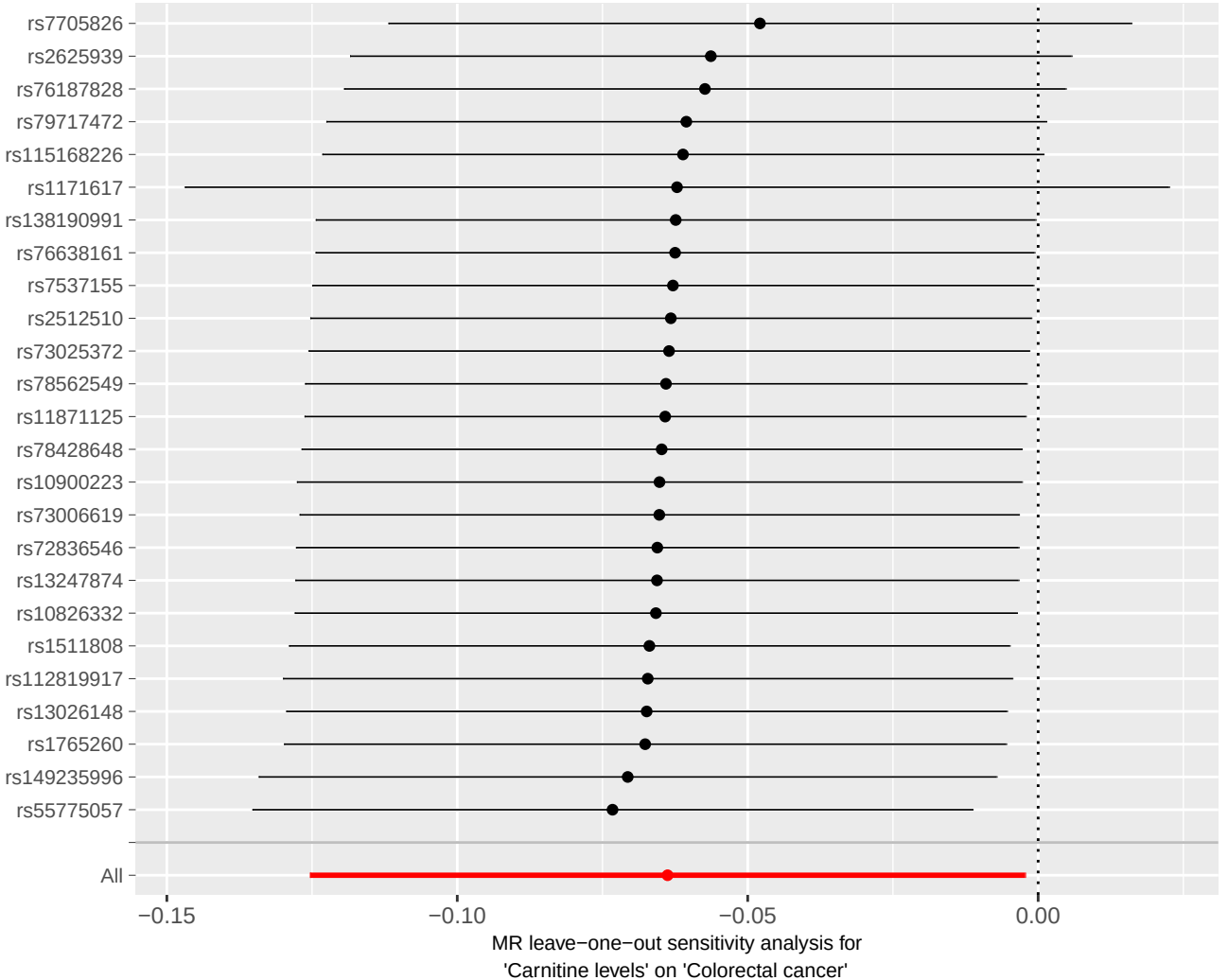
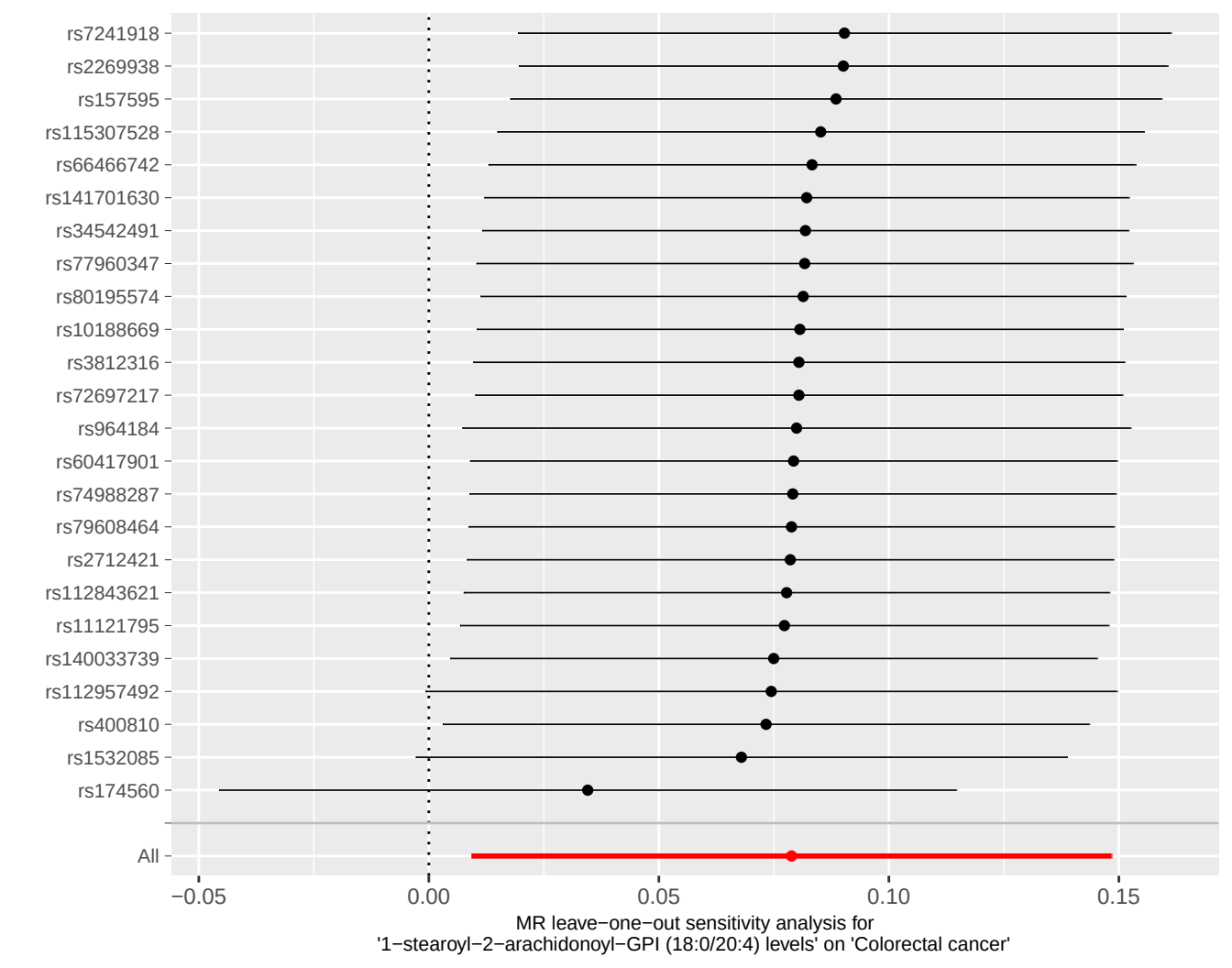
Supplementary Figure S1. Leave-one-out analysis ofthe causal effect of 85 metabolites on Colorectal cancer

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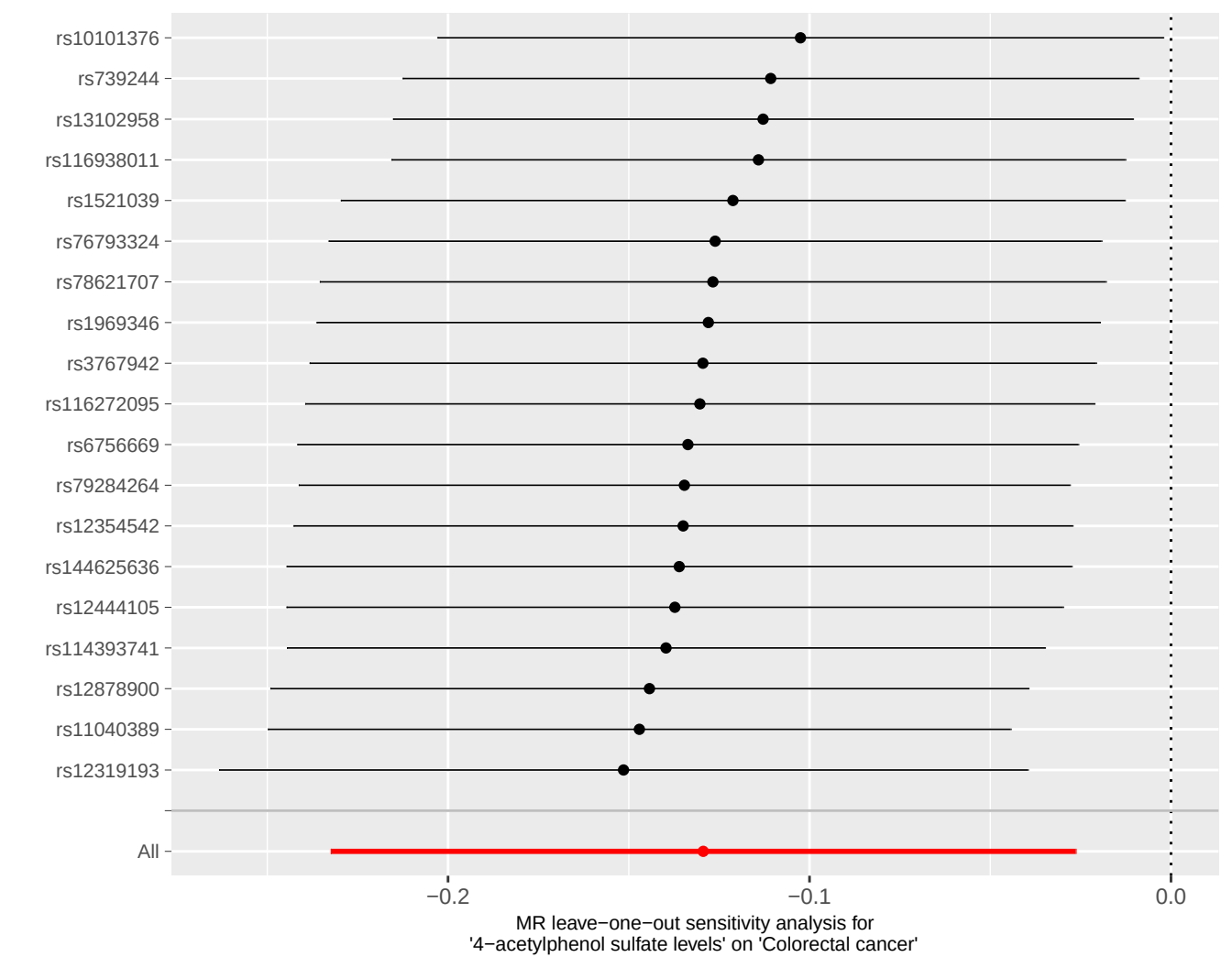
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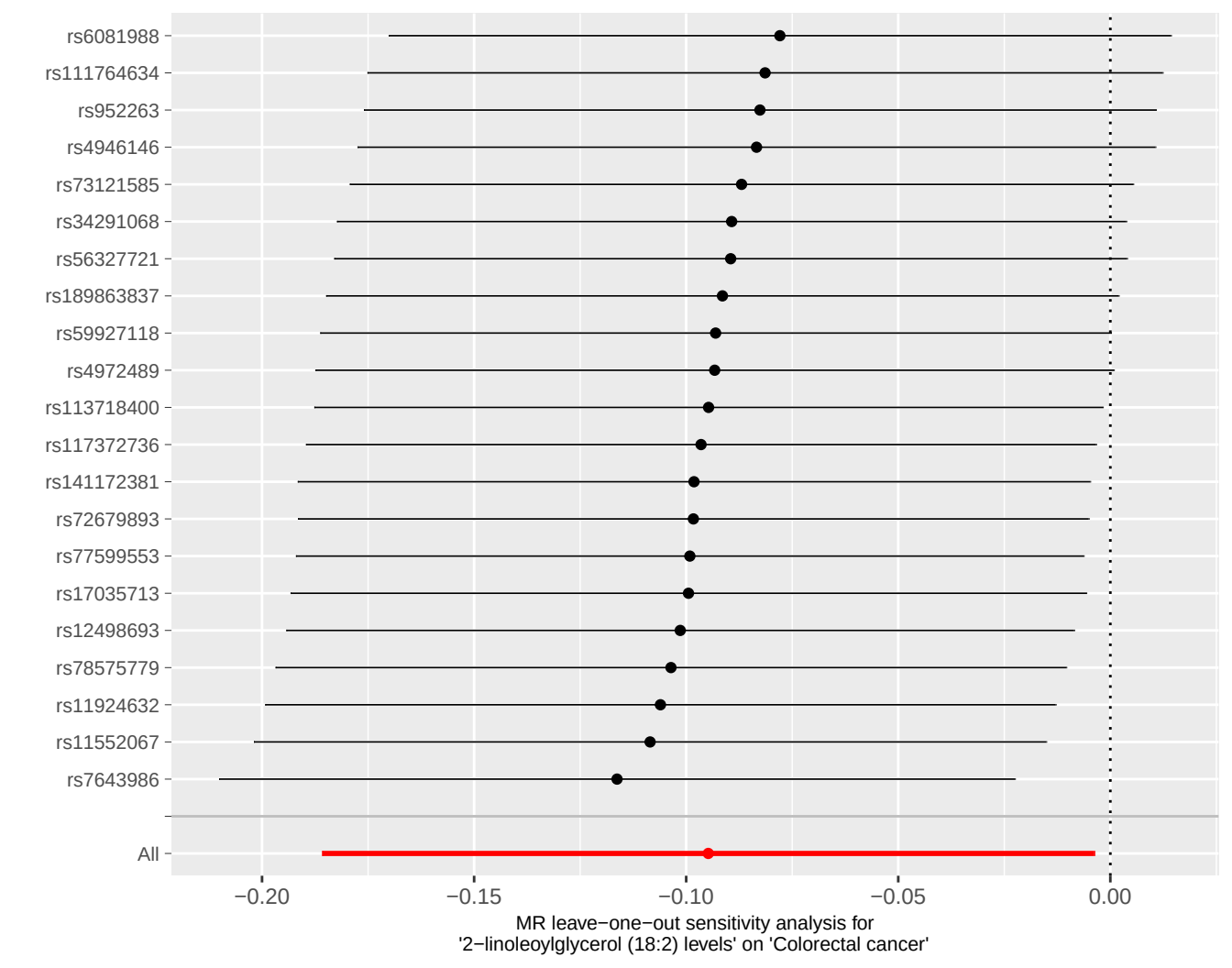
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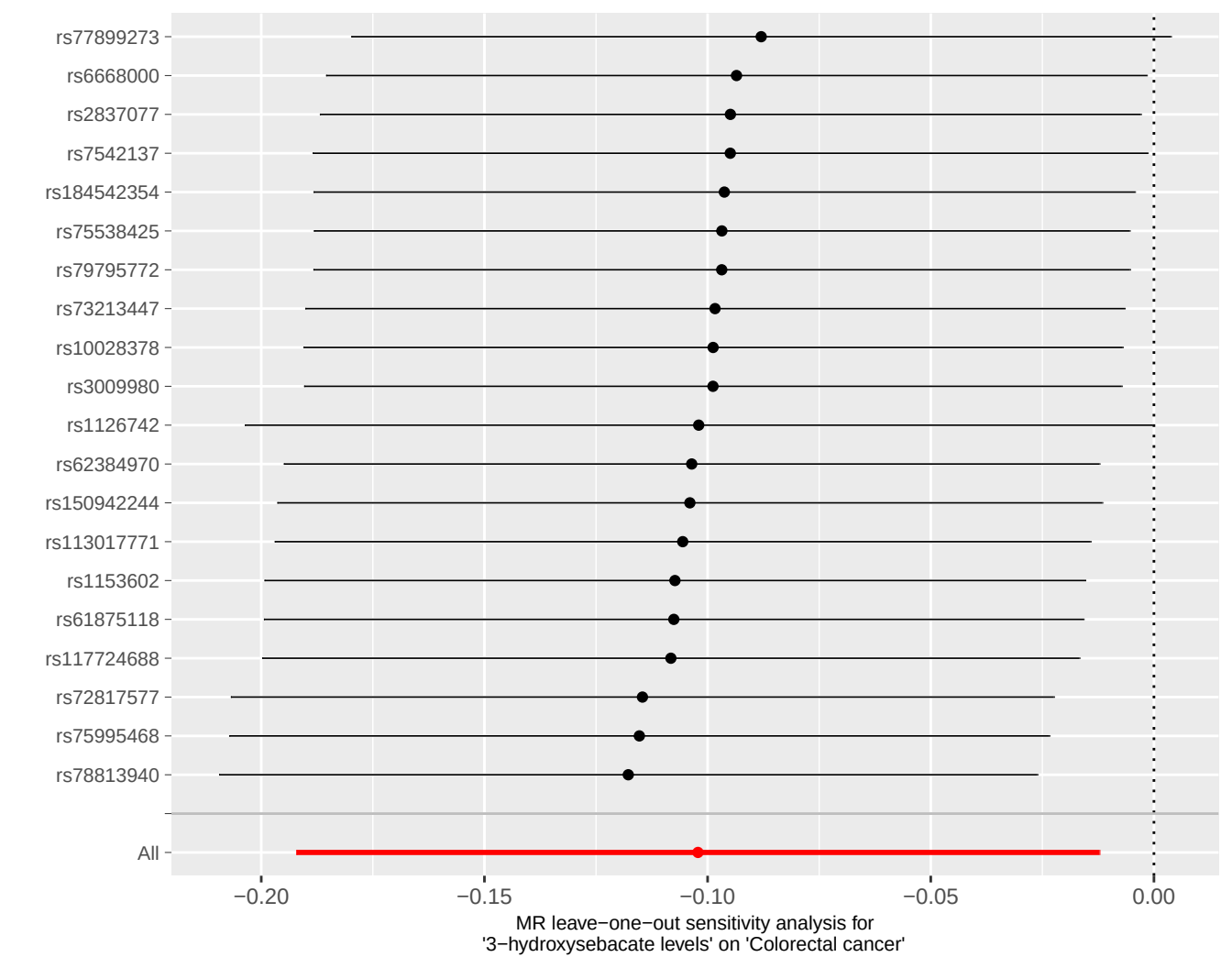
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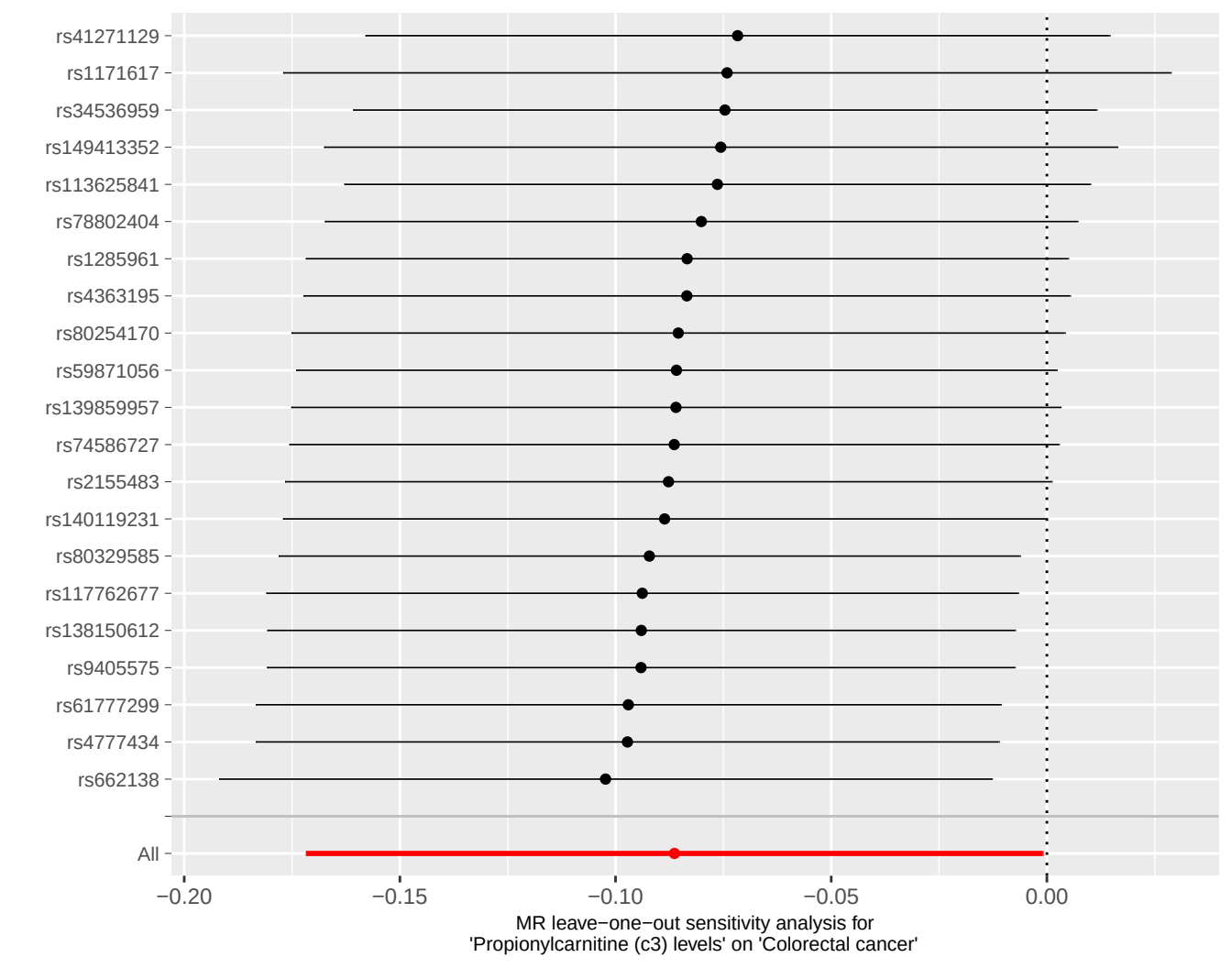
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All
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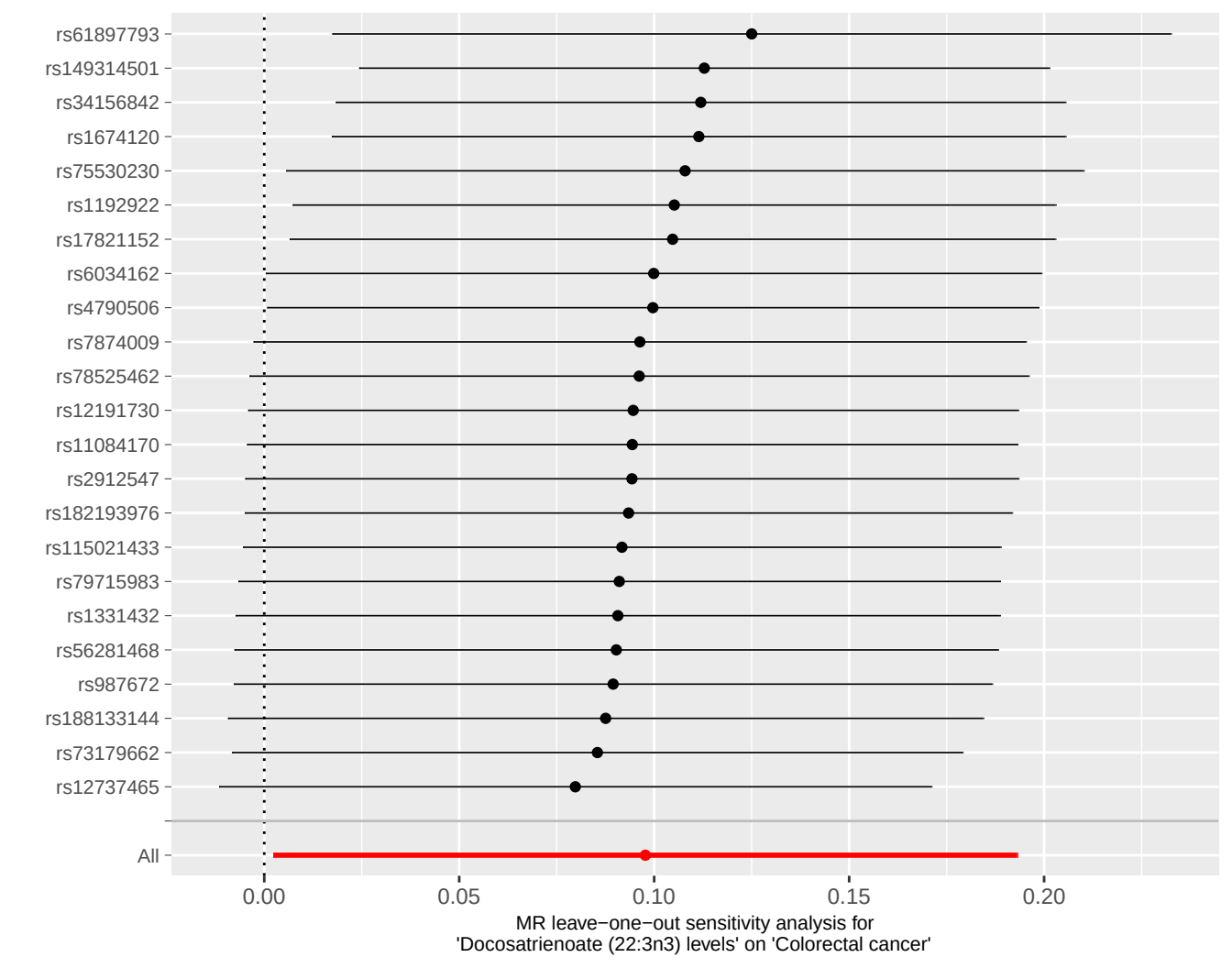
'Propionylcarnitine (c3) levels' on 'Colorectal cancer'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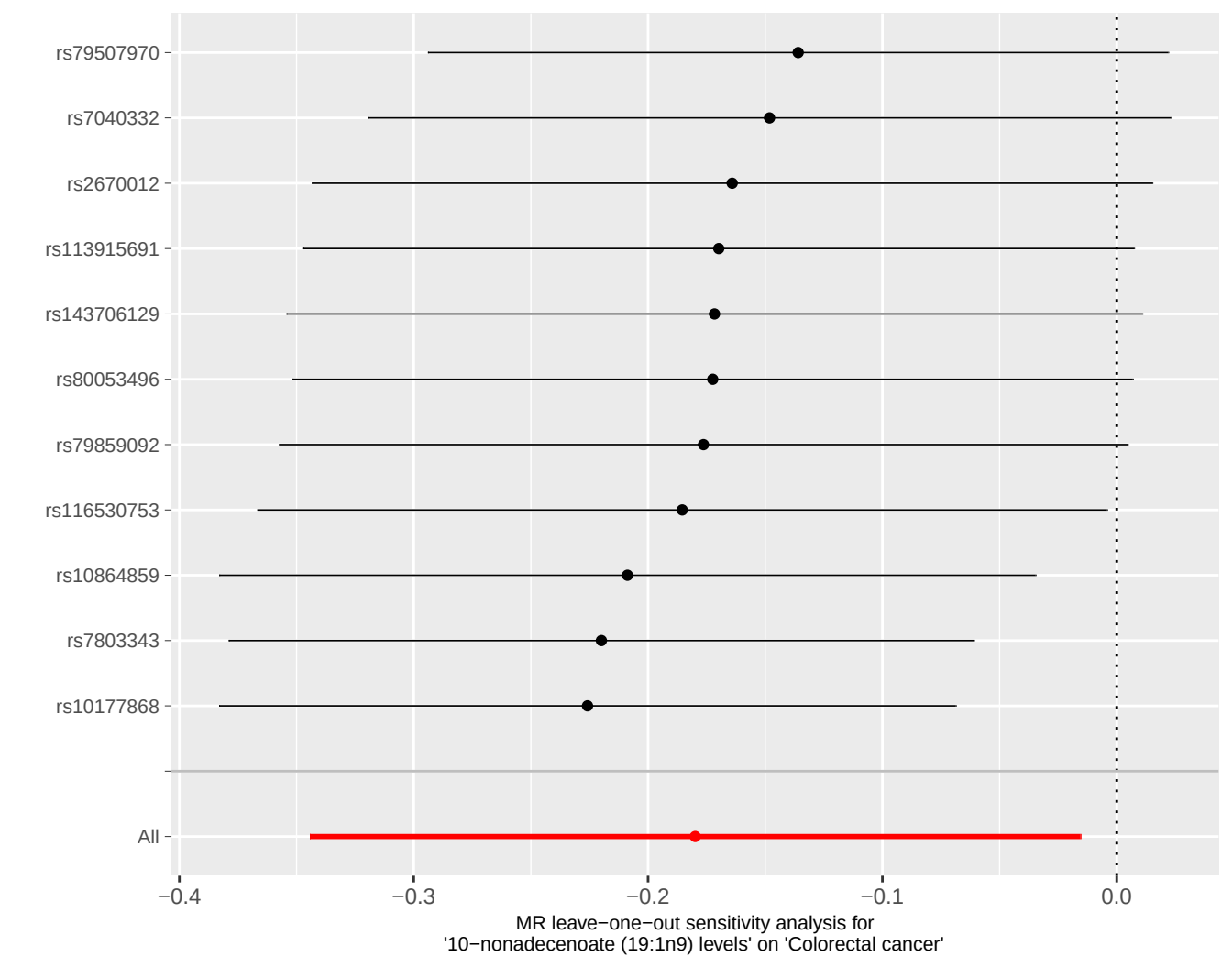
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All
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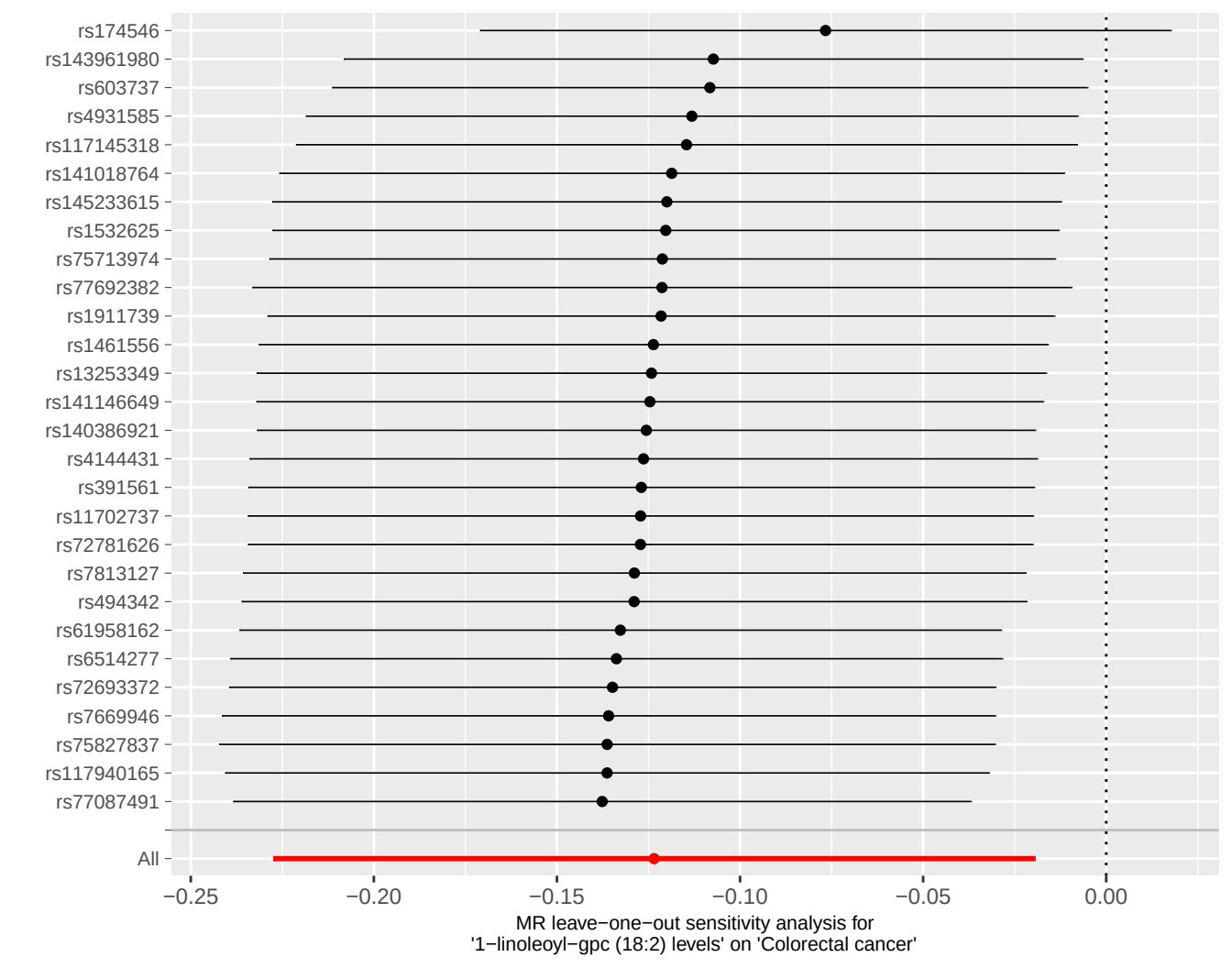
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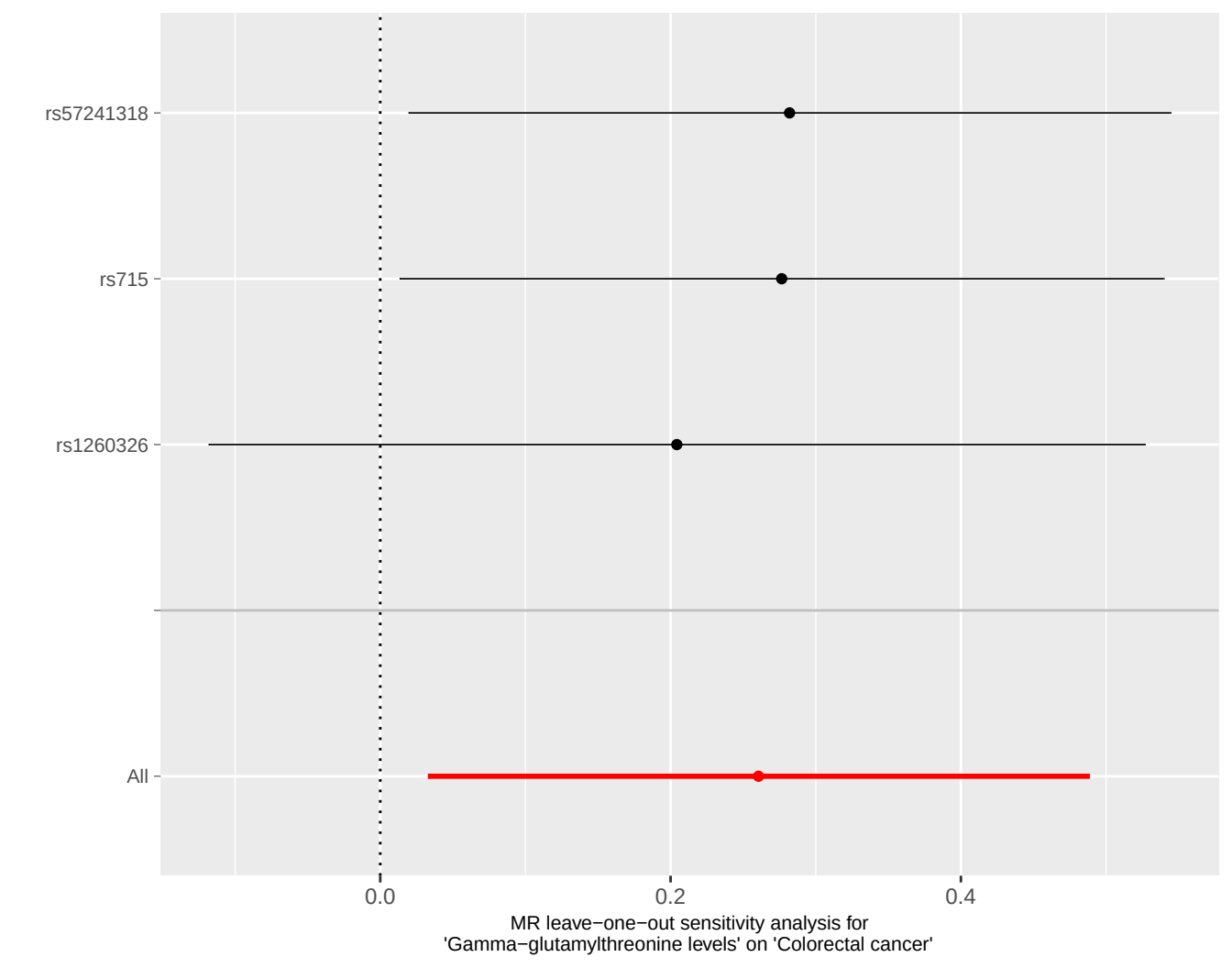
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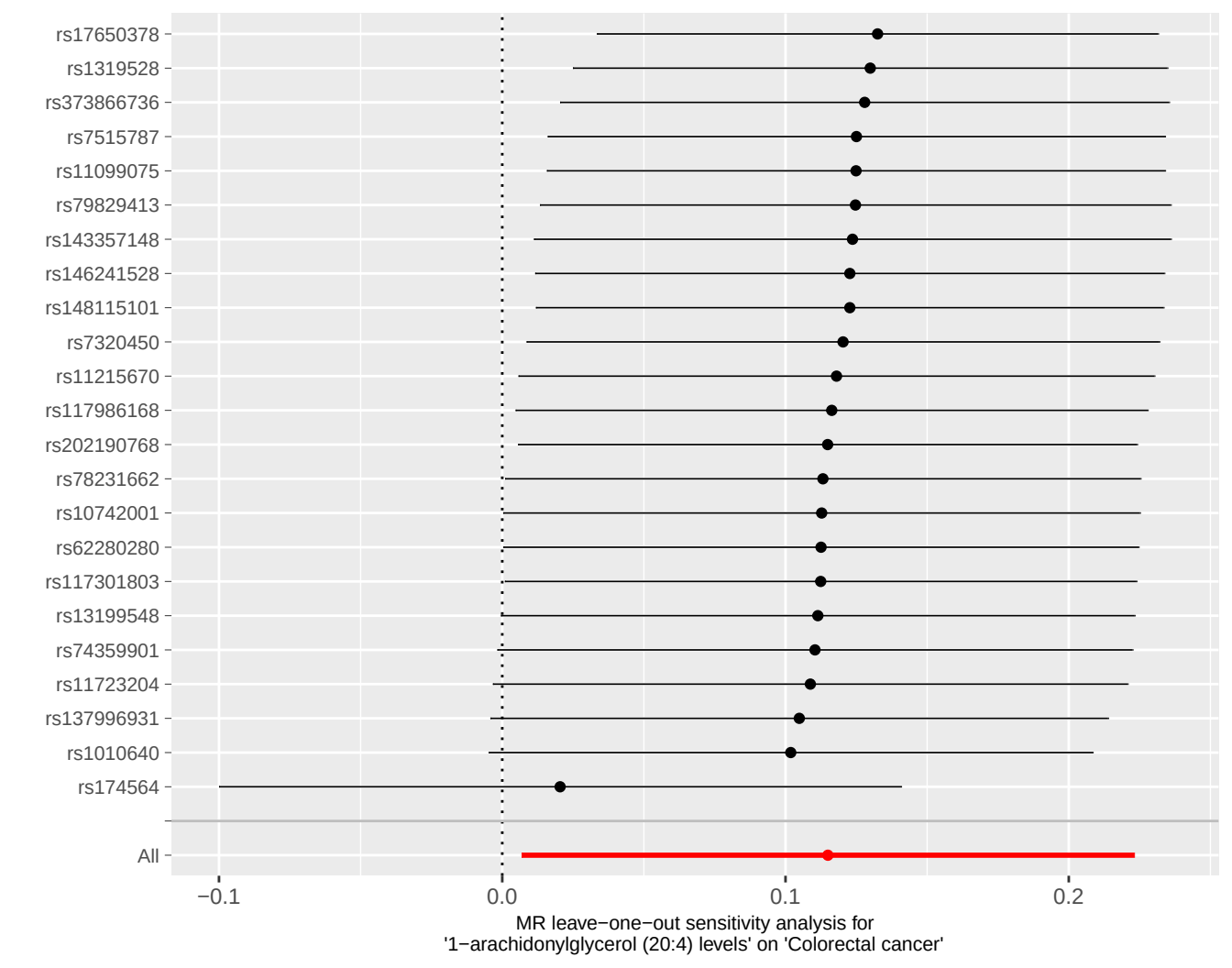
