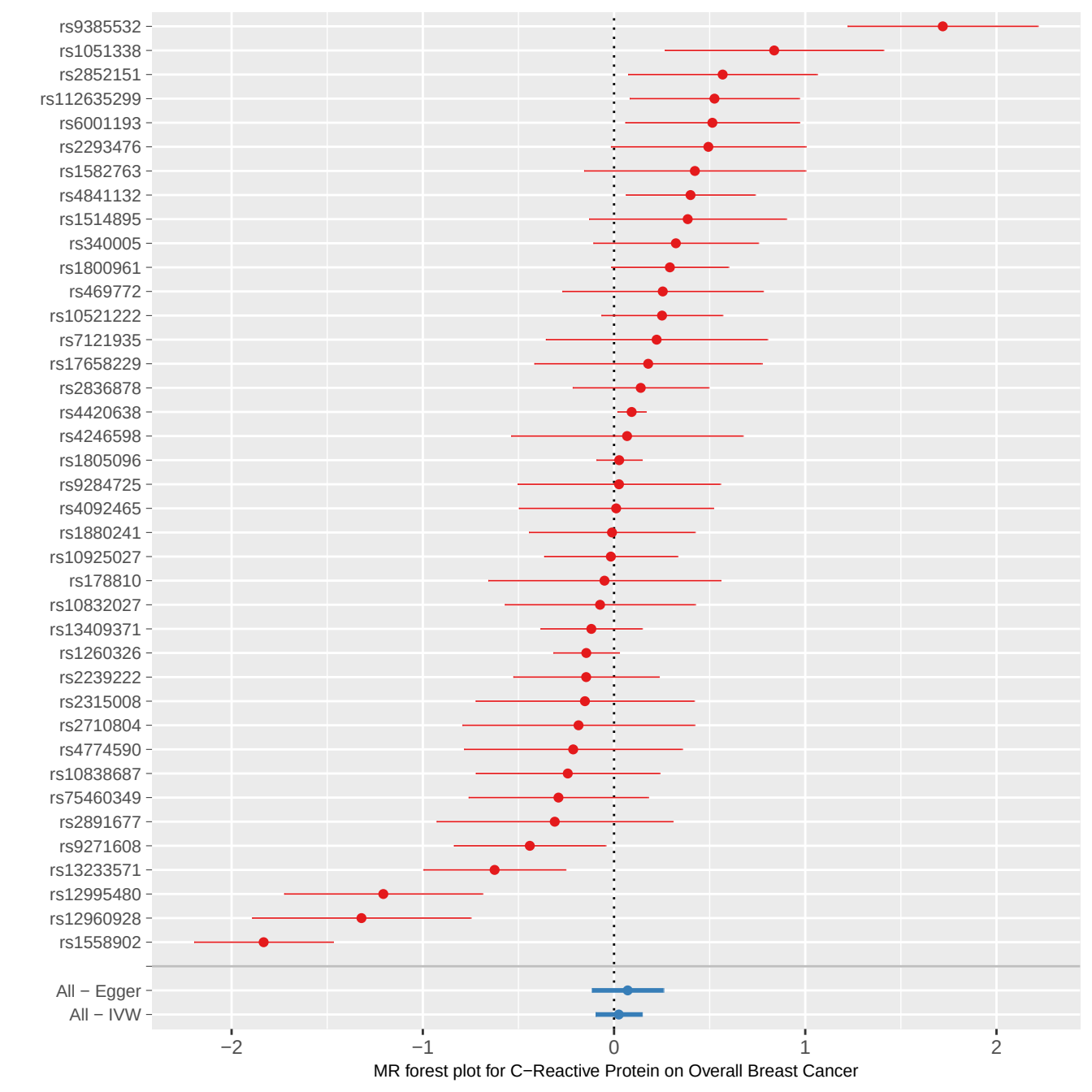
All
−0.2
−0.1
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for C−Reactive Protein on ER− Breast Cancer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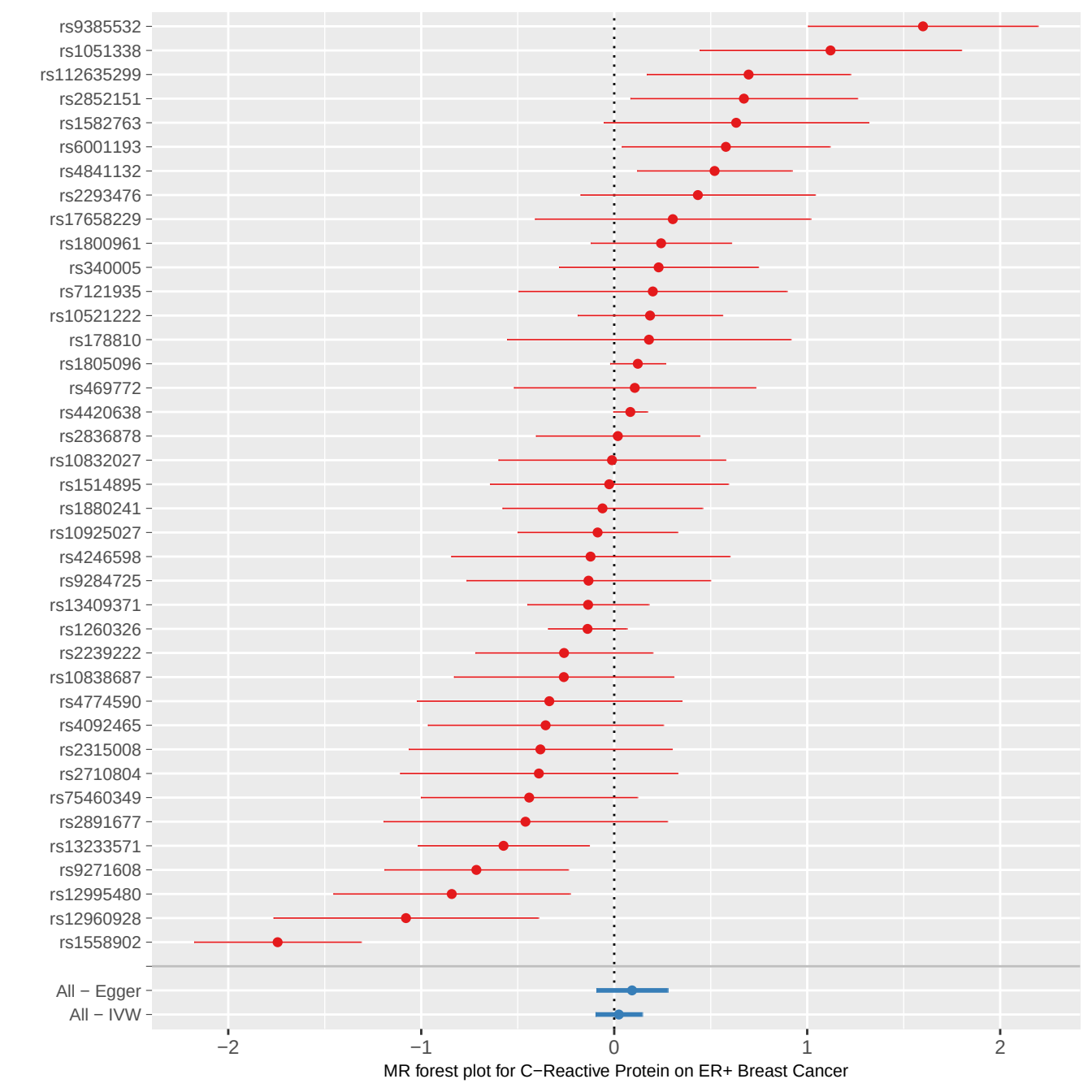
rs4774590
rs10838687
rs75460349
rs2891677
rs9271608
rs13233571
rs12995480
rs12960928
rs1558902
All − Egger
All − IVW
−2
−1
0
1
2