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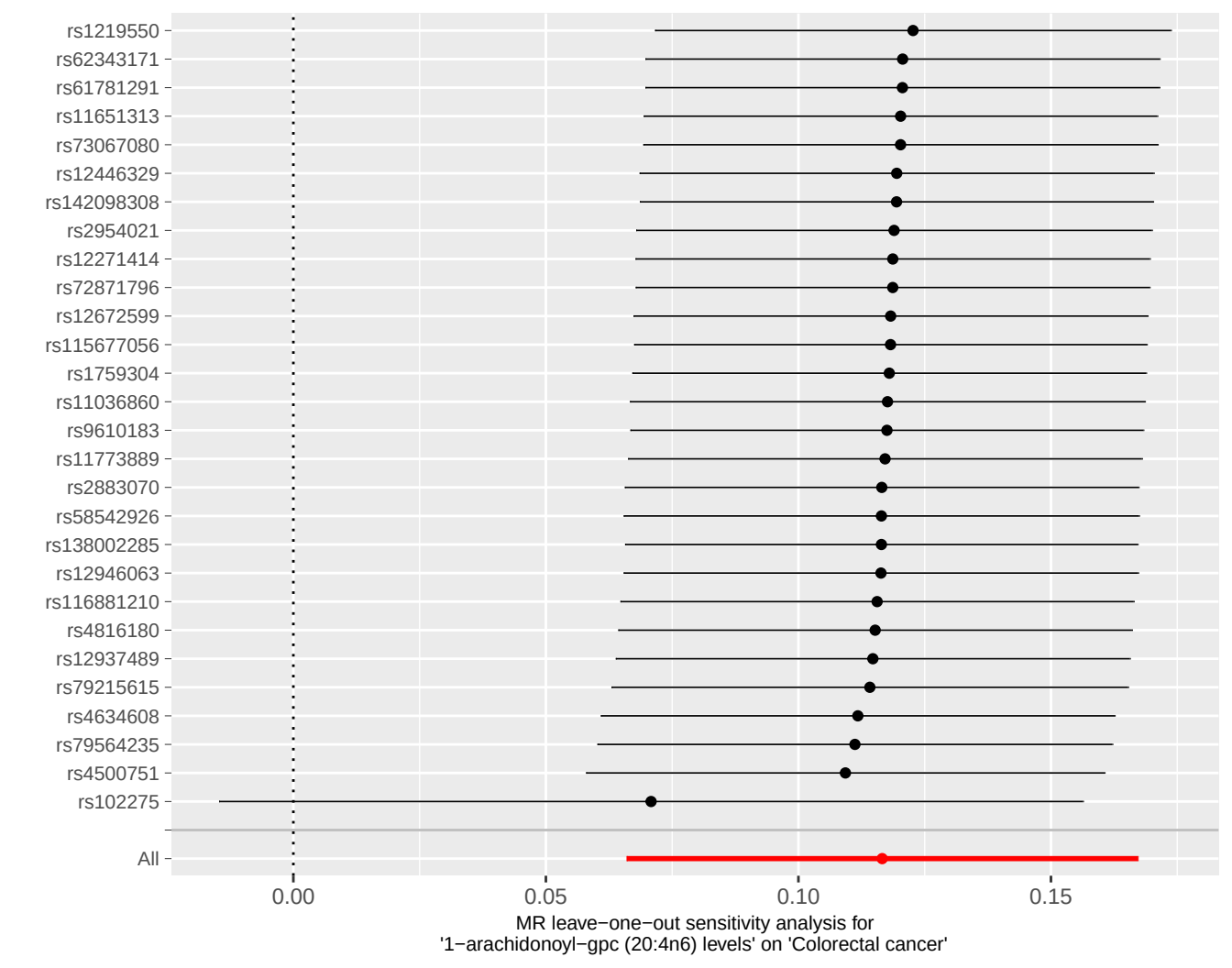
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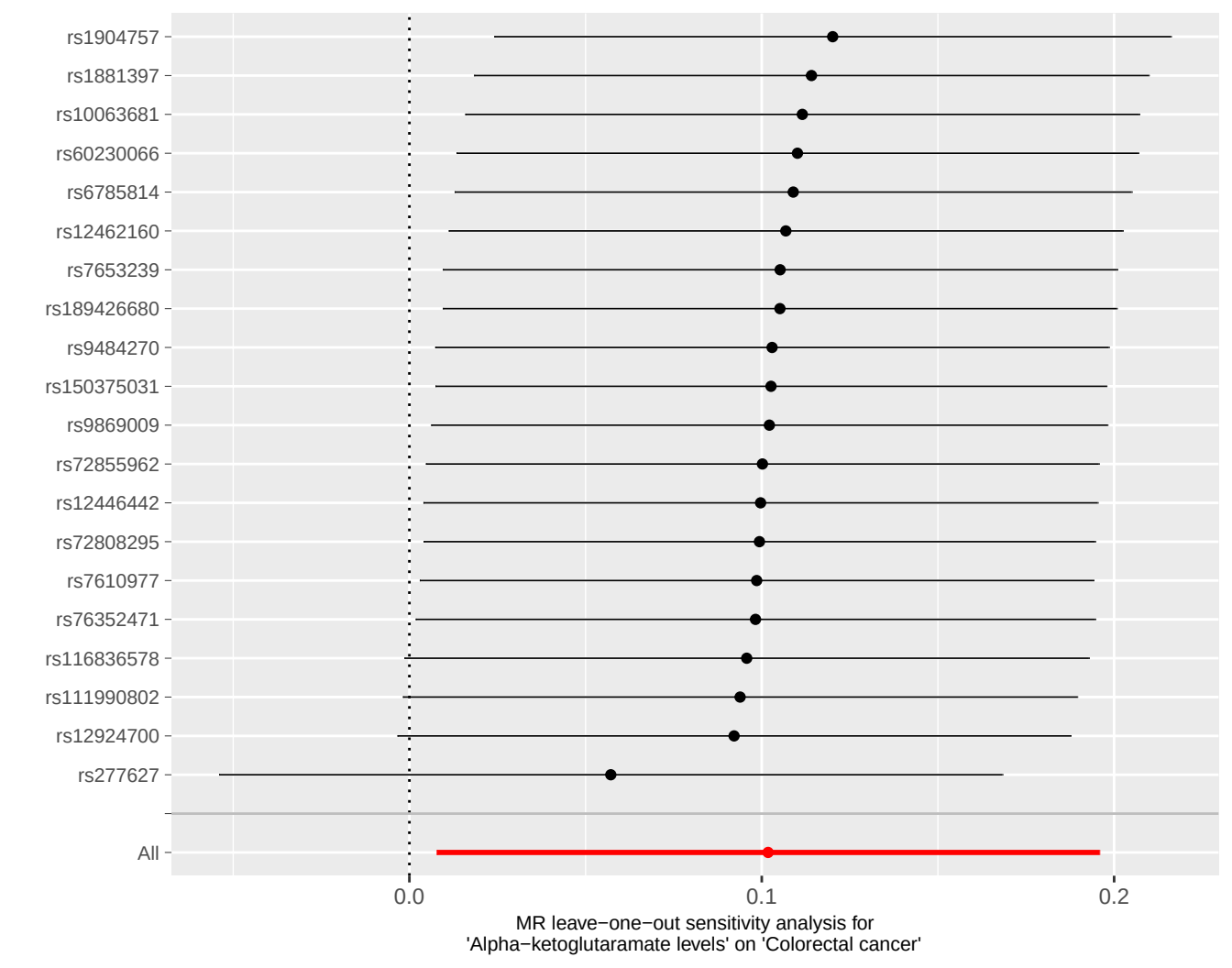
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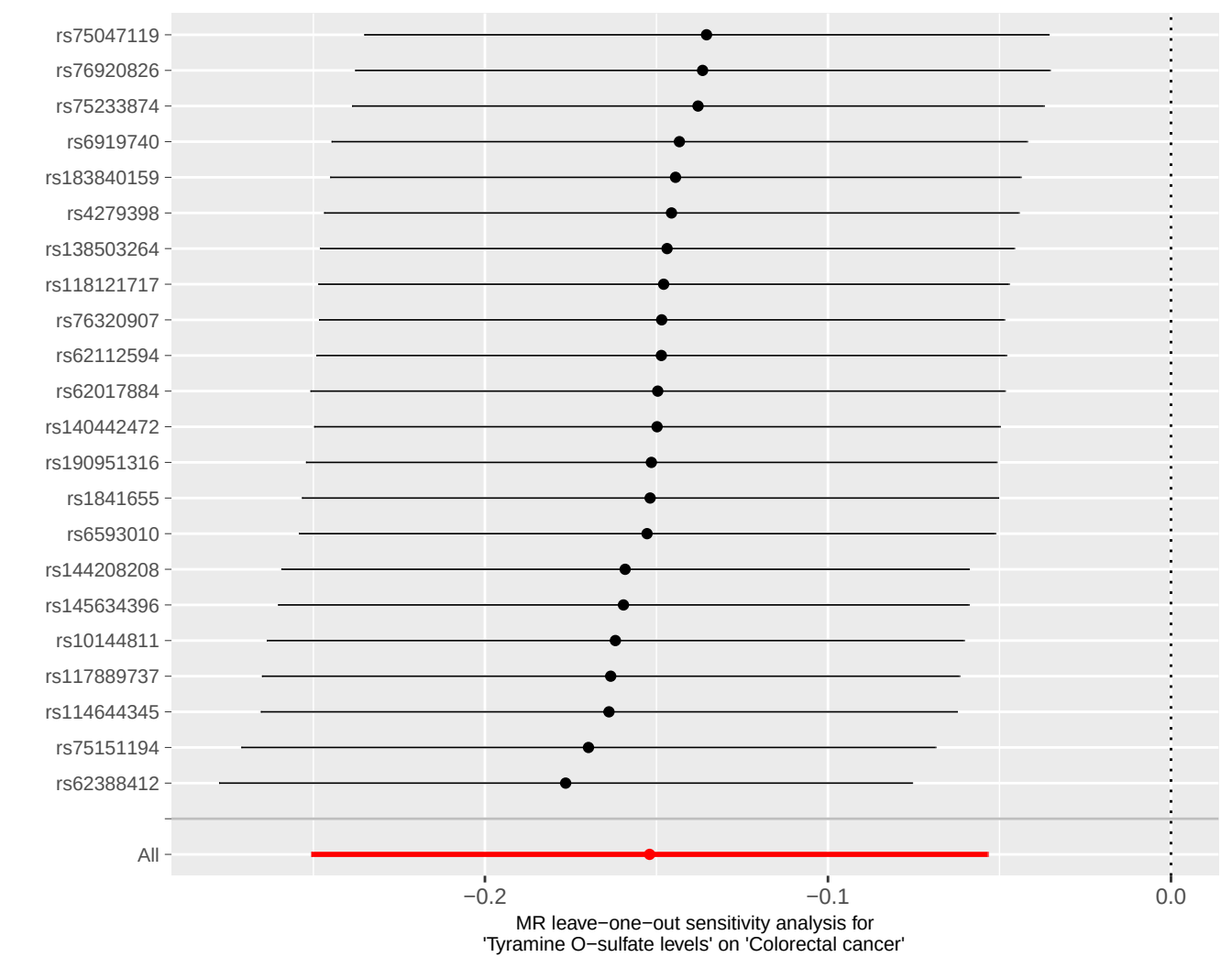
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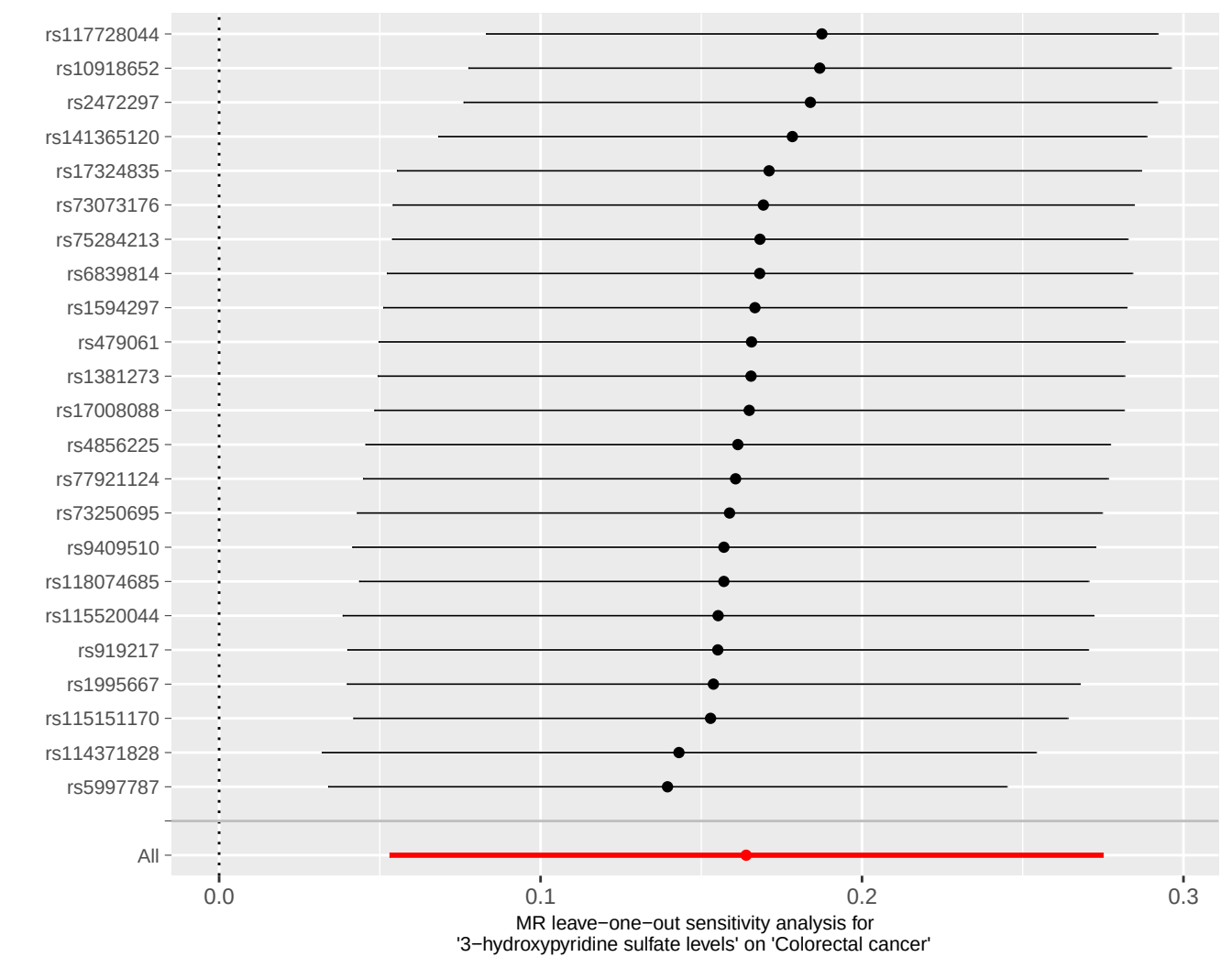
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rs114371828
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0.3
MR leave−one−out sensitivity analysis for
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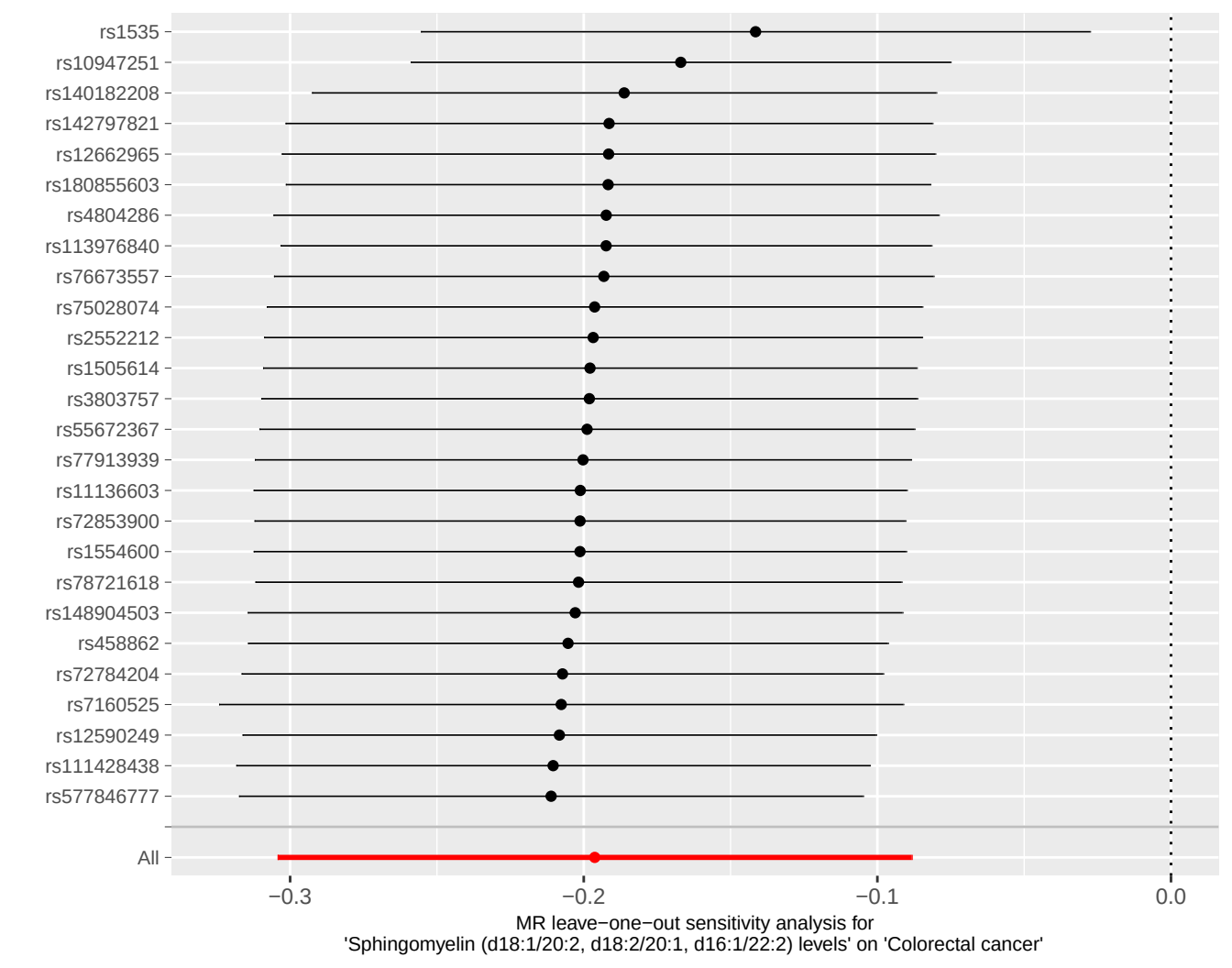
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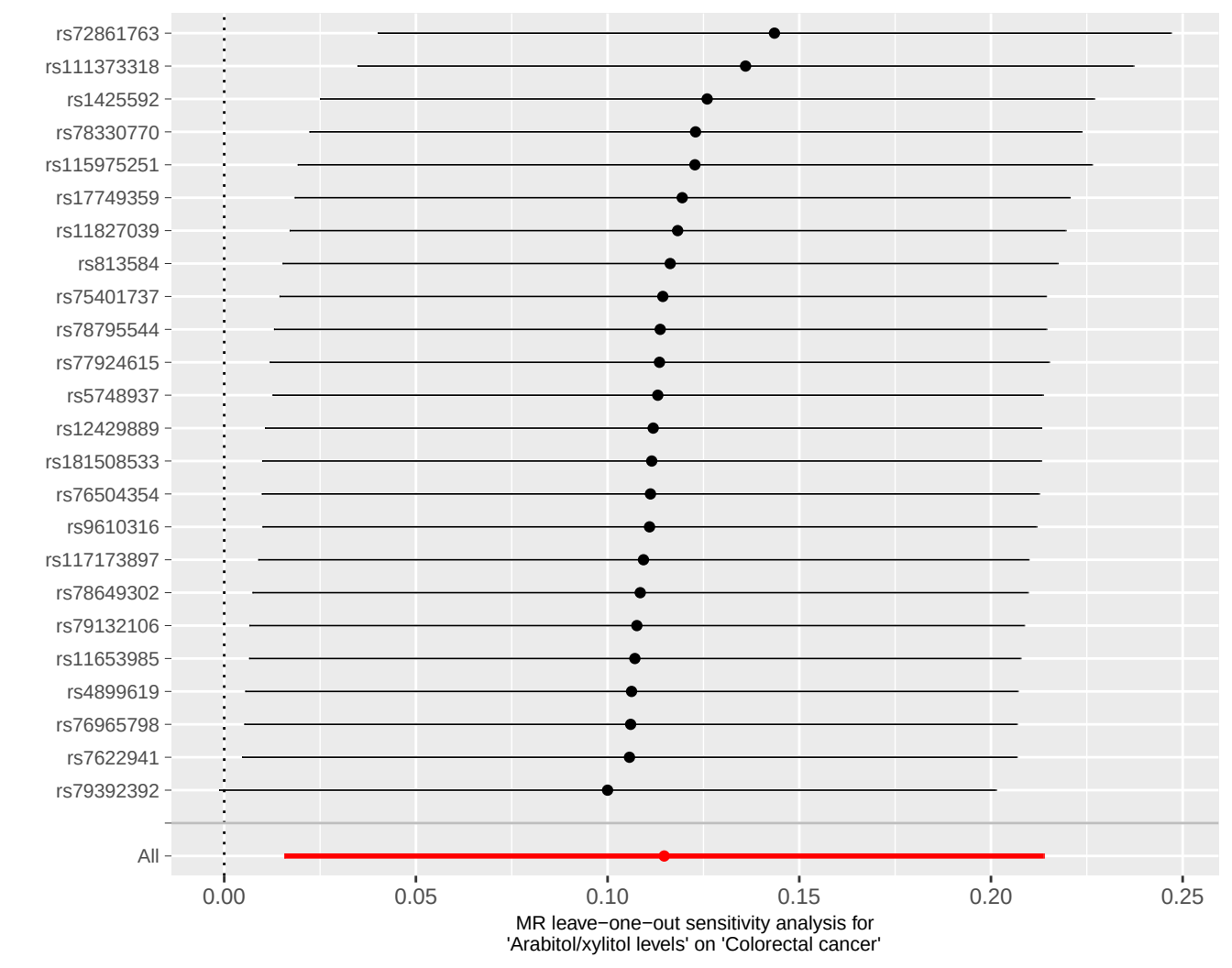
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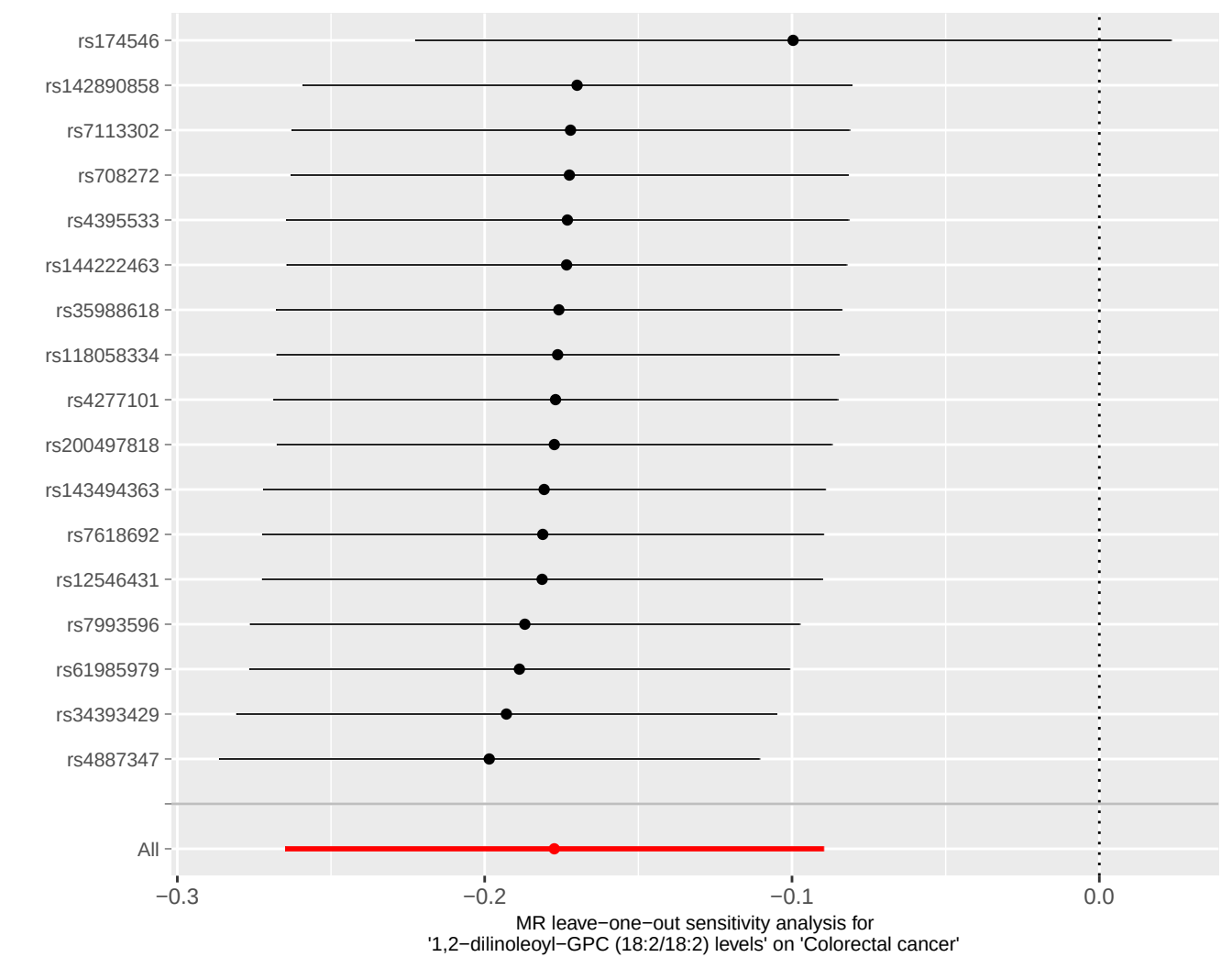
'Arabitol/xylitol levels' on 'Colorectal cancer'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All
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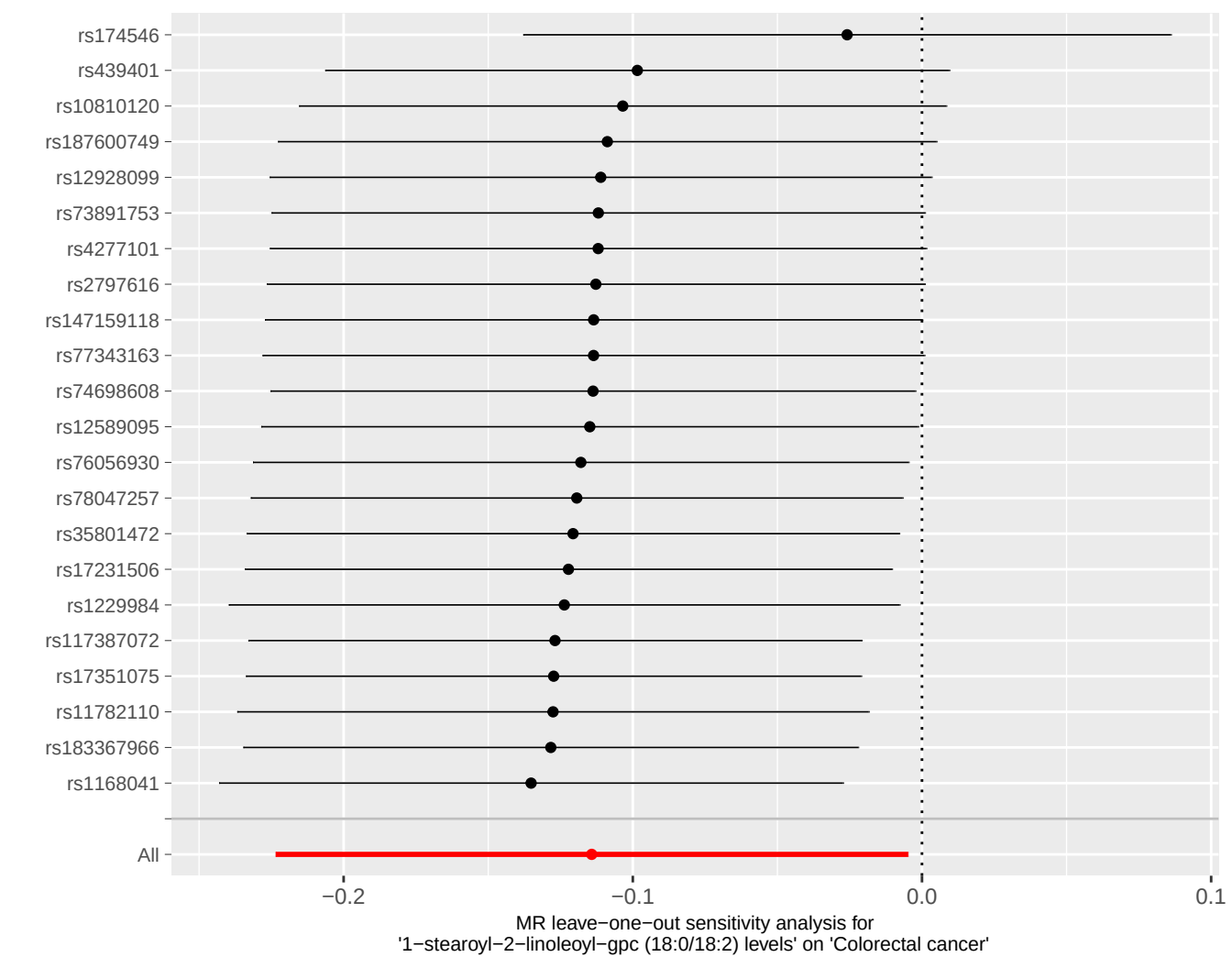
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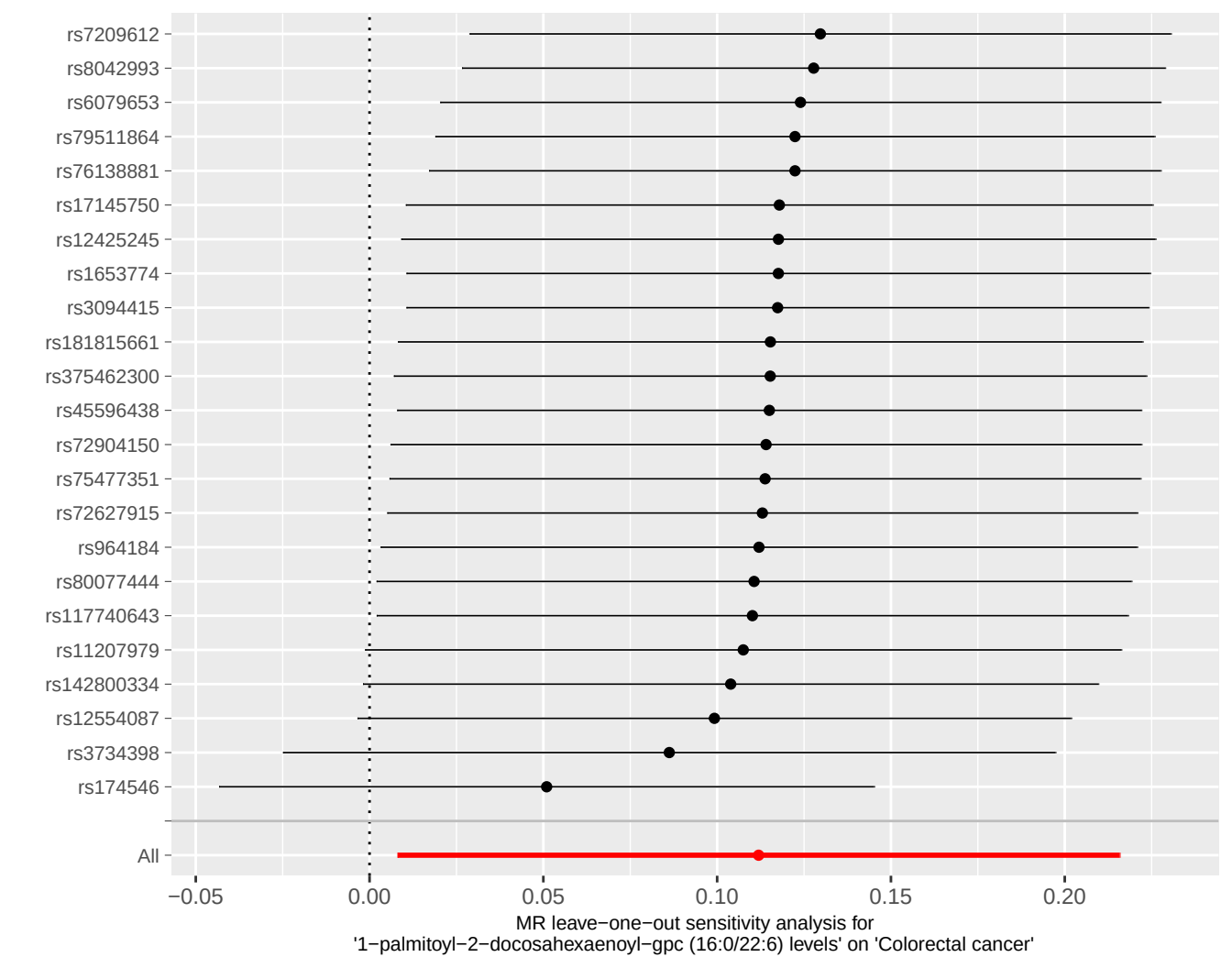
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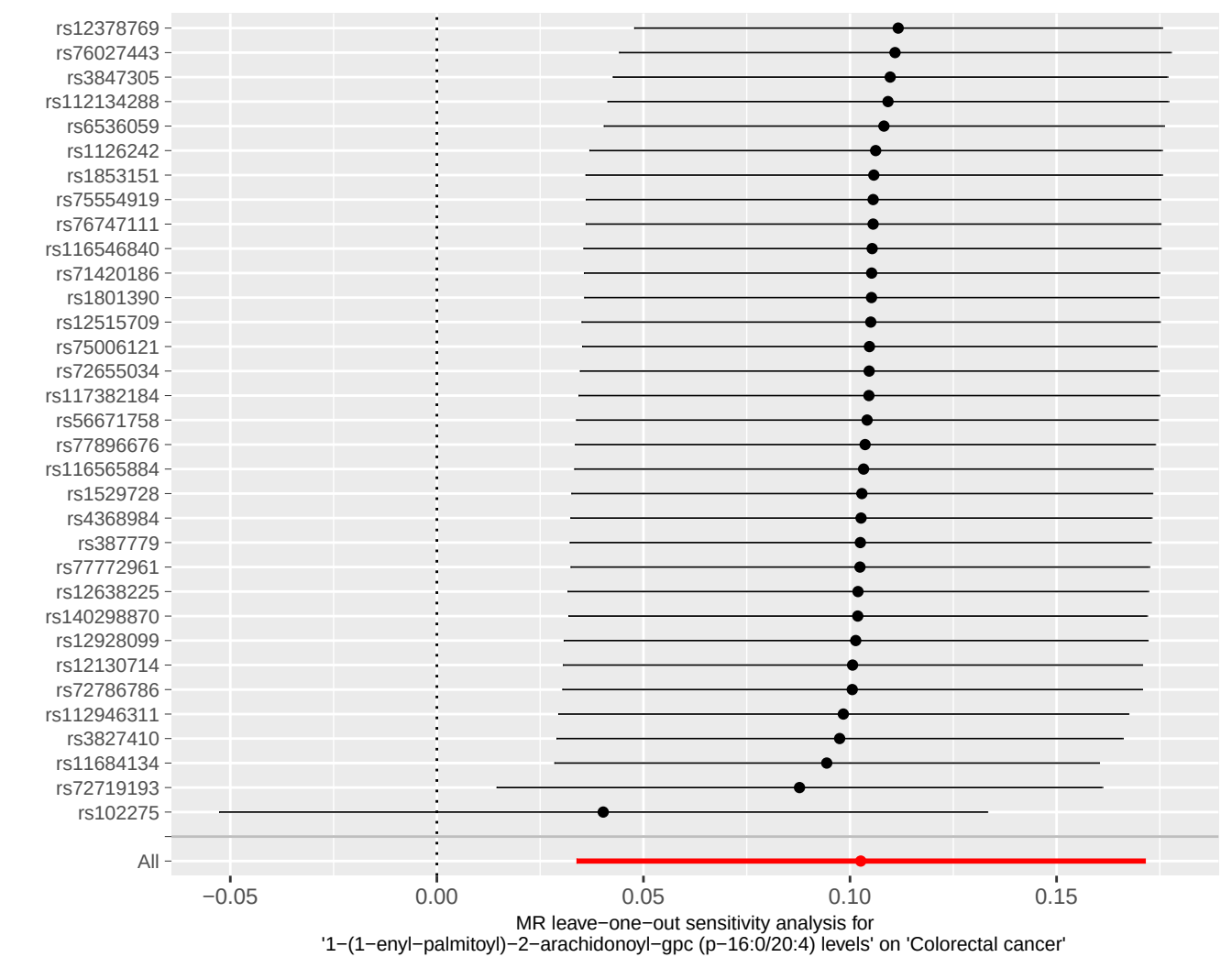
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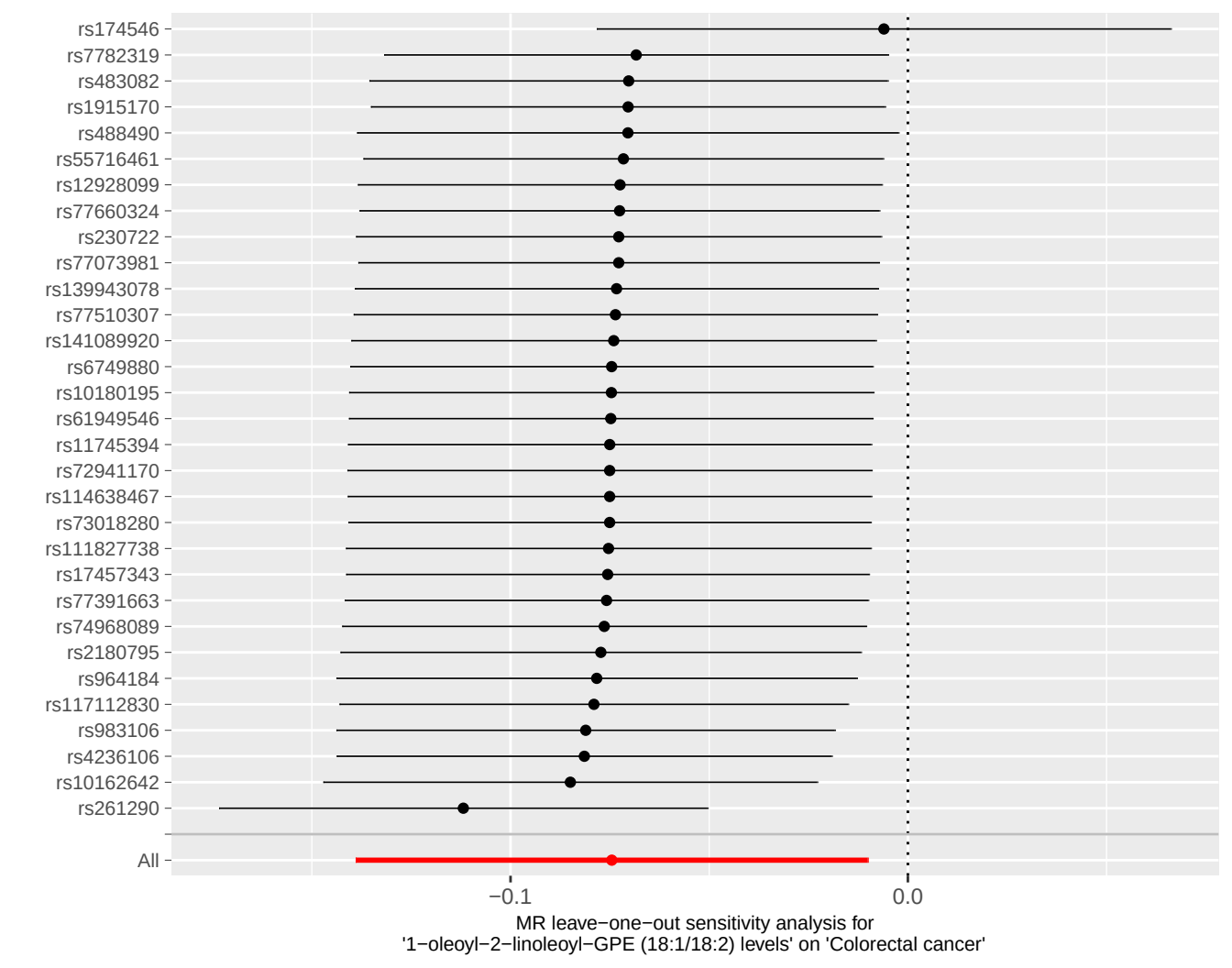
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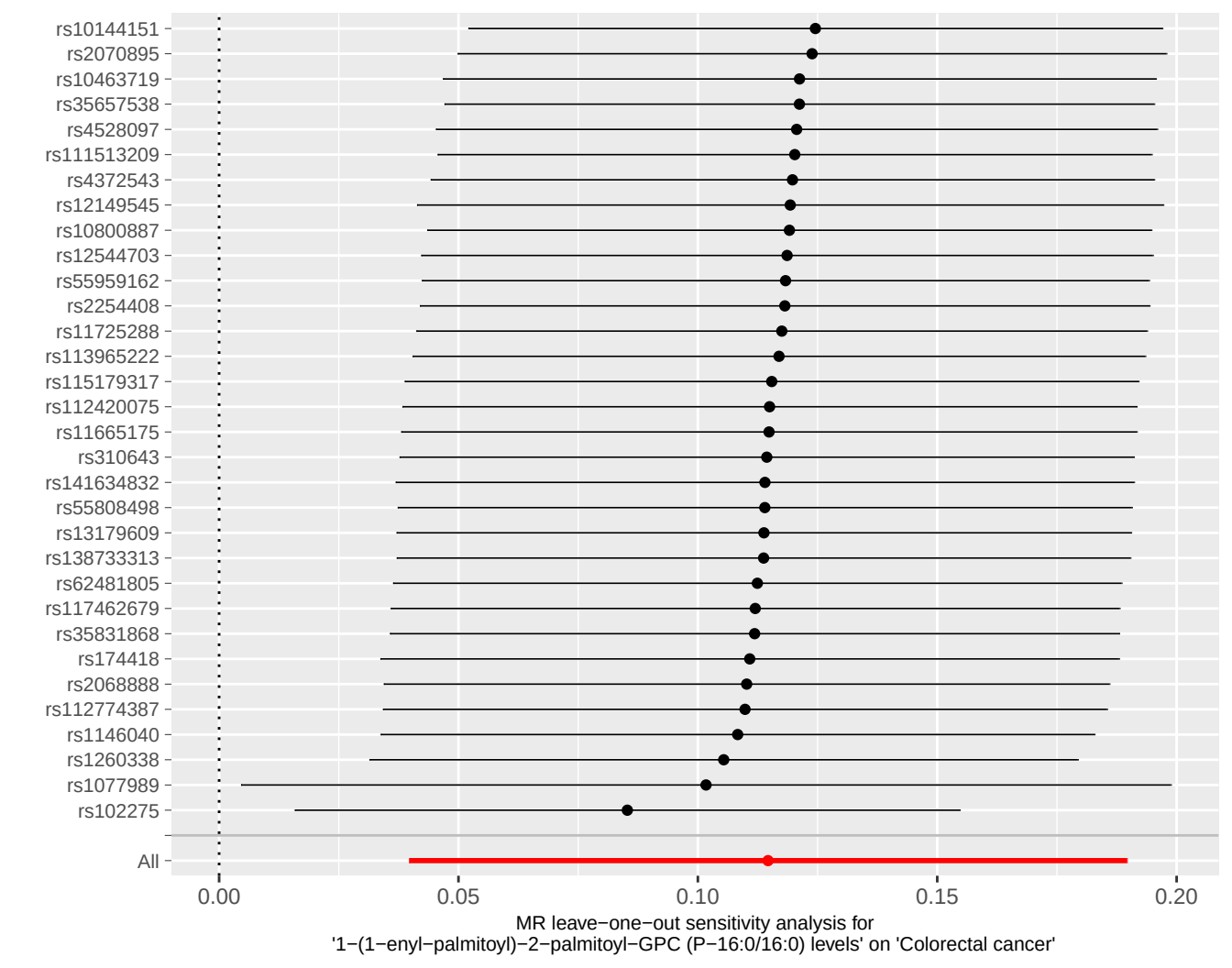
'1−oleoyl−2−linoleoyl−GPE (18:1/18:2) levels' on 'Colorectal cancer'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All
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0.10
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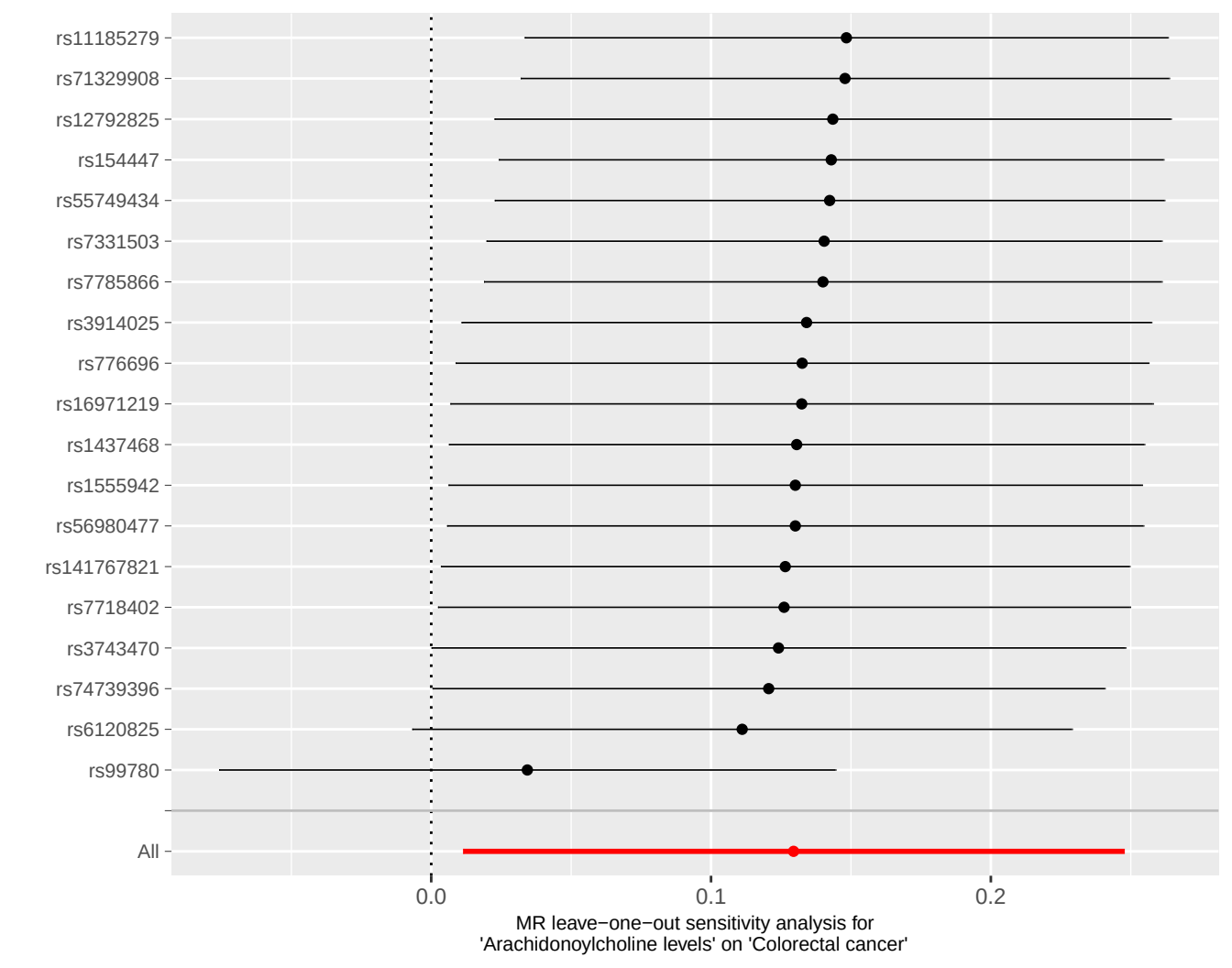
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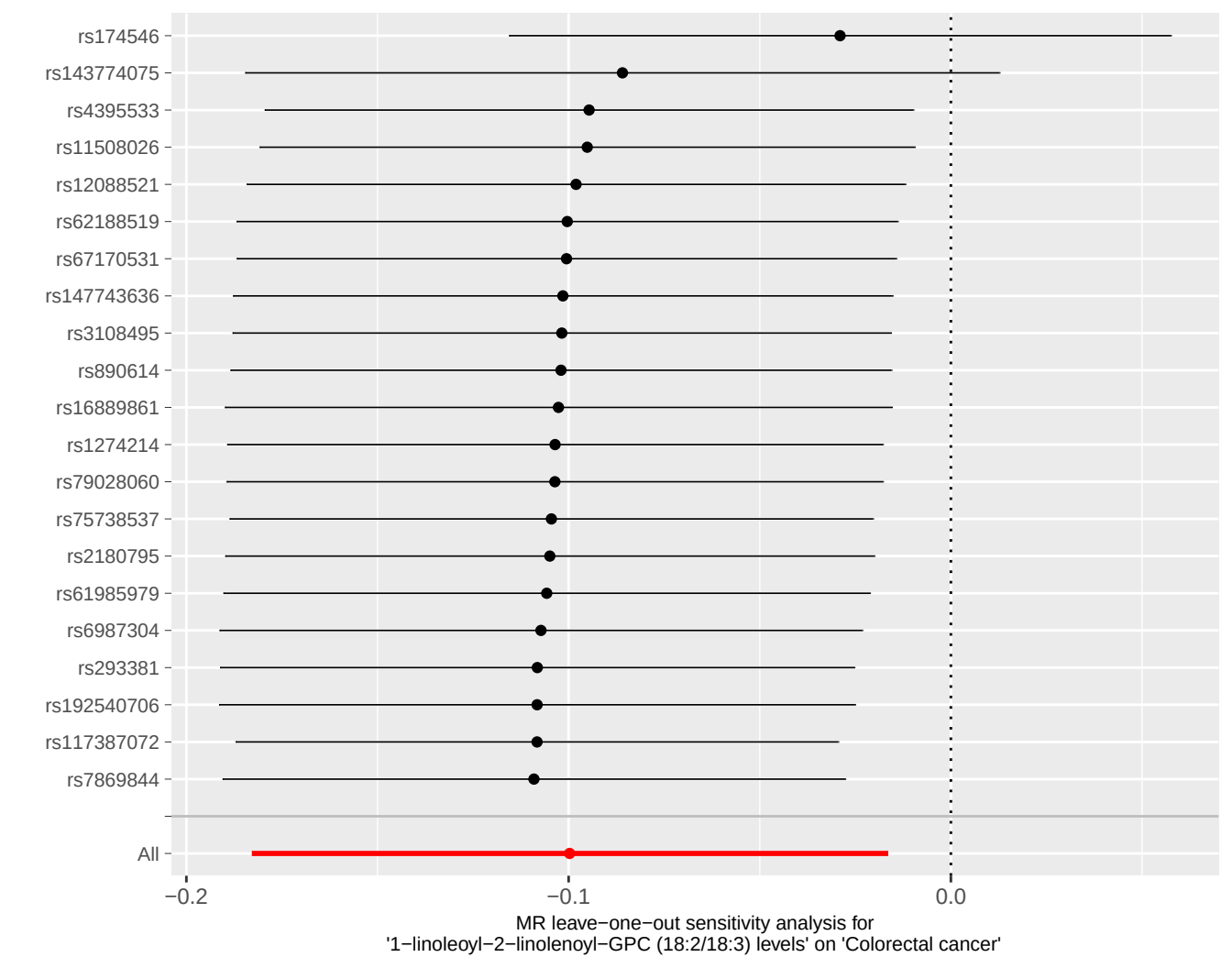
'Arachidonoylcholine levels' on 'Colorectal cancer'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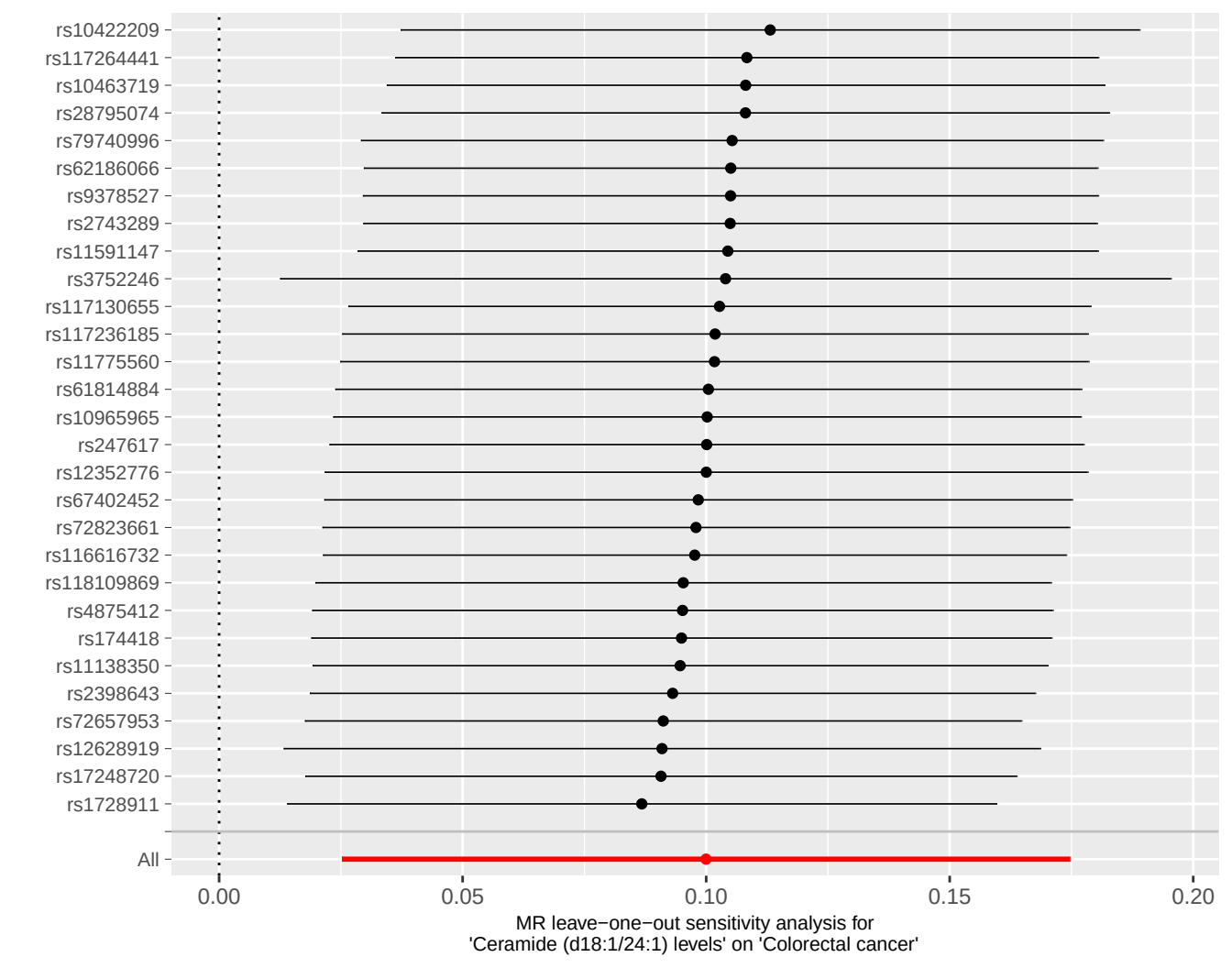
MR leave−one−out sensitivity analysis for
'1−linoleoyl−2−linolenoyl−GPC (18:2/18:3) levels' on 'Colorectal cancer'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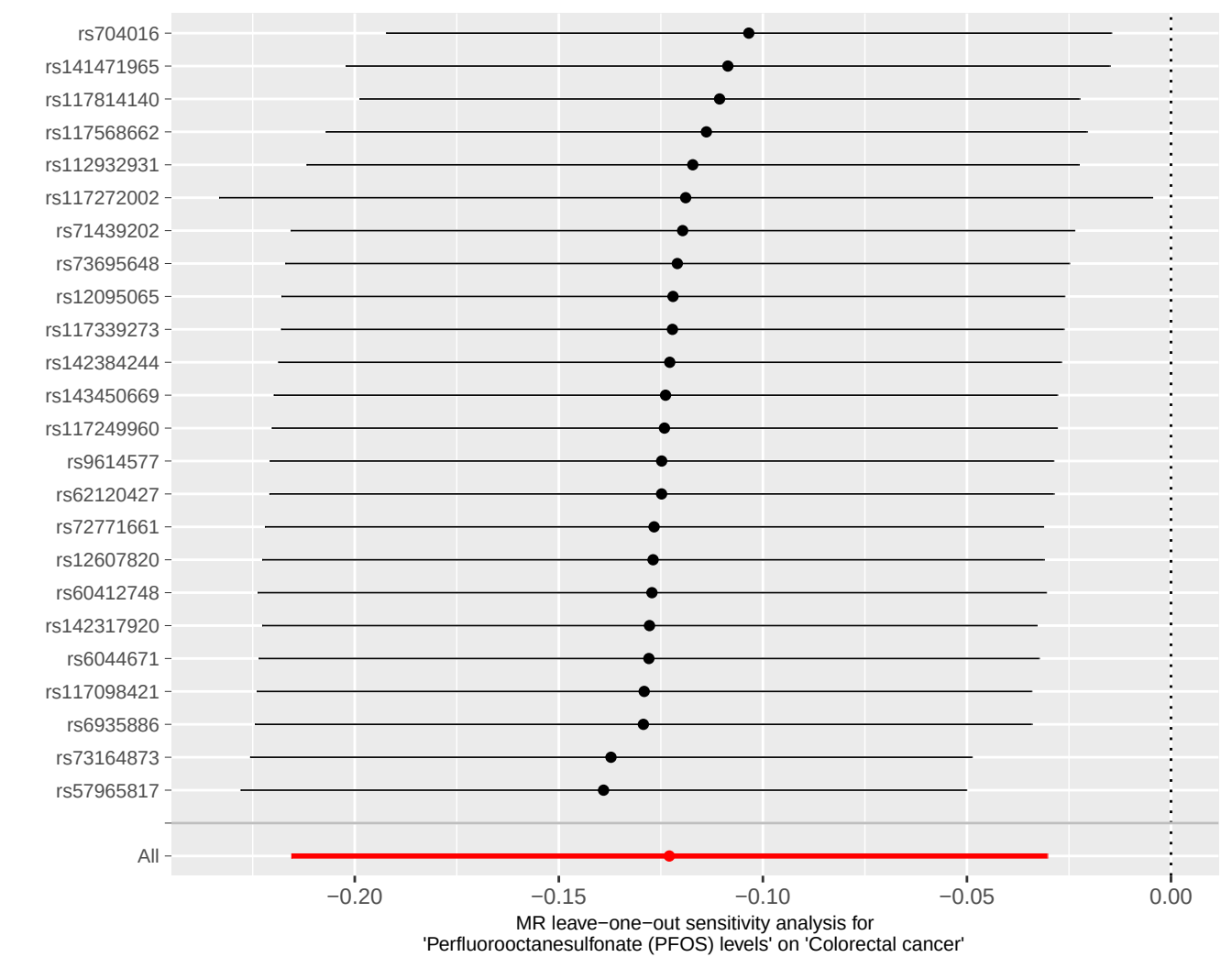
rs174418
rs11138350
rs2398643
rs72657953
rs12628919
rs17248720
rs1728911
All
0.00
0.05
0.10
0.15
0.20
MR leave−one−out sensitivity analysis for
'Ceramide (d18:1/24:1) levels' on 'Colorectal cancer'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rs142317920
rs6044671
rs117098421
rs6935886