MR forest plot for C−Reactive Protein on Overall Breast Cancer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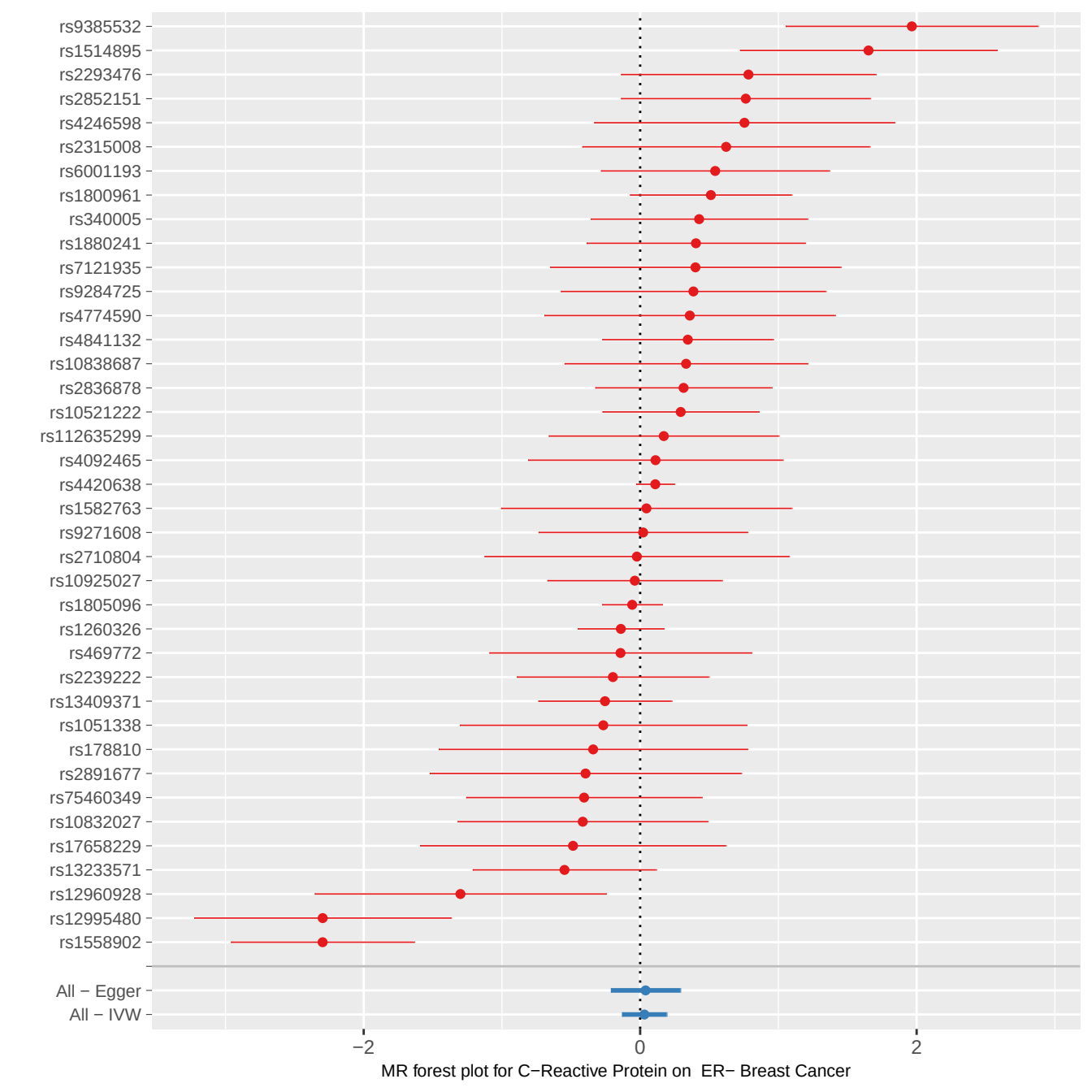
rs2315008
rs2710804
rs75460349
rs2891677
rs13233571
rs9271608
rs12995480
rs12960928
rs1558902
All − Egger
All − IVW
−2
−1
0
1
2
MR forest plot for C−Reactive Protein on ER+ Breast Cancer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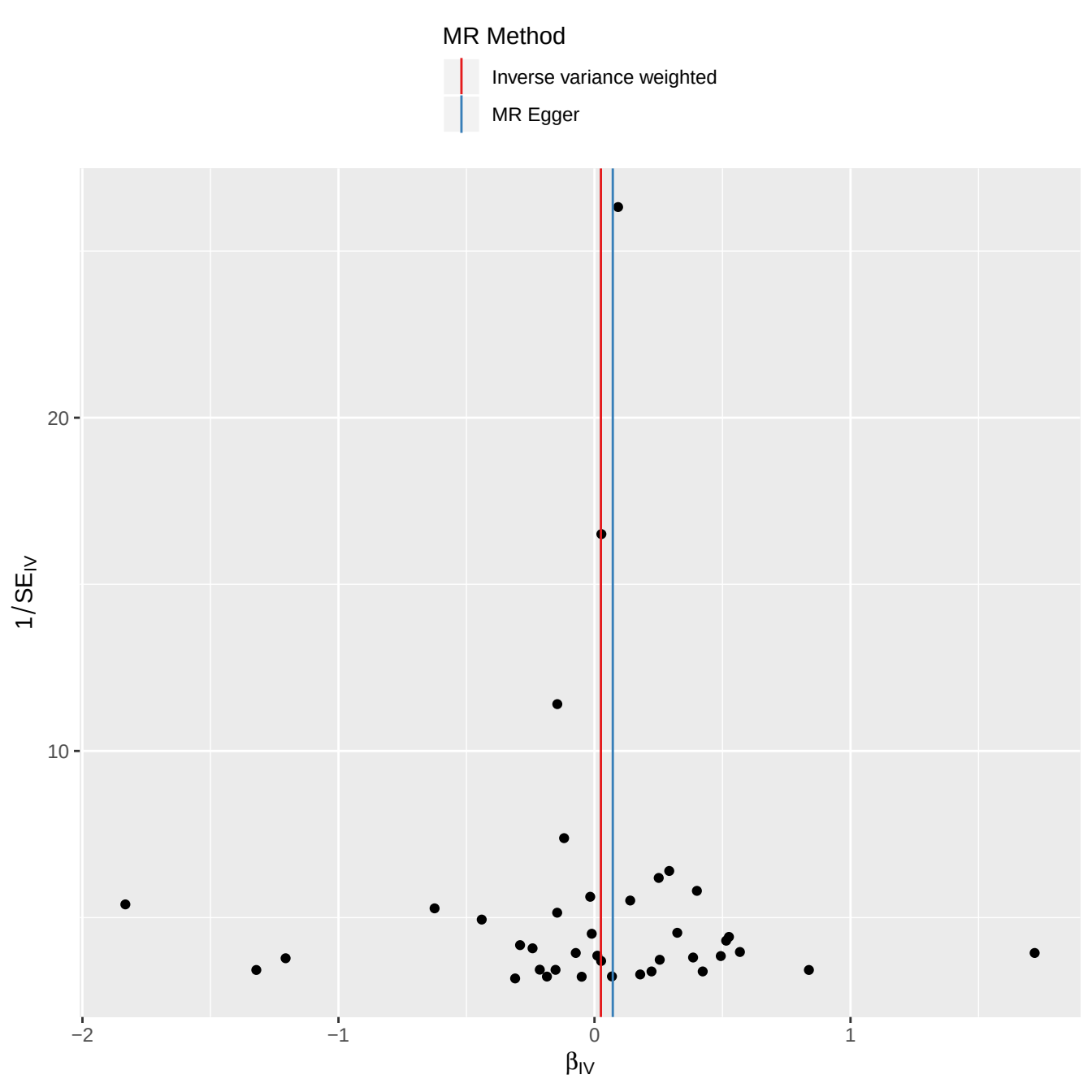