rs73164873
rs57965817
All
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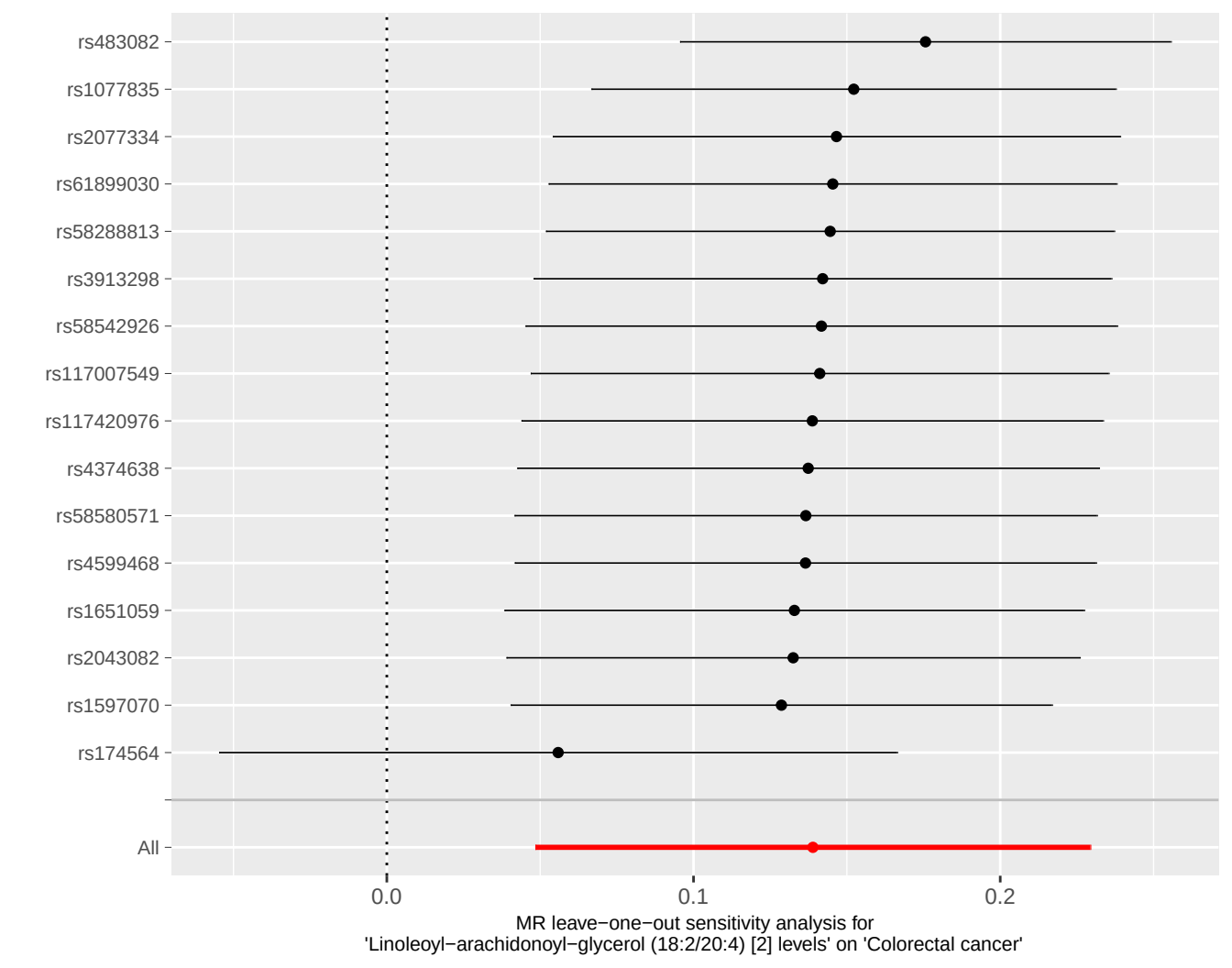
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Perfluorooctanesulfonate (PFOS) levels' on 'Colorectal cancer'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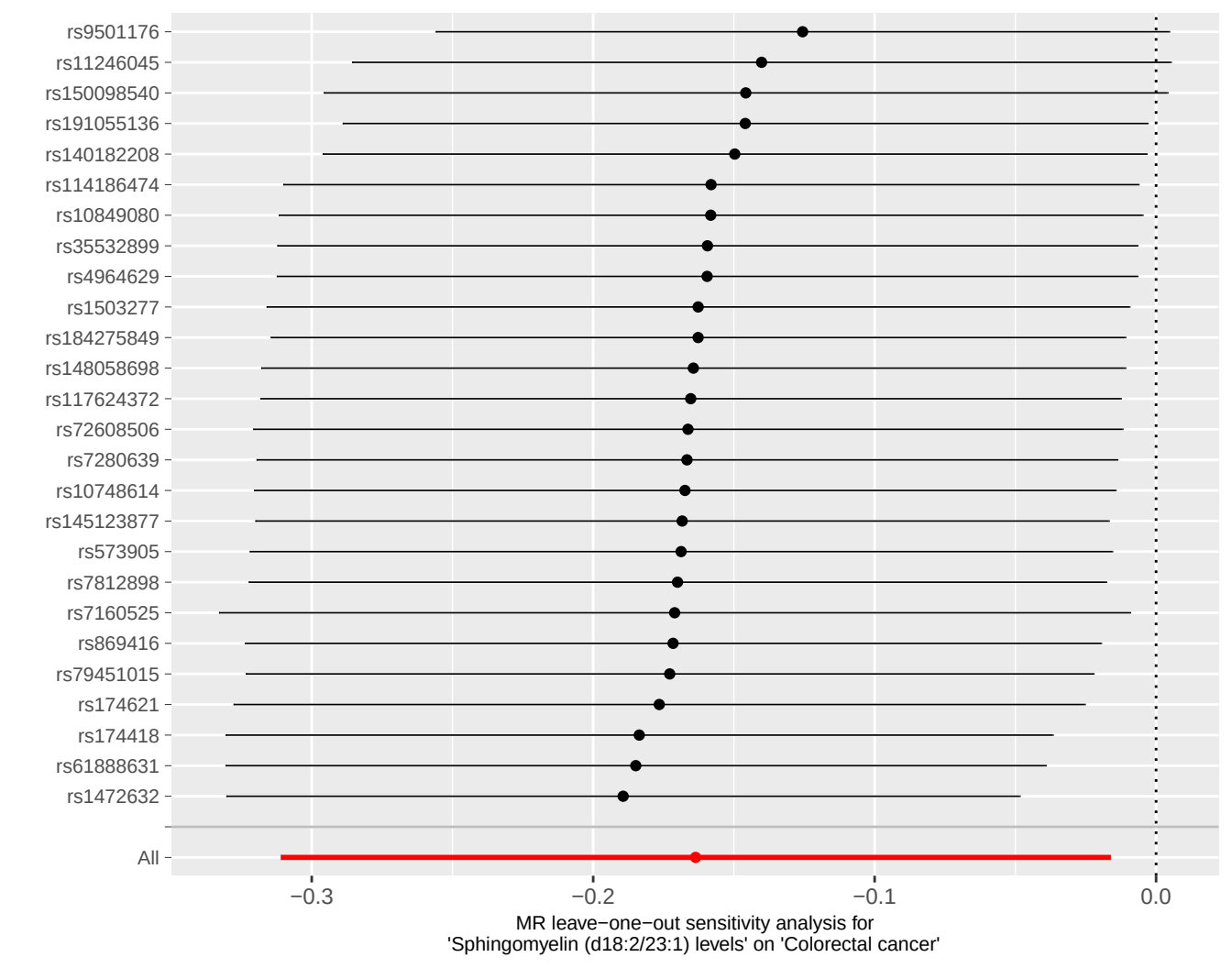
rs1651059
rs2043082
rs1597070
rs174564
All
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Linoleoyl−arachidonoyl−glycerol (18:2/20:4) [2] levels' on 'Colorectal cancer'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rs145123877
rs573905
rs7812898
rs7160525
rs869416
rs79451015
rs174621
rs174418
rs61888631
rs1472632
All
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−0.1
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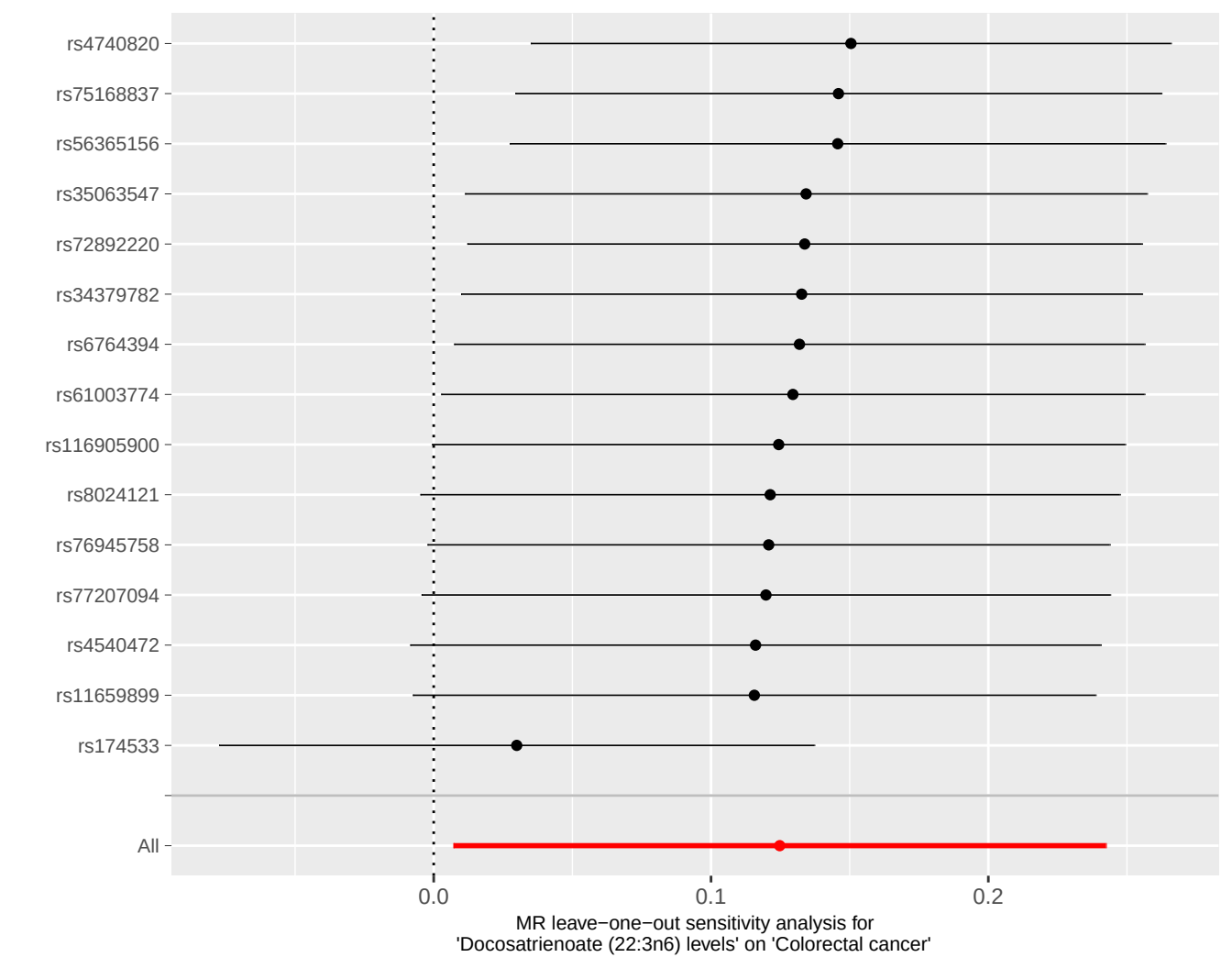
MR leave−one−out sensitivity analysis for
'Sphingomyelin (d18:2/23:1) levels' on 'Colorectal cancer'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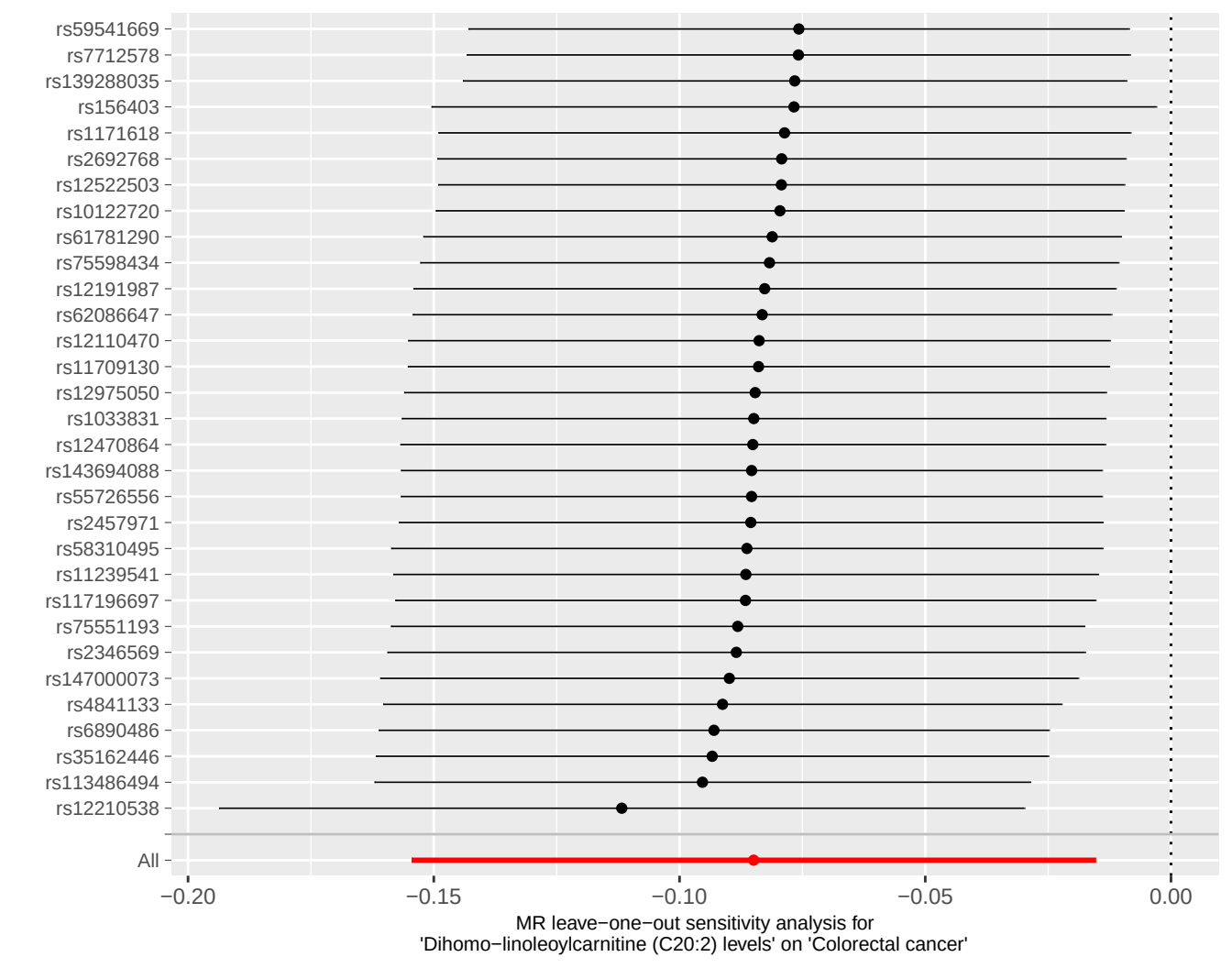
rs76945758
rs77207094
rs4540472
rs11659899
rs174533
All
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Docosatrienoate (22:3n6) levels' on 'Colorectal cancer'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rs11239541