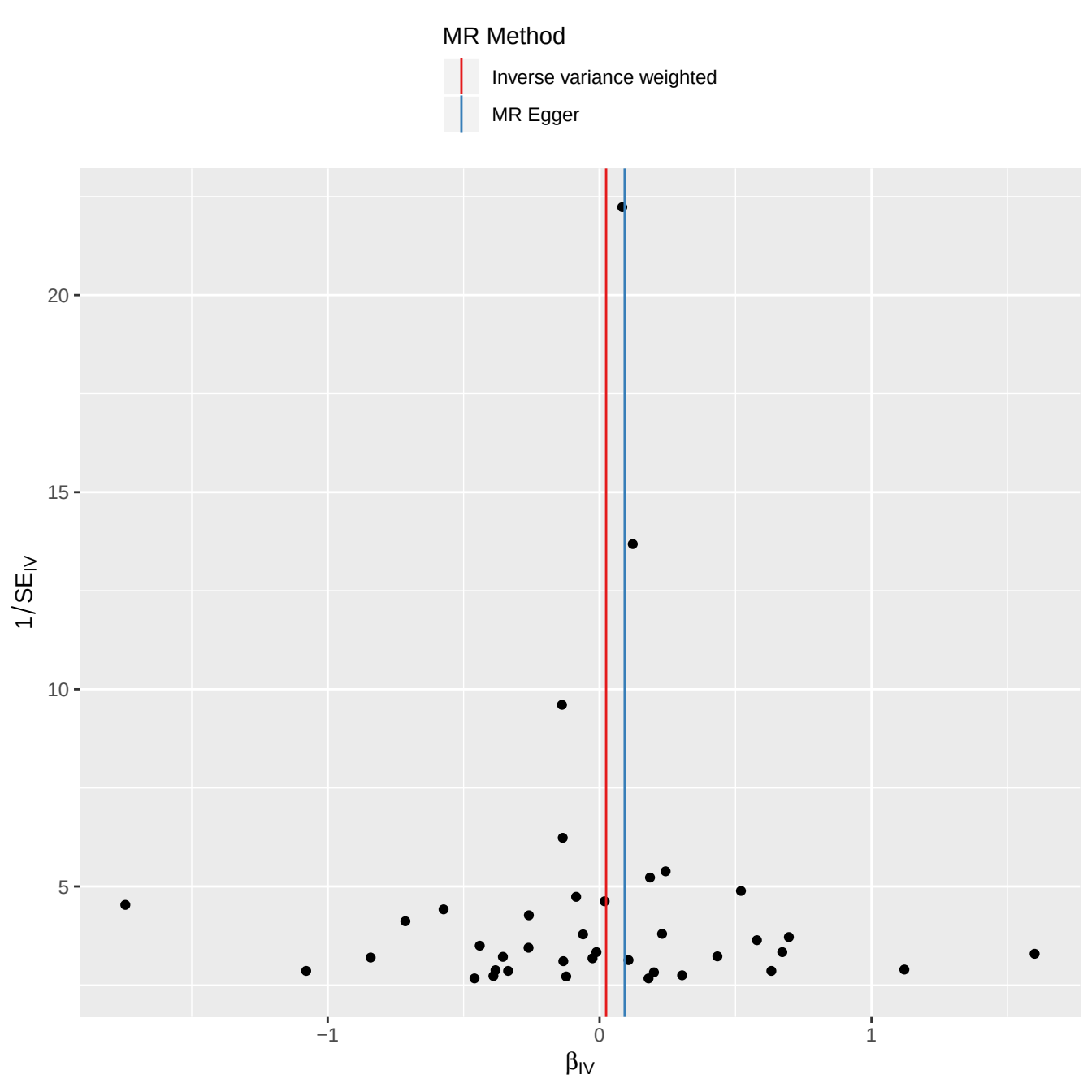
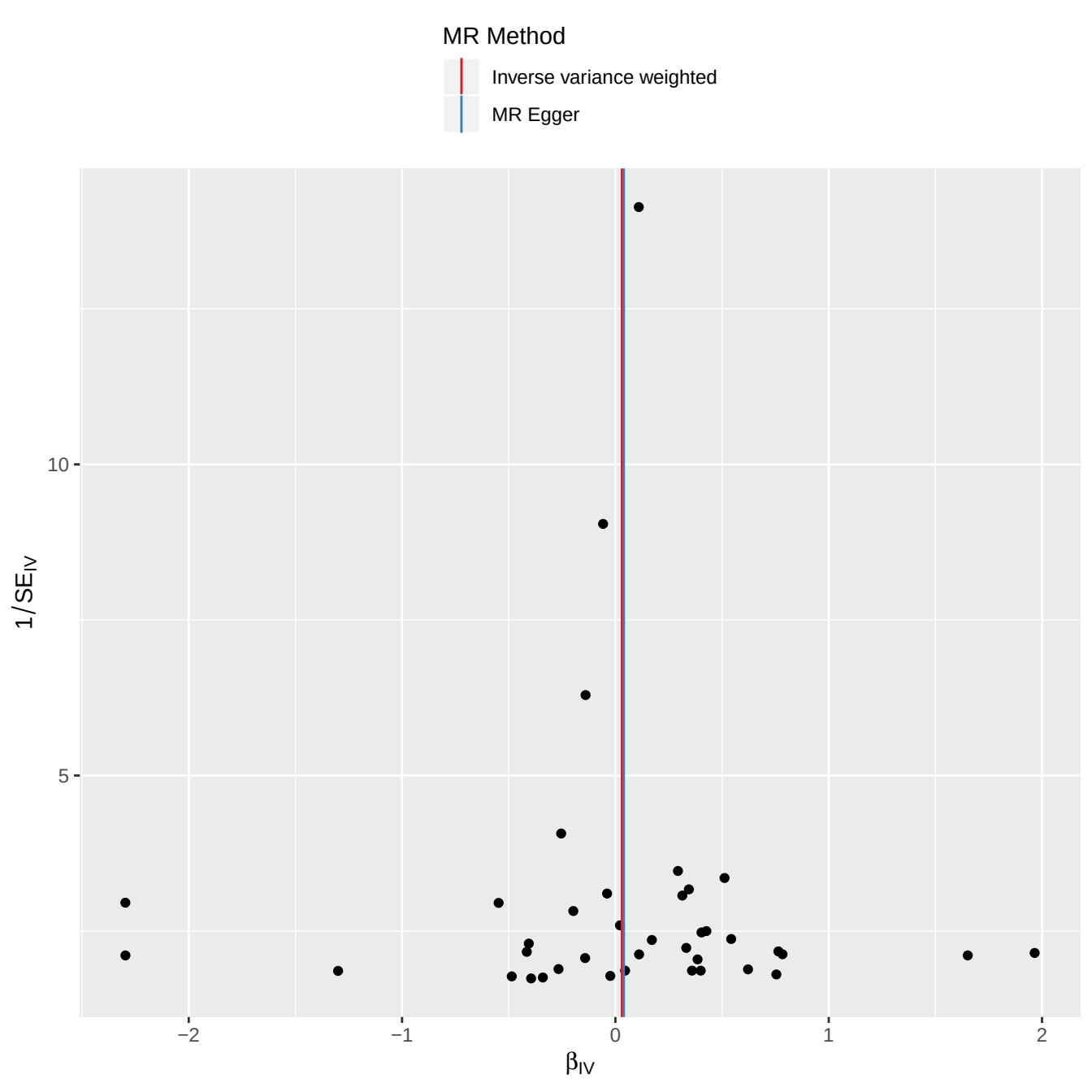
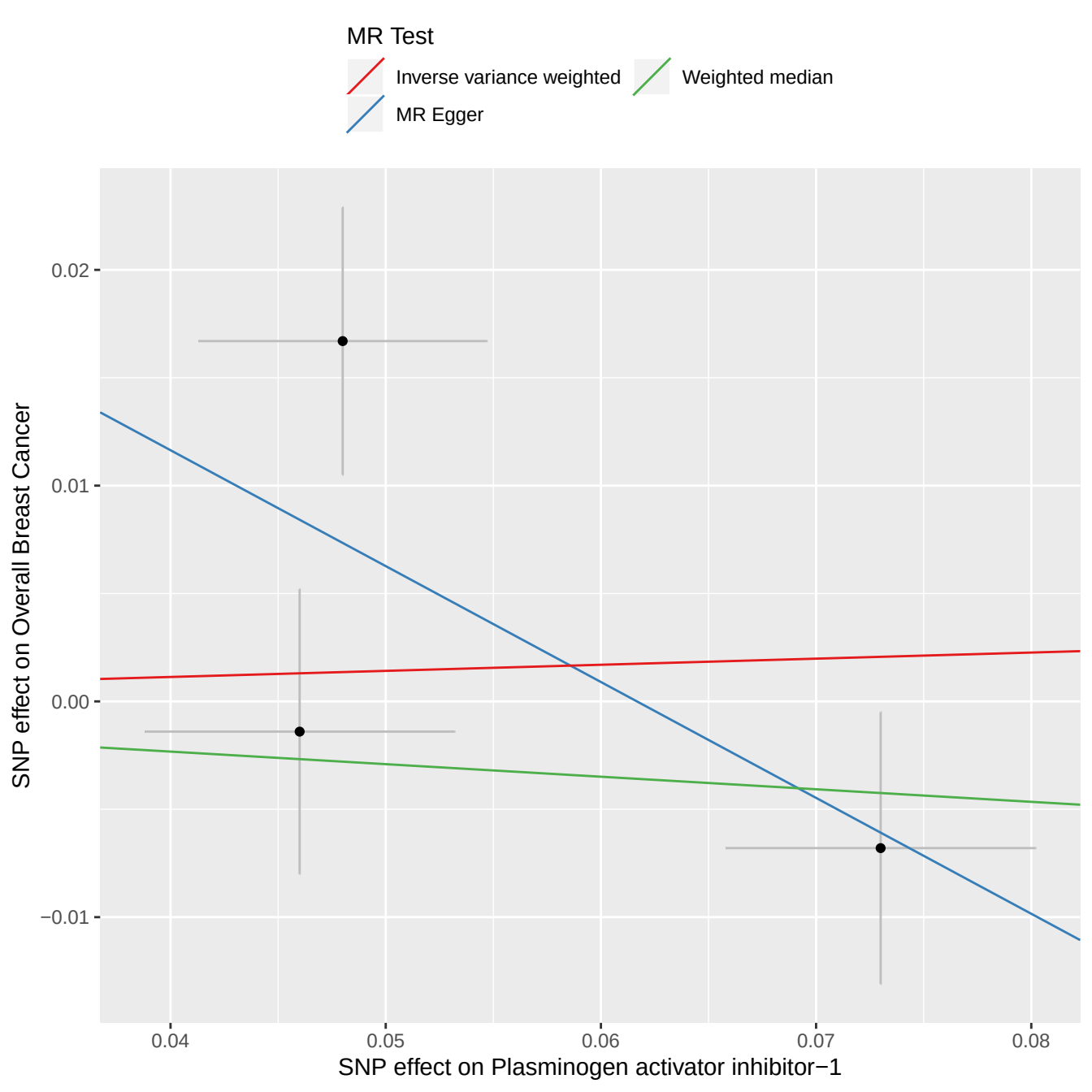
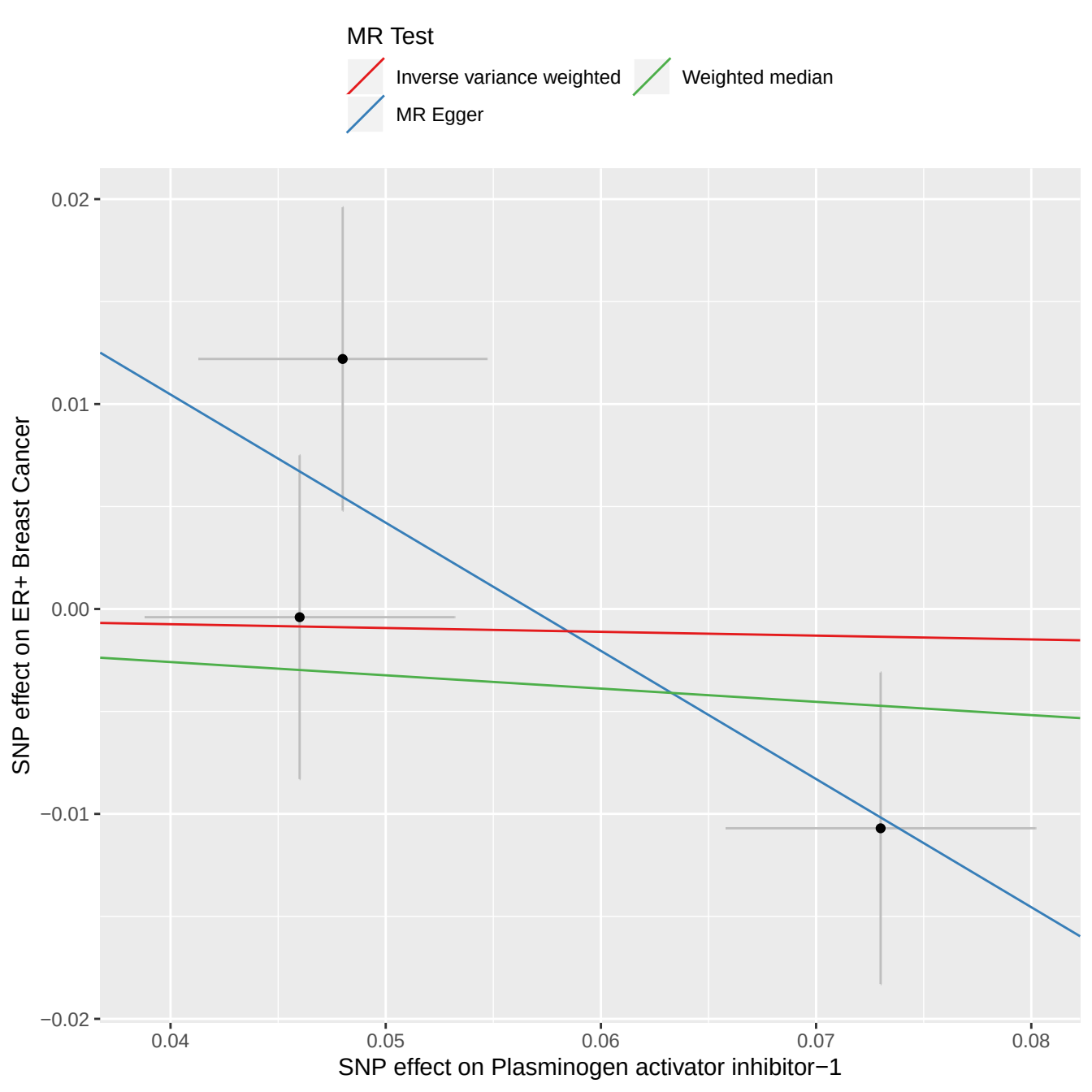
rs178810
rs2891677
rs75460349
rs10832027
rs17658229
rs13233571
rs12960928
rs12995480
rs1558902
All − Egger
All − IVW
−2
0
2
MR forest plot for C−Reactive Protein on ER− Breast Cancer