rs117196697
rs75551193
rs2346569
rs147000073
rs4841133
rs6890486
rs35162446
rs113486494
rs12210538
All
−0.20
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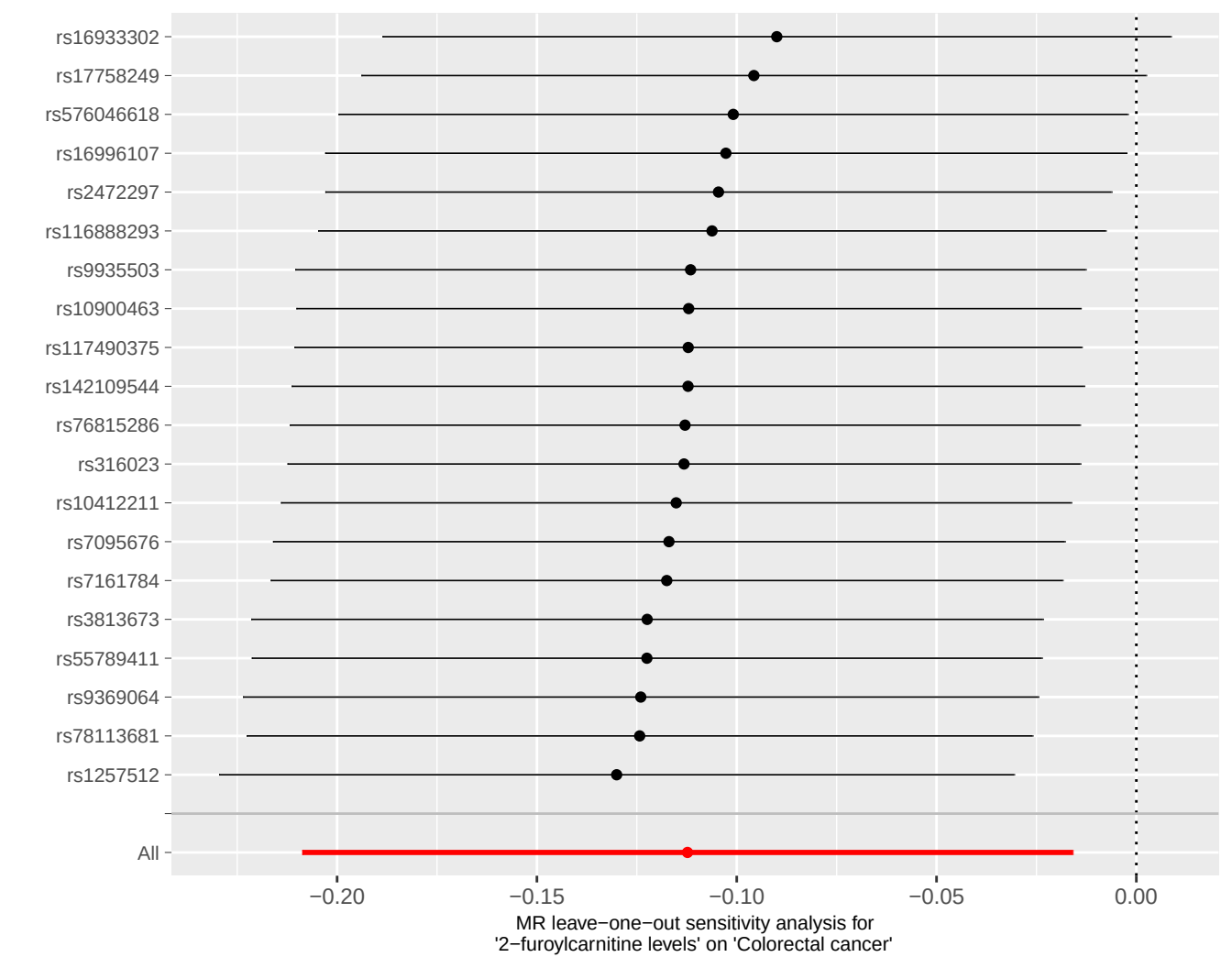
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Dihomo−linoleoylcarnitine (C20:2) levels' on 'Colorectal cancer'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rs76815286
rs316023
rs10412211
rs7095676
rs7161784
rs3813673
rs55789411
rs9369064
rs78113681
rs1257512
All
−0.20
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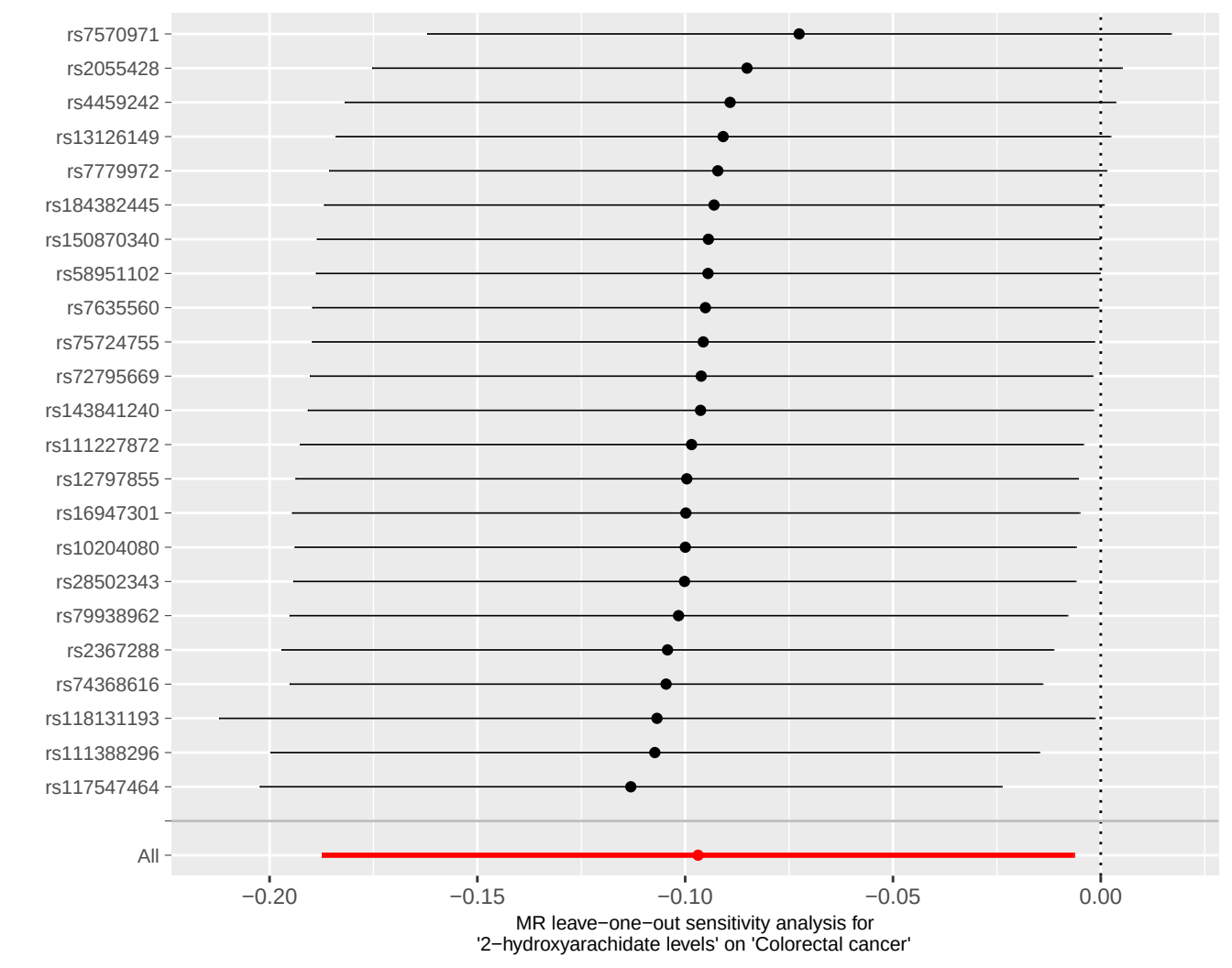
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'2−furoylcarnitine levels' on 'Colorectal cancer'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rs10204080
rs28502343
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rs2367288
rs74368616
rs118131193
rs111388296
rs117547464
All
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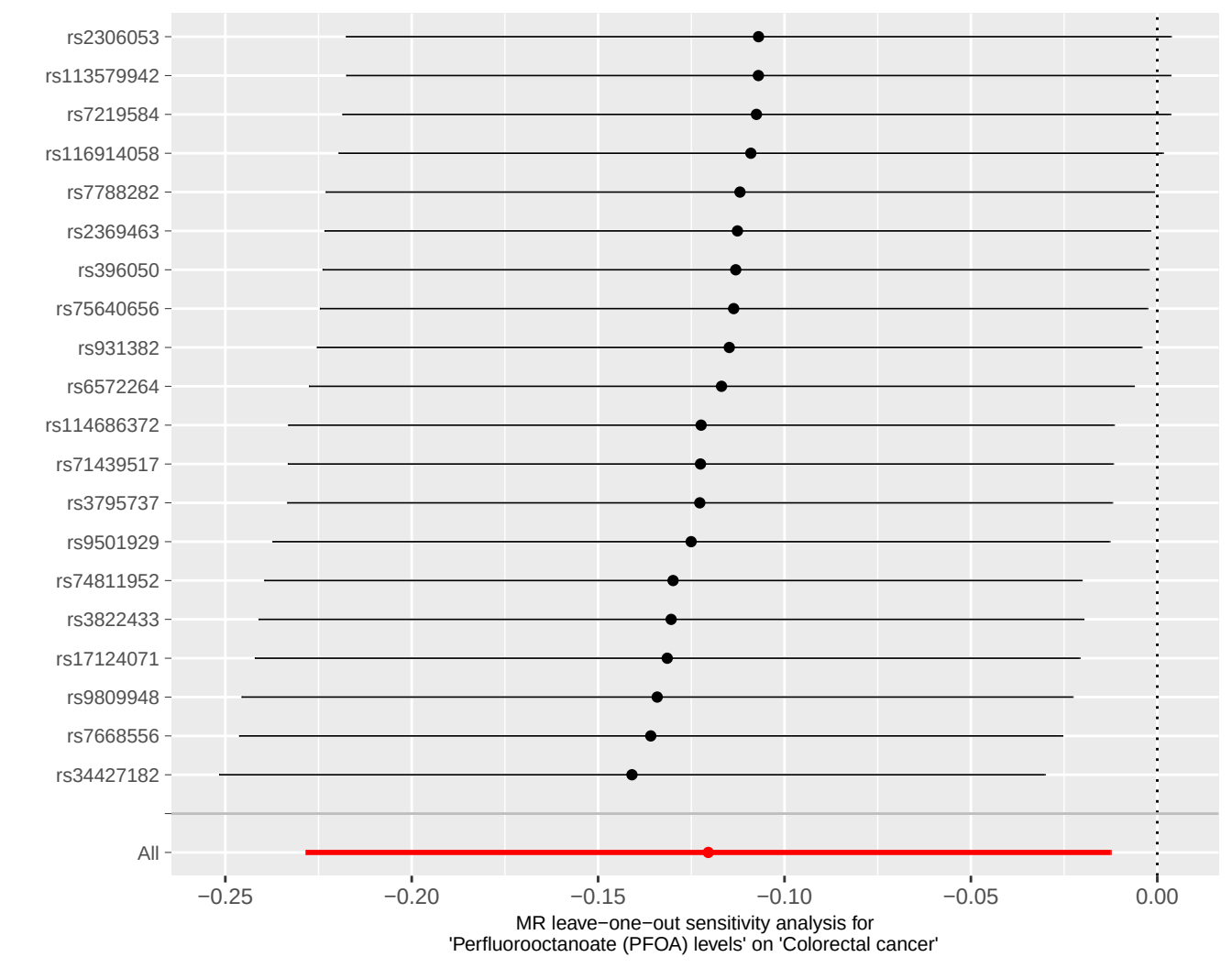
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'2−hydroxyarachidate levels' on 'Colorectal cancer'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rs71439517
rs3795737
rs9501929
rs74811952
rs3822433
rs17124071