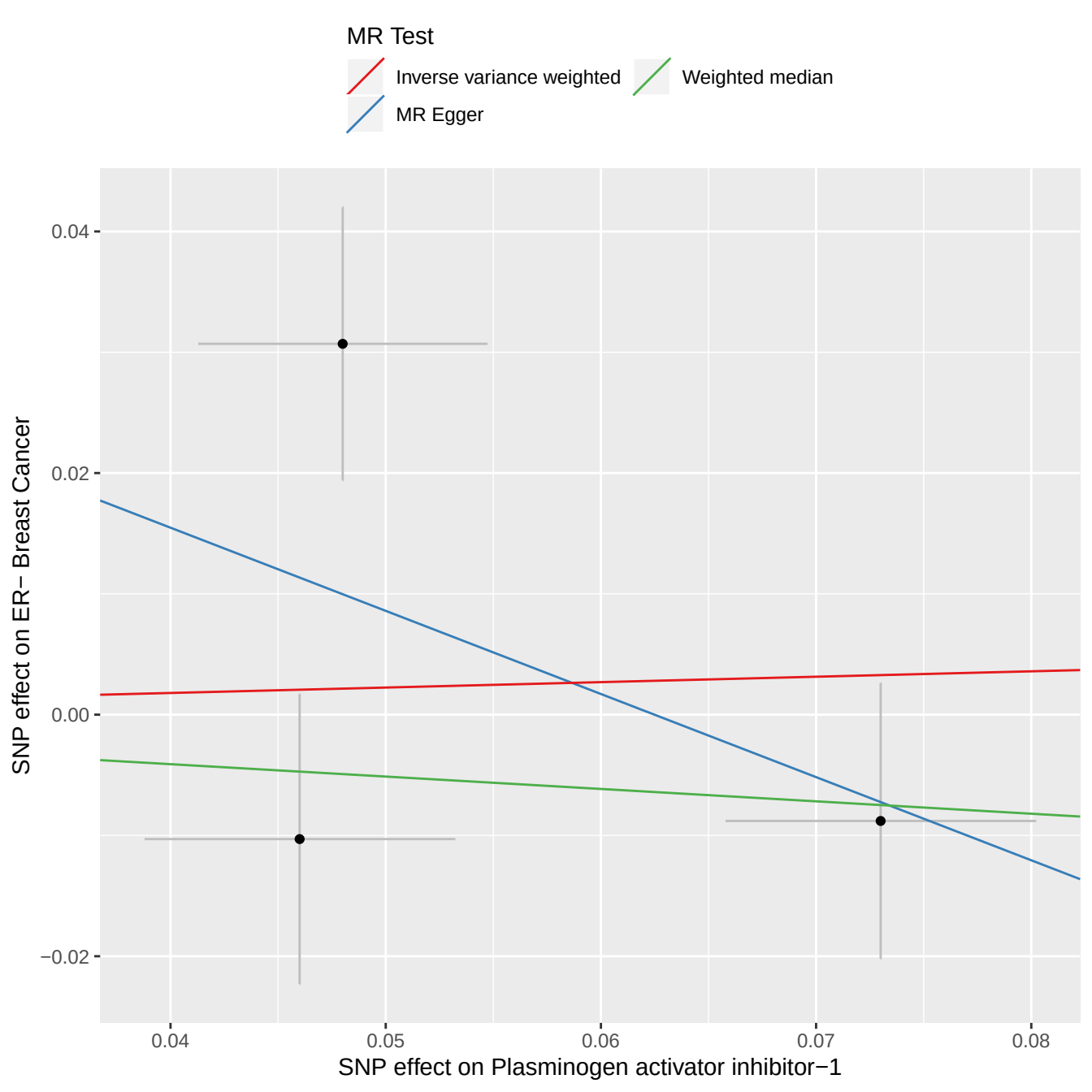

MR Method
Inverse variance weighted
MR Egger
20
10
1/SE_IV
−2
−1
0
1
β_IV

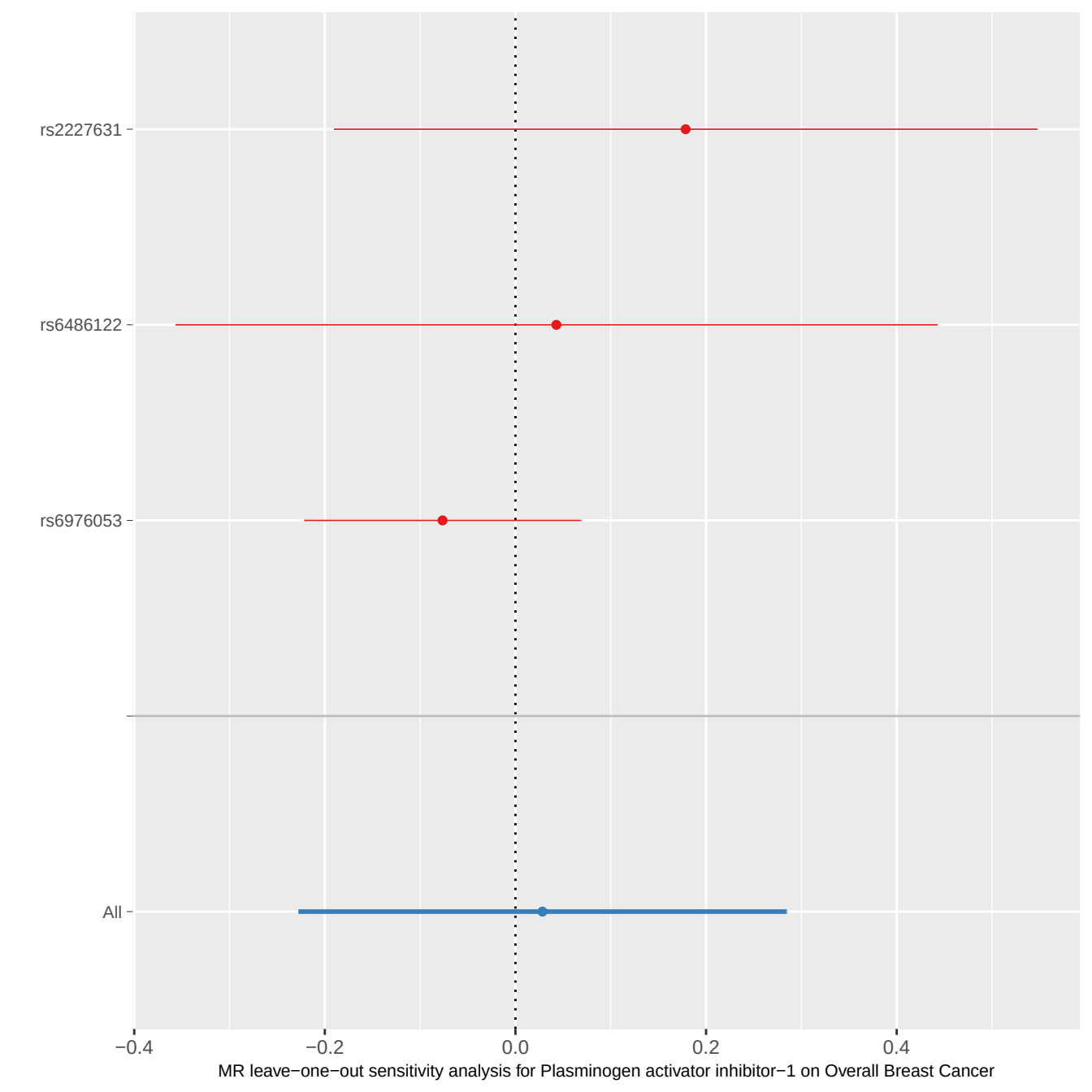

MR Method
Inverse variance weighted
MR Egger
20
15
10
5
1/SE_IV
−1
0
1
β_IV

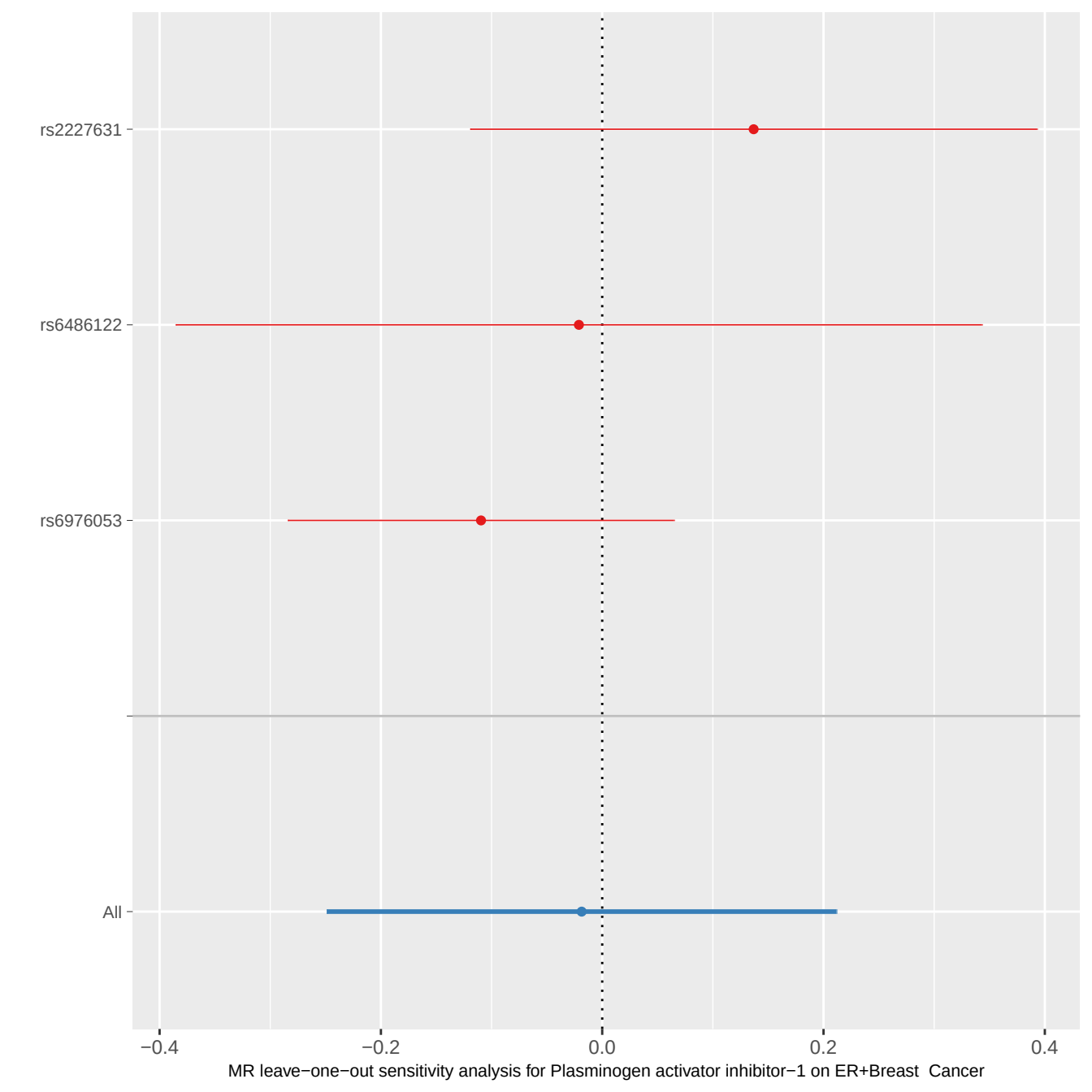

MR Method
Inverse variance weighted
MR Egger
10
5
1/SE_IV
−2
−1
0
1
2
β_IV

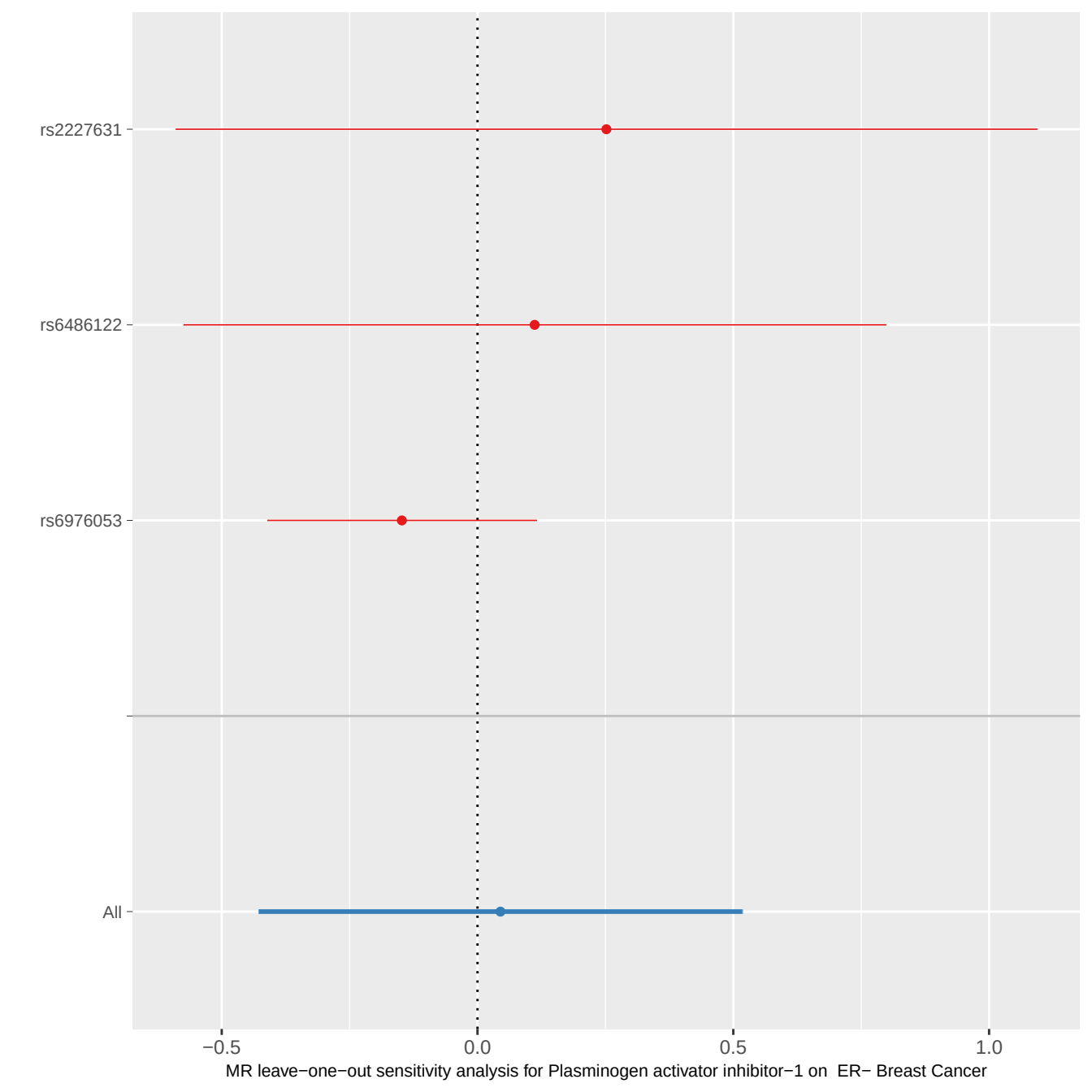

MR Test
Inverse variance weighted
Weighted median
MR Egger
SNP effect on Overall Breast Cancer
0.02
0.01
0.00
−0.01
0.04
0.05
0.06
0.07
0.08
SNP effect on Plasminogen activator inhibitor−1

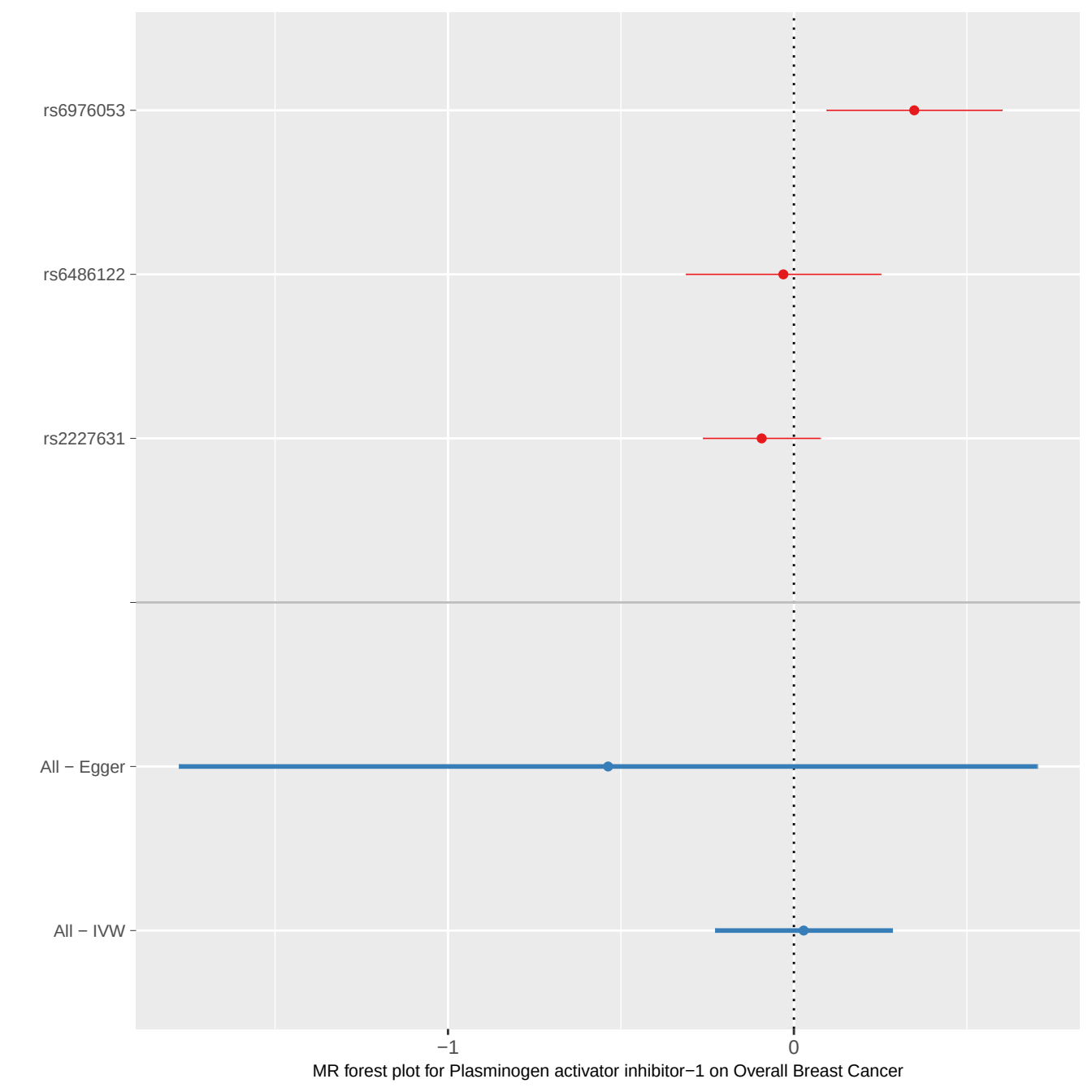

MR Test
Inverse variance weighted
Weighted median
MR Egger
0.02
0.01