rs9809948
rs7668556
rs34427182
All
−0.25
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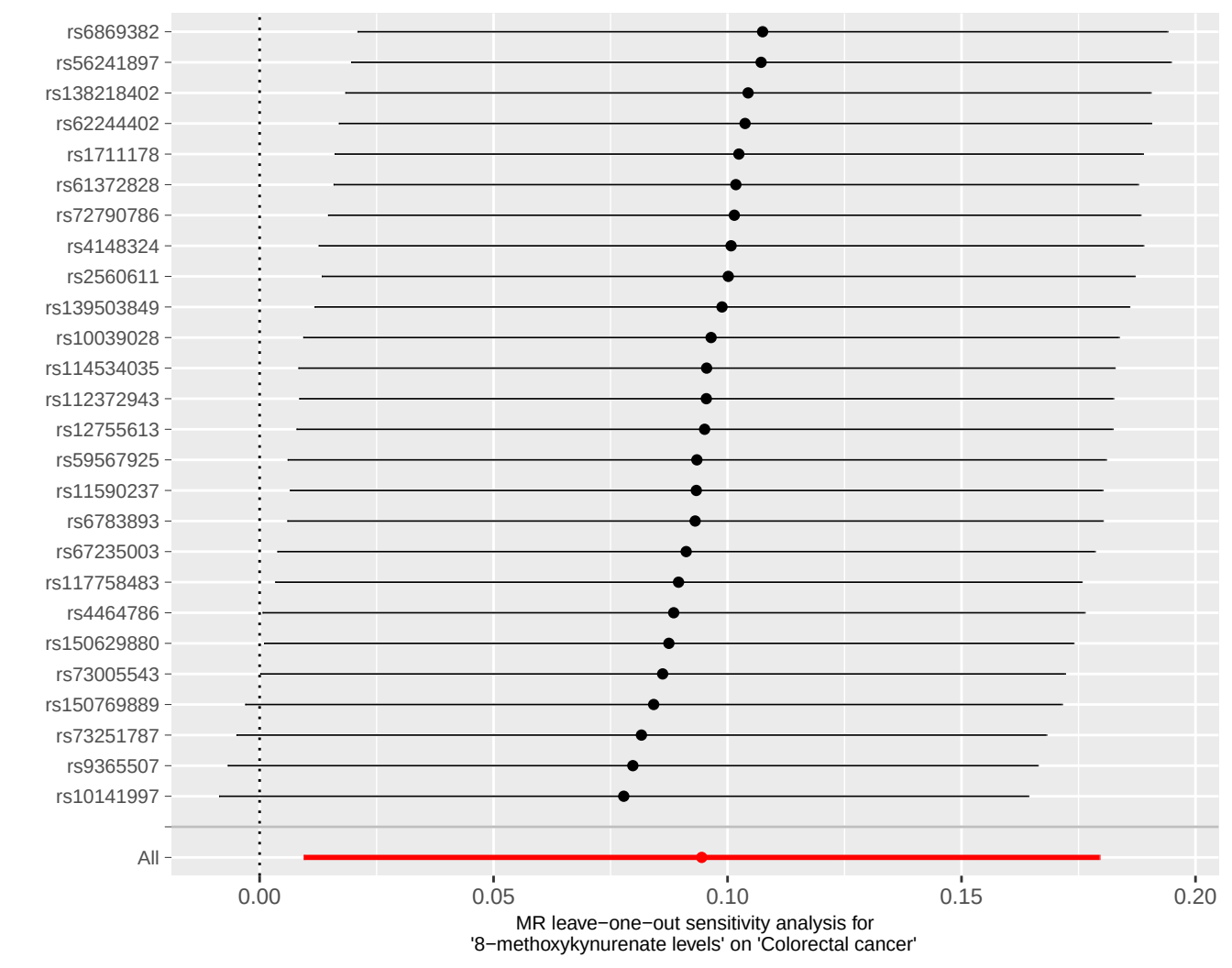
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Perfluorooctanoate (PFOA) levels' on 'Colorectal cancer'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rs6783893
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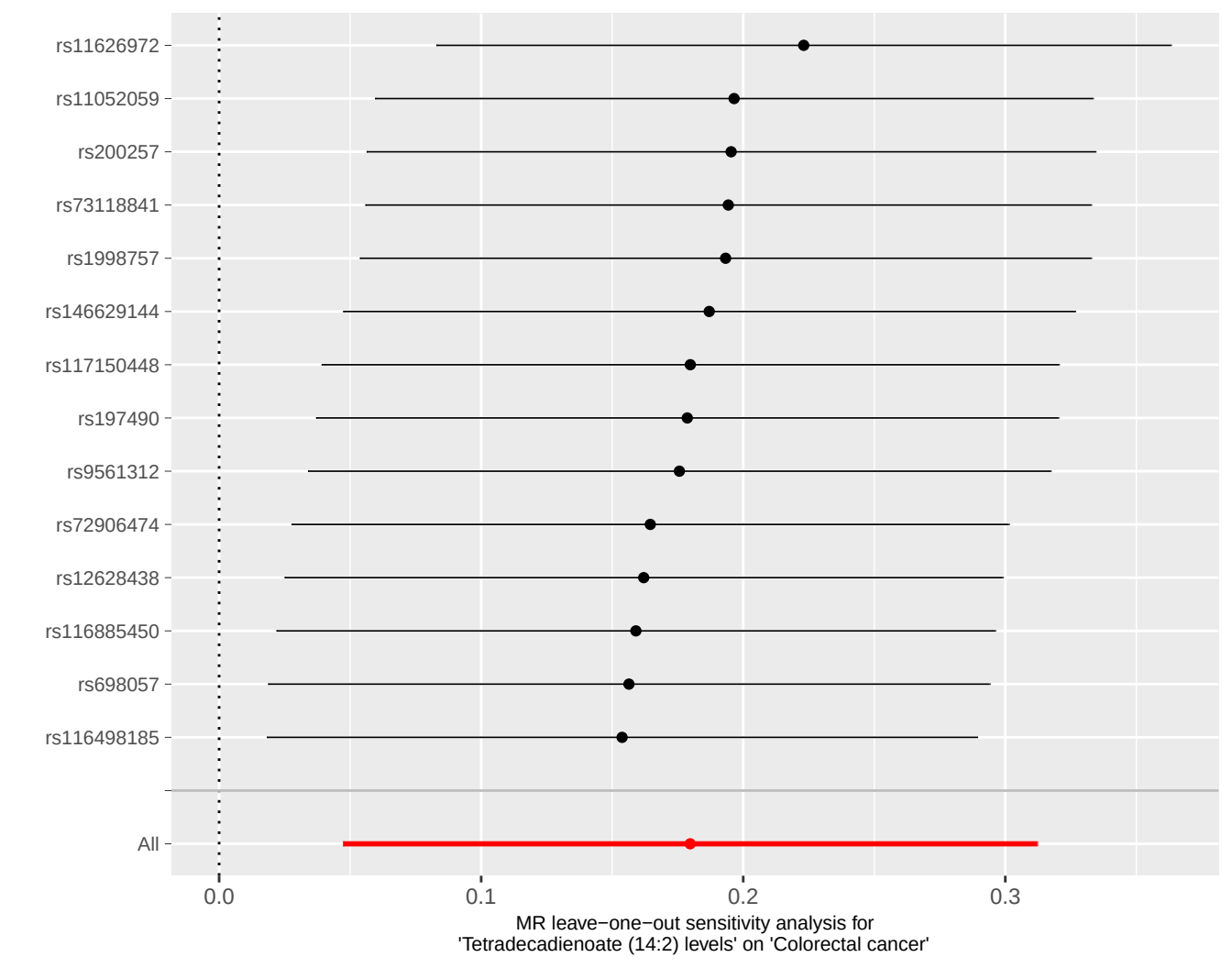
rs4464786
rs150629880
rs73005543
rs150769889
rs73251787
rs9365507
rs10141997
All
0.00
0.05
0.10
0.15
0.20
MR leave−one−out sensitivity analysis for
'8−methoxykynurenate levels' on 'Colorectal cancer'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rs12628438
rs116885450
rs698057
rs116498185
All
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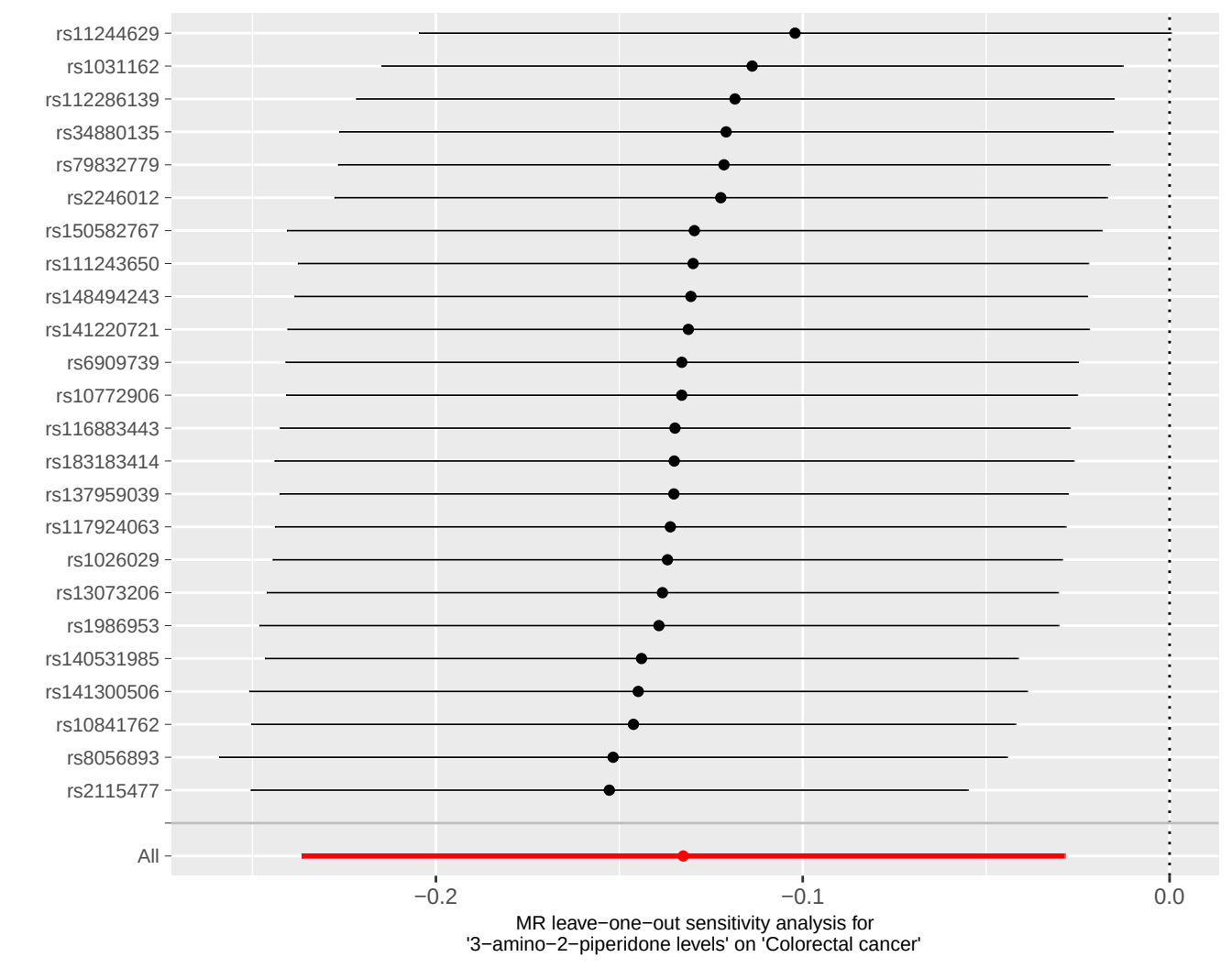
0.1
0.2
0.3
MR leave−one−out sensitivity analysis for
'Tetradecadienoate (14:2) levels' on 'Colorectal cancer'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rs137959039
rs117924063
rs1026029
rs13073206
rs1986953
rs140531985
rs141300506
rs10841762
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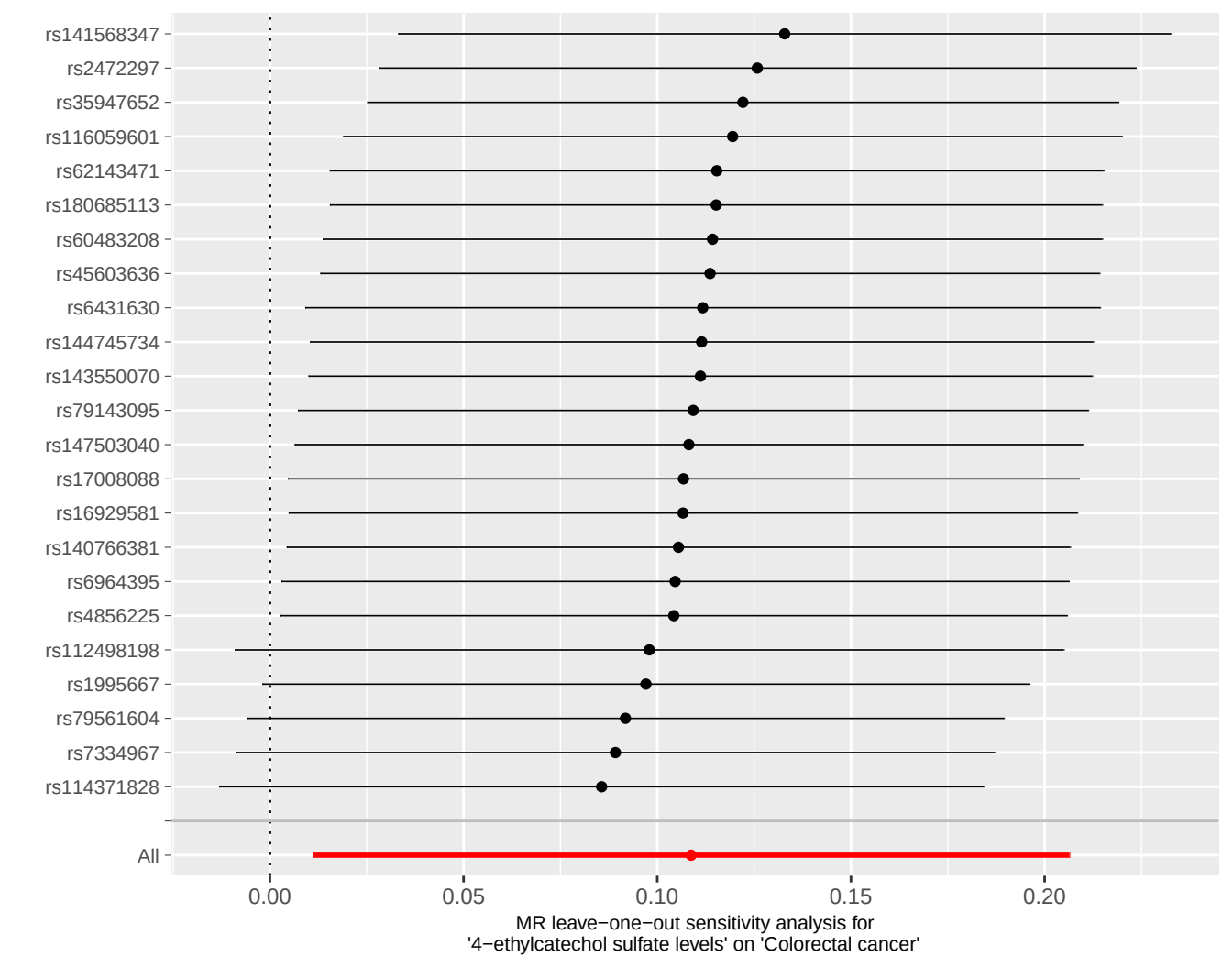
rs2115477
All
−0.2
−0.1
0.0
MR leave−one−out sensitivity analysis for