0.00
−0.01
−0.02
SNP effect on ER+ Breast Cancer
0.04
0.05
0.06
0.07
0.08
SNP effect on Plasminogen activator inhibitor−1

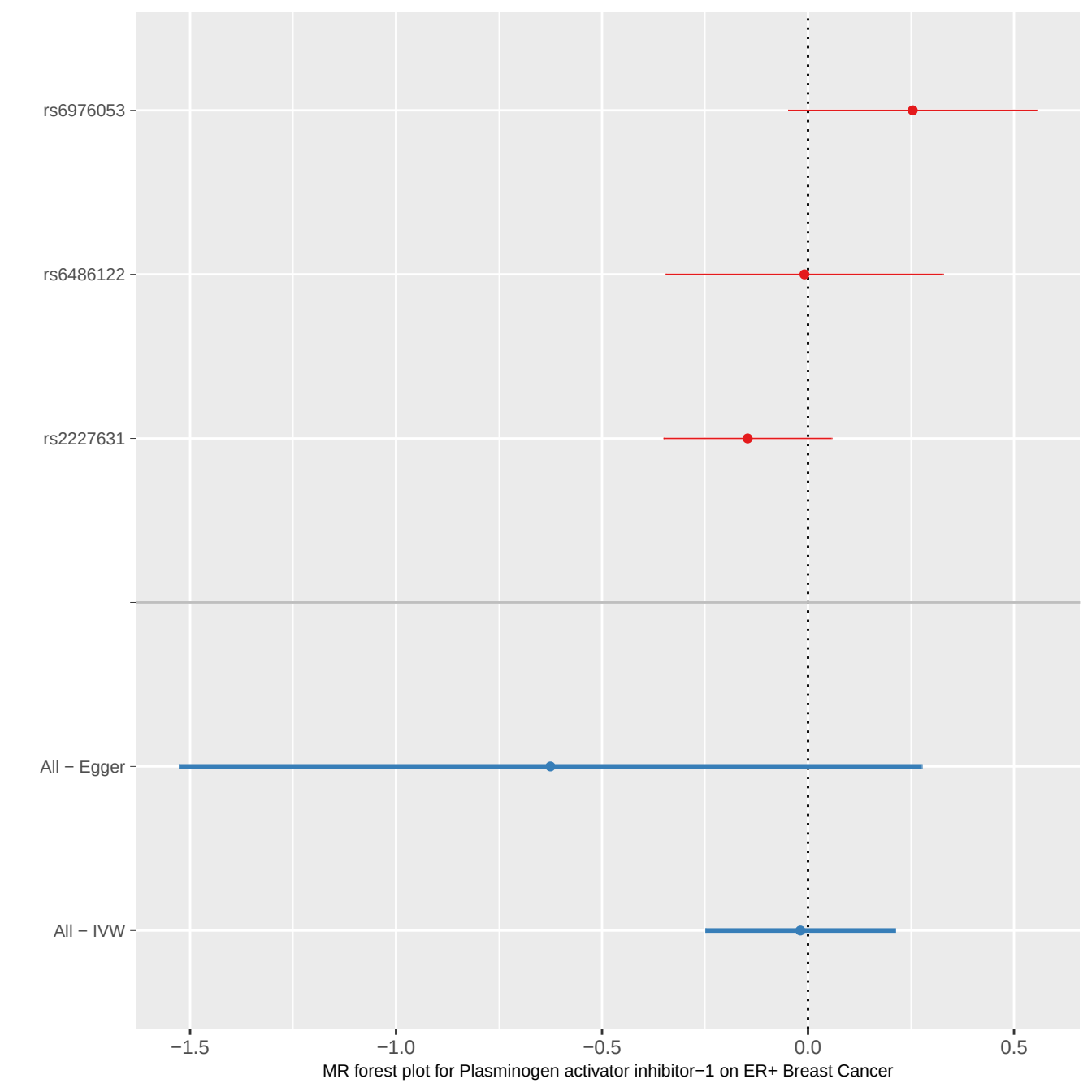

MR Test
Inverse variance weighted
Weighted median
MR Egger
SNP effect on ER− Breast Cancer
0.04
0.02
0.00
−0.02
0.04
0.05
0.06
0.07
0.08
SNP effect on Plasminogen activator inhibitor−1

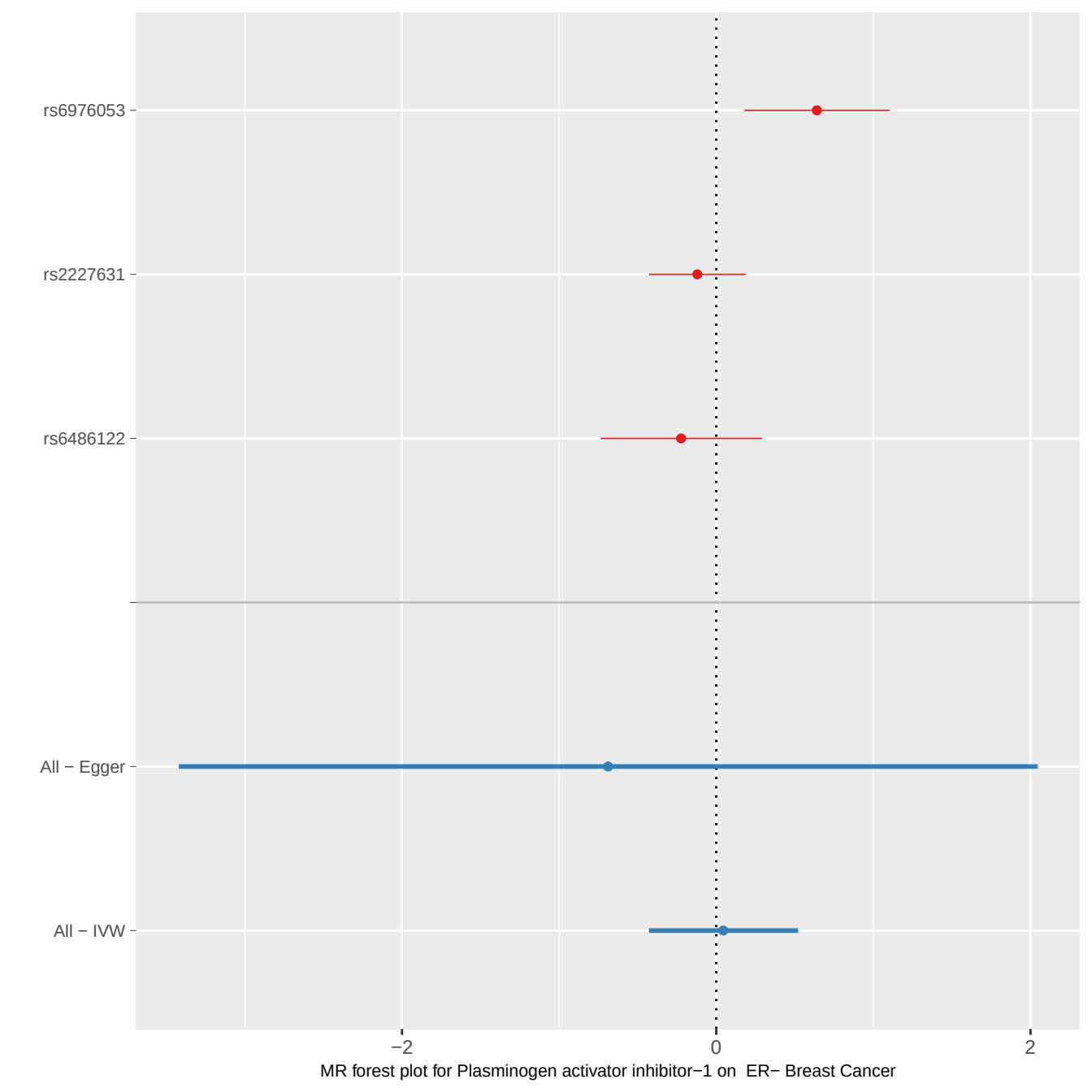

rs2227631
rs6486122
rs6976053
All
−0.4
−0.2
0.0
0.2
0.4
MR leave−one−out sensitivity analysis for Plasminogen activator inhibitor−1 on Overall Breast Cancer

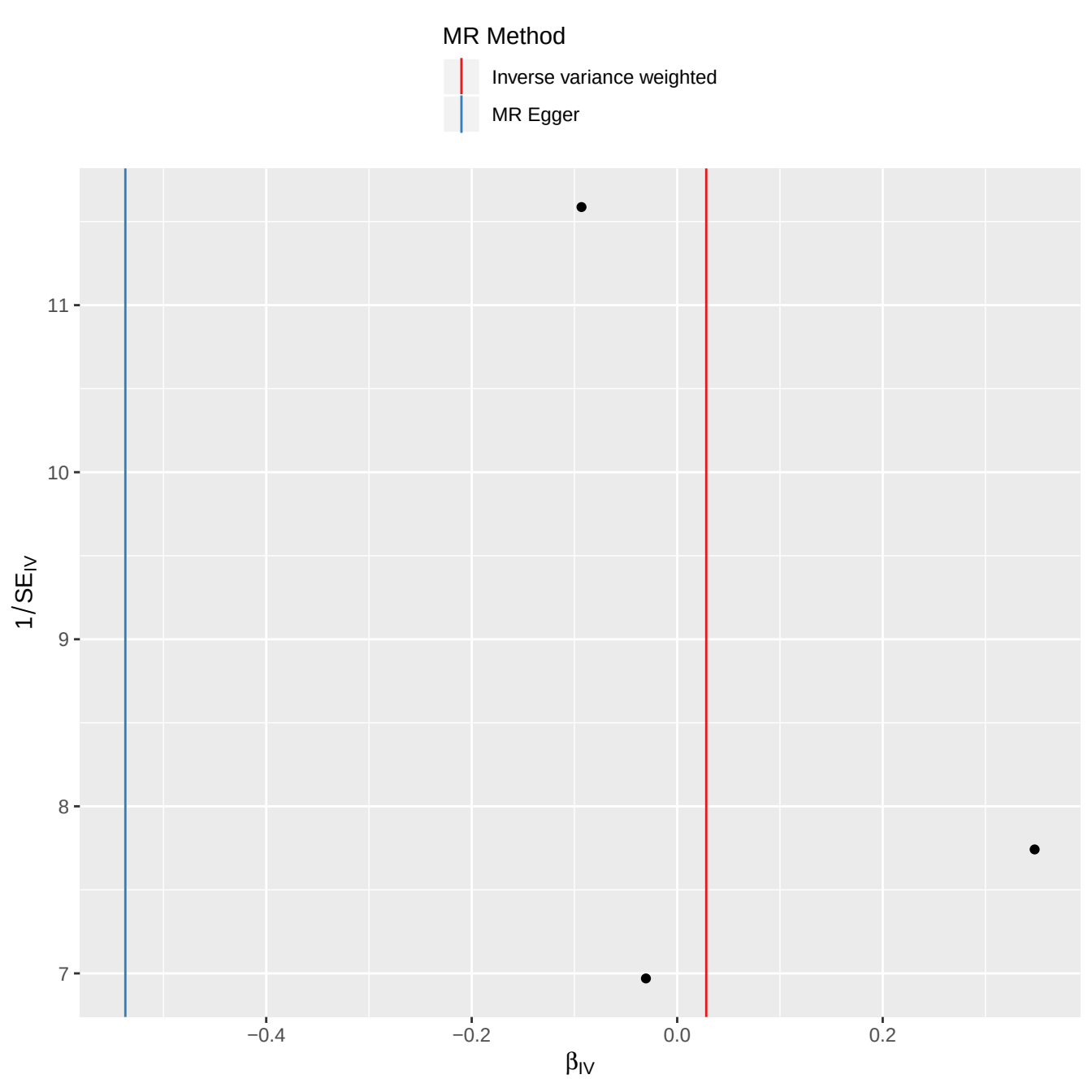

rs2227631
rs6486122
rs6976053
All
−0.4
−0.2
0.0
0.2
0.4
MR leave−one−out sensitivity analysis for Plasminogen activator inhibitor−1 on ER+Breast Cancer