'3−amino−2−piperidone levels' on 'Colorectal cancer'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rs7334967
rs114371828
All
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0.10
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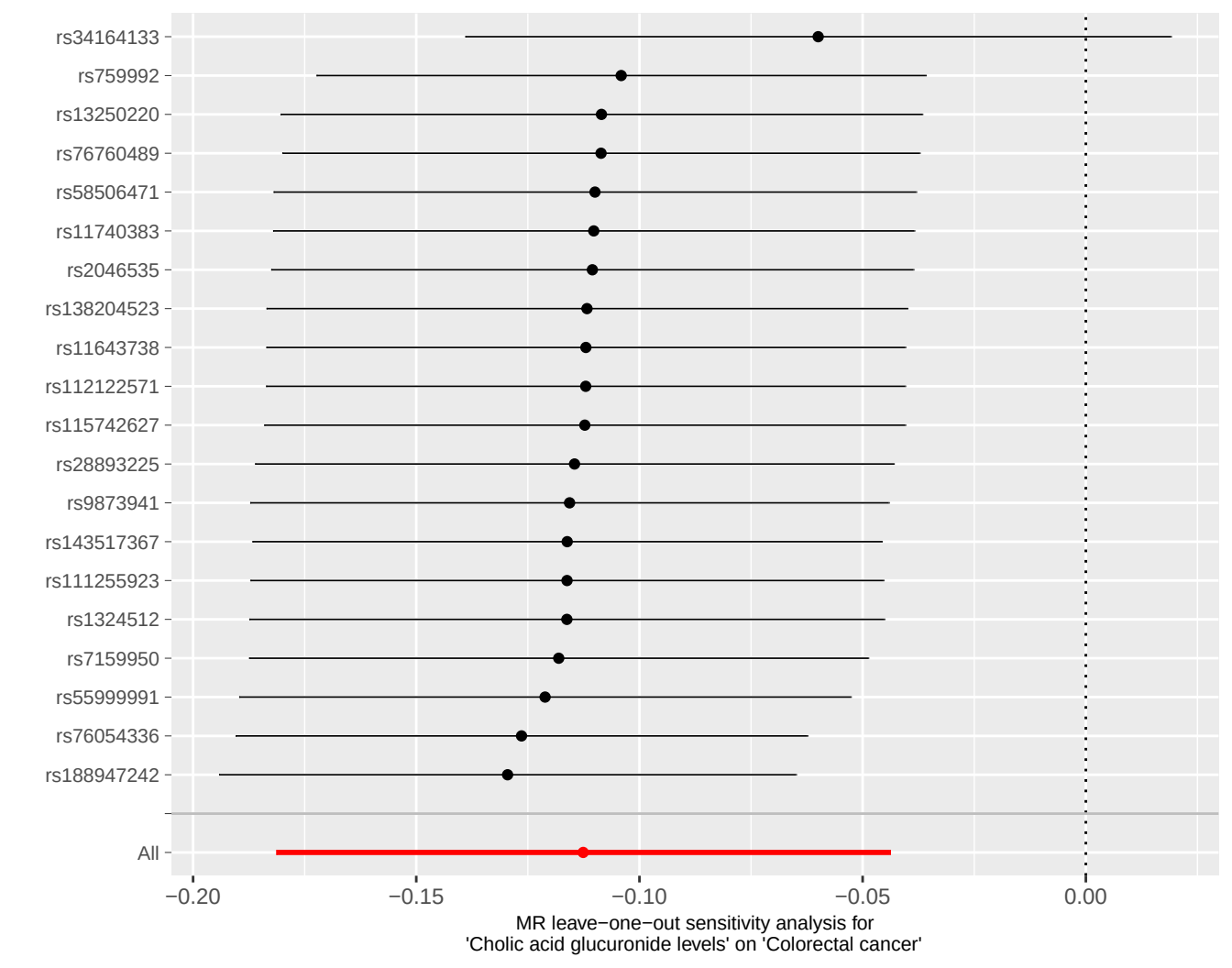
0.20
MR leave−one−out sensitivity analysis for
'4−ethylcatechol sulfate levels' on 'Colorectal cancer'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rs76054336
rs188947242
All
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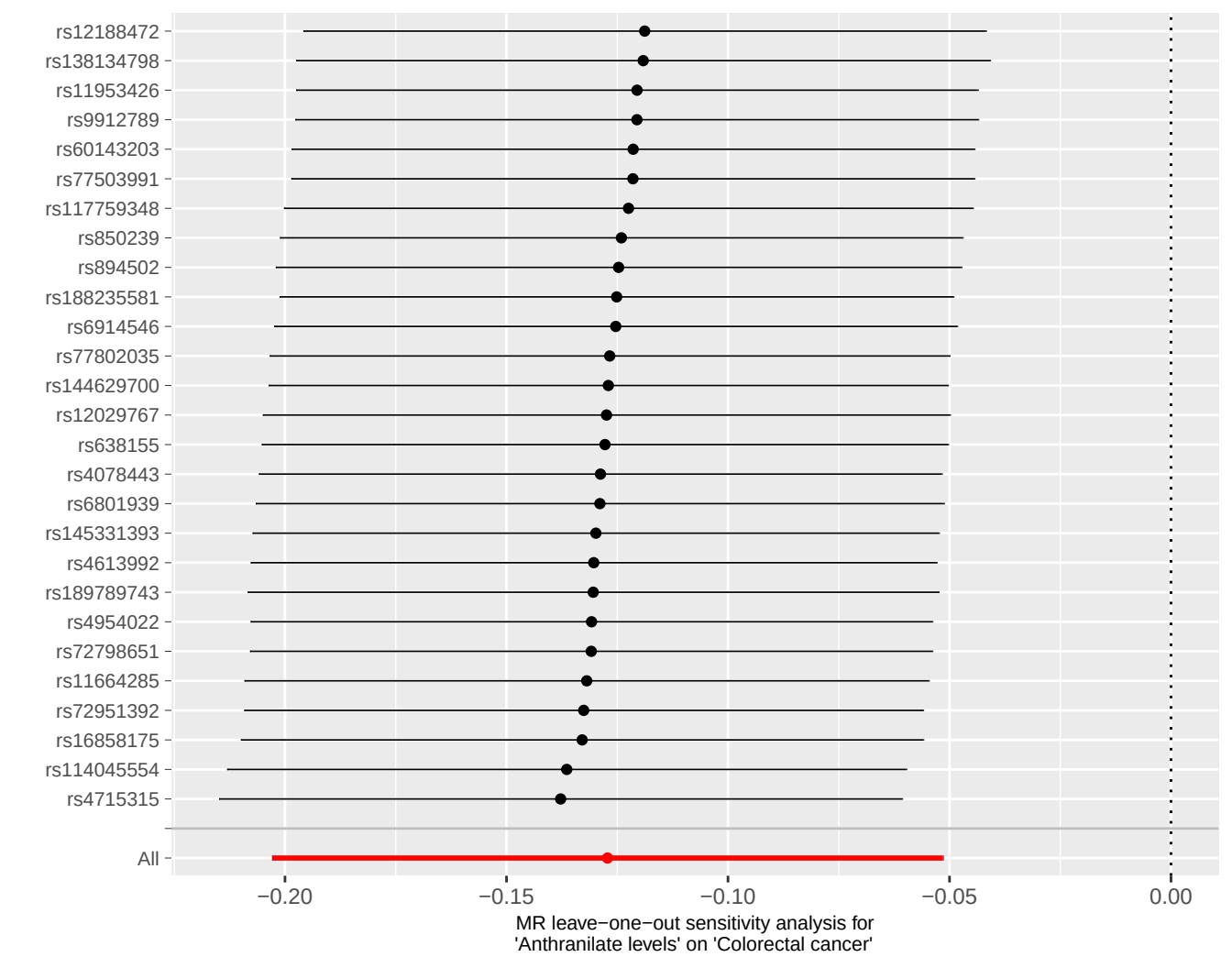
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Cholic acid glucuronide levels' on 'Colorectal cancer'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rs4613992
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rs11664285
rs72951392
rs16858175
rs114045554
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All
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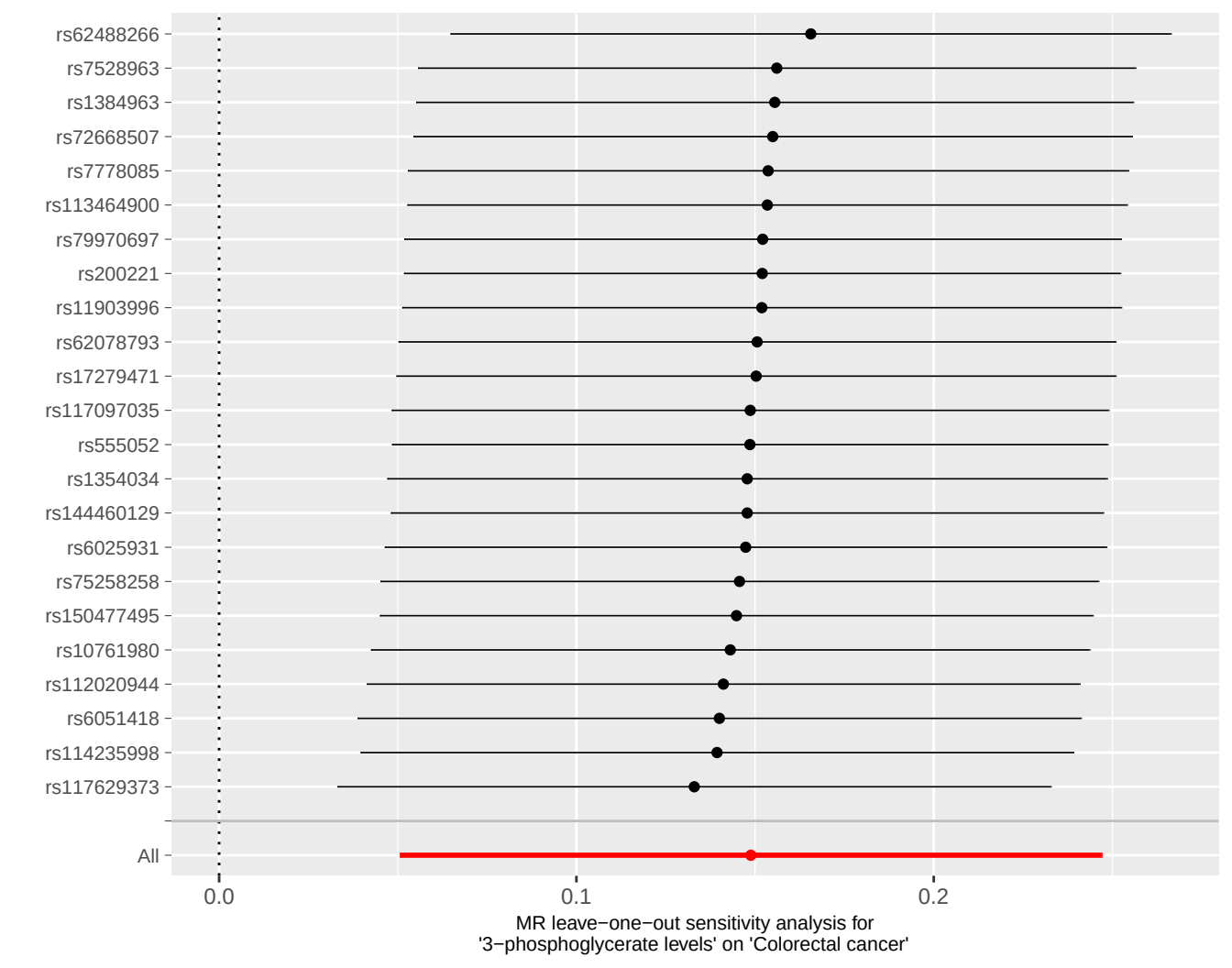
−0.15
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Anthranilate levels' on 'Colorectal cancer'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rs112020944
rs6051418
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All