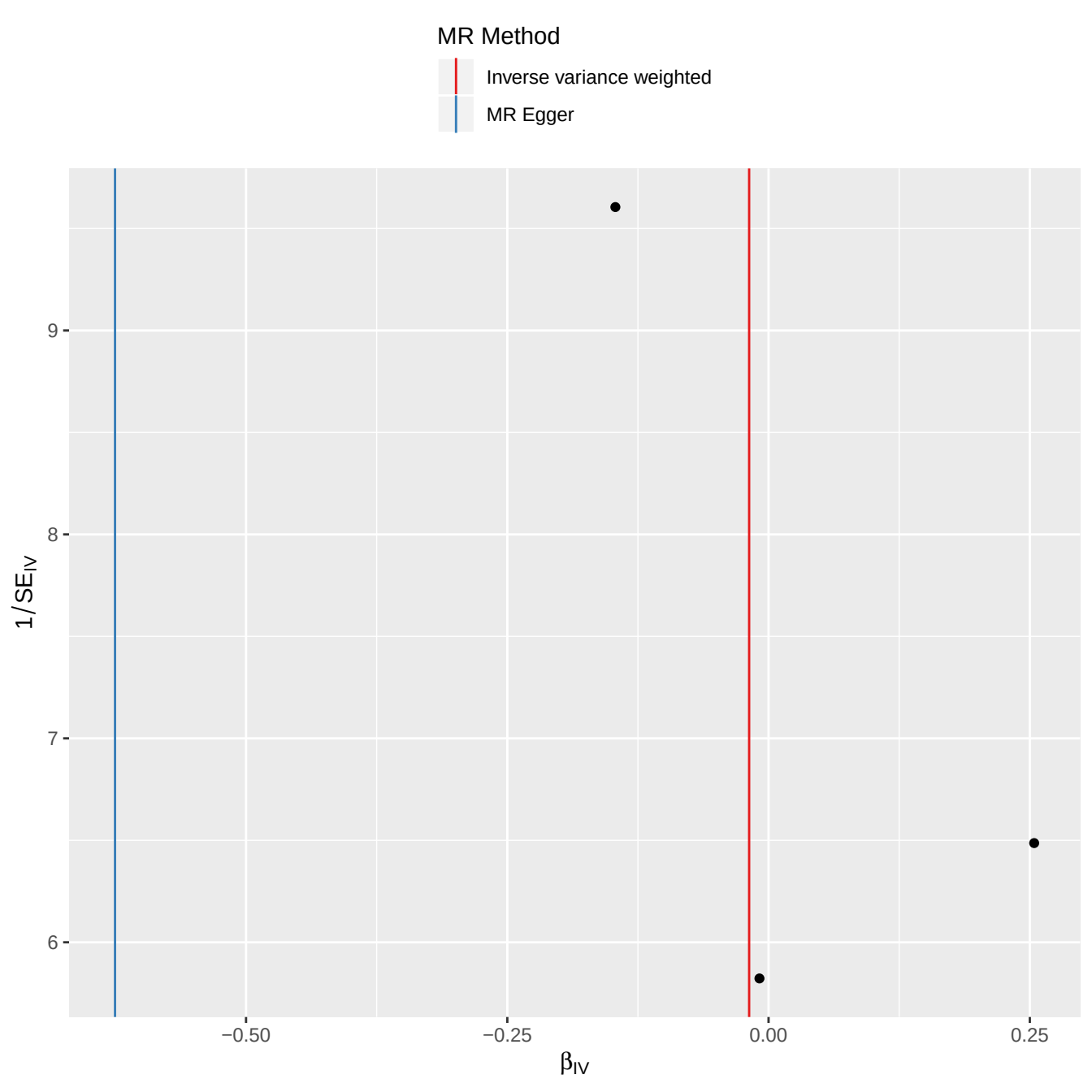

rs2227631
rs6486122
rs6976053
All
−0.5
0.0
0.5
1.0
MR leave−one−out sensitivity analysis for Plasminogen activator inhibitor−1 on ER− Breast Cancer

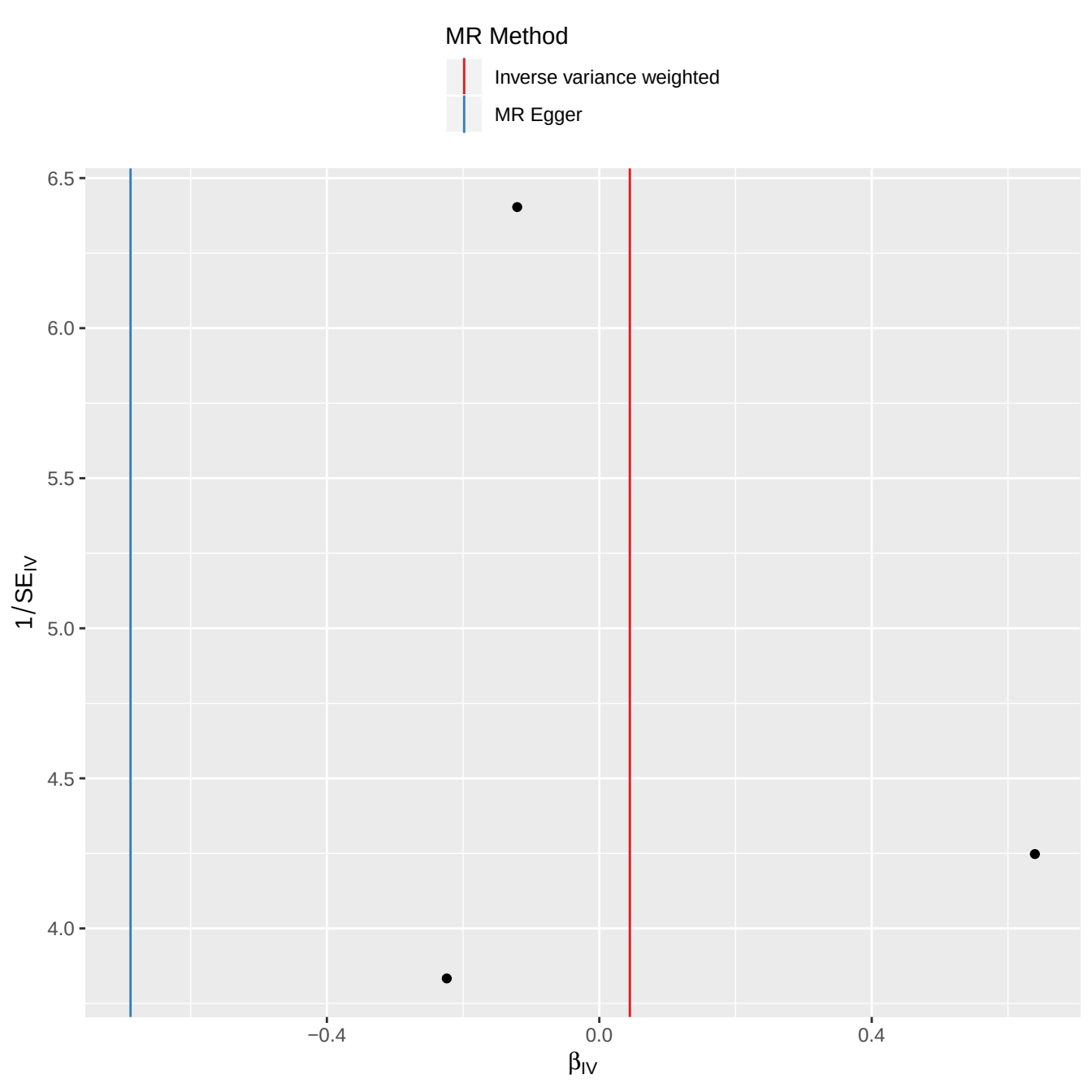

rs6976053
rs6486122
rs2227631
All − Egger
All − IVW
−1
0
MR forest plot for Plasminogen activator inhibitor−1 on Overall Breast Cancer


rs6976053
rs6486122
rs2227631
All − Egger
All − IVW
−1.5
−1.0
−0.5
0.0
0.5
MR forest plot for Plasminogen activator inhibitor−1 on ER+ Breast Cancer


rs6976053
rs2227631
rs6486122
All − Egger
All − IVW
−2
0
2
MR forest plot for Plasminogen activator inhibitor−1 on ER− Breast Cancer


MR Method
Inverse variance weighted
MR Egger
11
10
9
8
7
1/SE_IV
−0.4
−0.2
0.0
0.2
β_IV


MR Method
Inverse variance weighted
MR Egger
9
8
7
6
1/SE_IV
−0.50
−0.25
0.00
0.25
β_IV


MR Method
Inverse variance weighted
MR Egger
6.5
6.0
5.5
5.0
4.5
4.0
1/SE_IV
−0.4
0.0
0.4
β_IV