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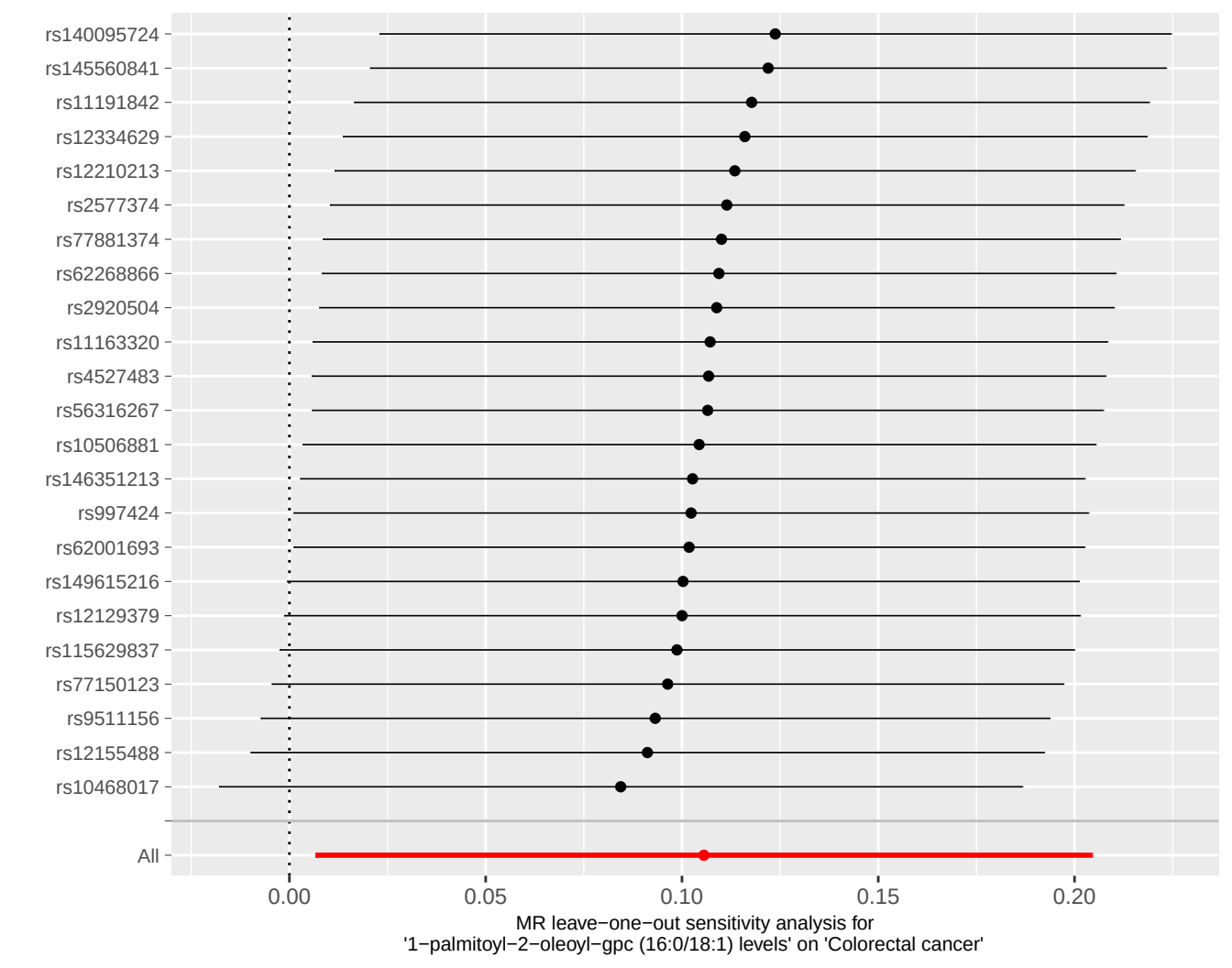
0.1
0.2
MR leave−one−out sensitivity analysis for
'3−phosphoglycerate levels' on 'Colorectal cancer'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rs9511156
rs12155488
rs10468017
All
0.00
0.05
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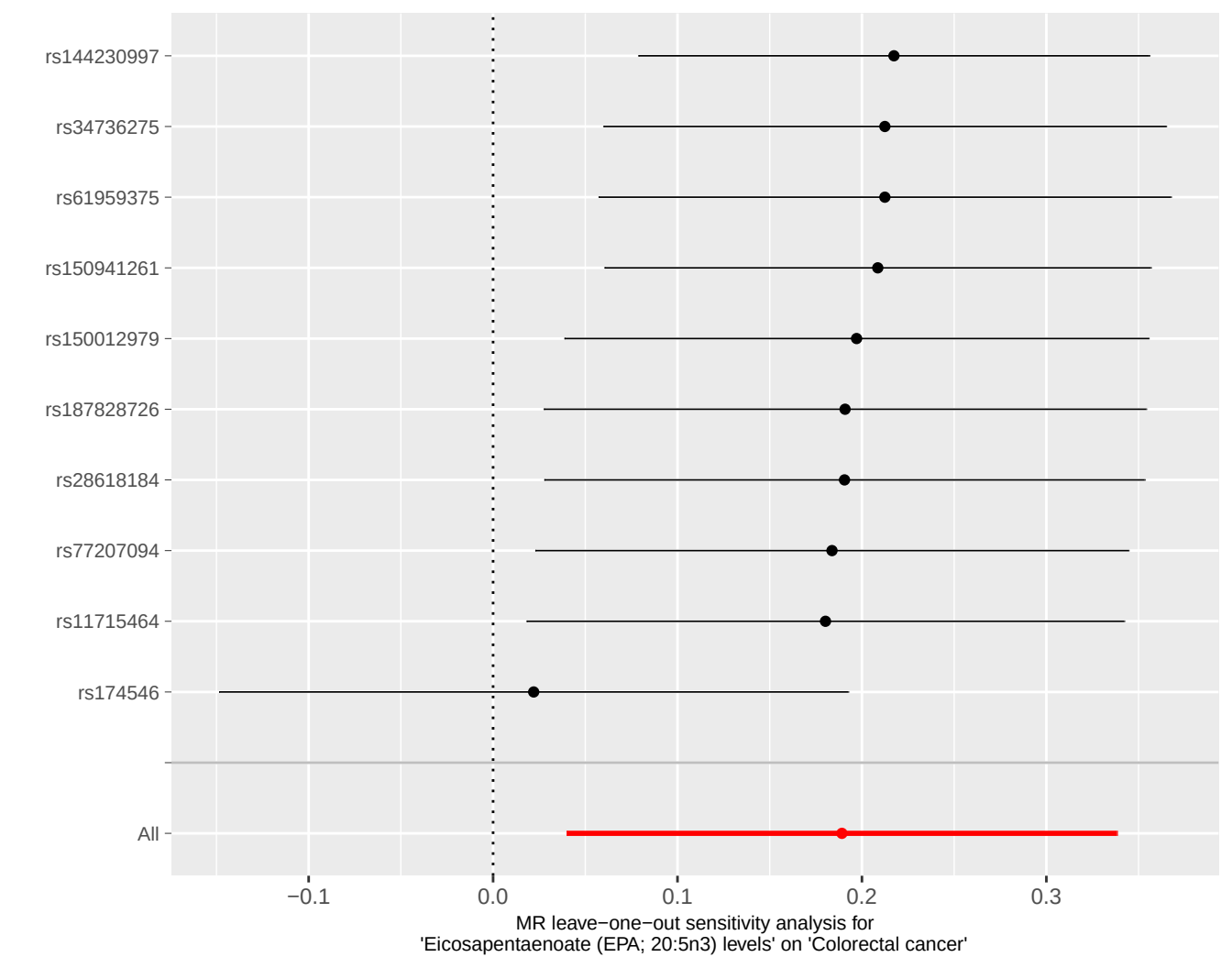
0.15
0.20
MR leave−one−out sensitivity analysis for
'1−palmitoyl−2−oleoyl−gpc (16:0/18:1) levels' on 'Colorectal cancer'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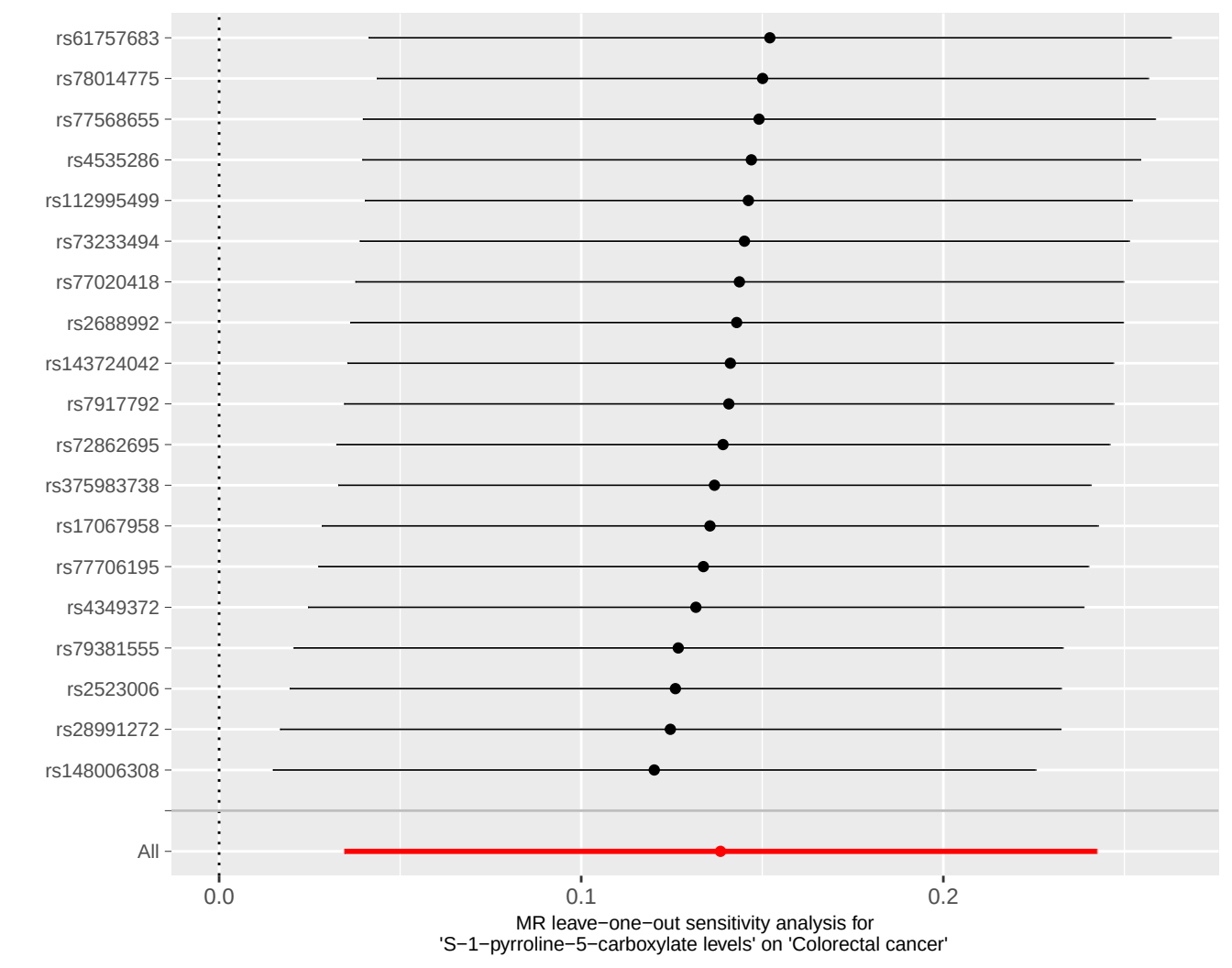
rs174546
All
−0.1
0.0
0.1
0.2
0.3
MR leave−one−out sensitivity analysis for
'Eicosapentaenoate (EPA; 20:5n3) levels' on 'Colorectal cancer'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rs17067958
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rs79381555
rs2523006
rs28991272
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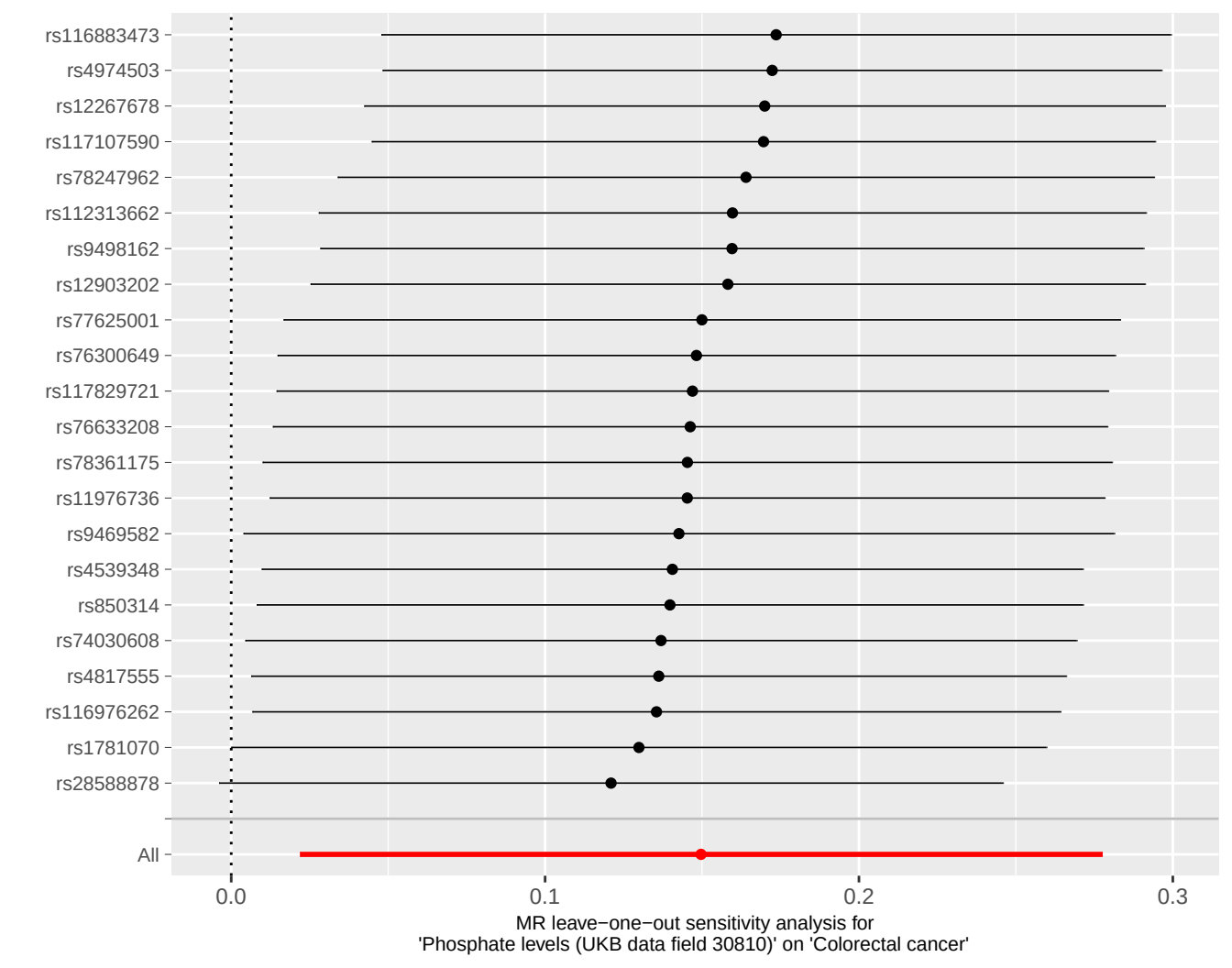
0.1
0.2
MR leave−one−out sensitivity analysis for
'S−1−pyrroline−5−carboxylate levels' on 'Colorectal cancer'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All
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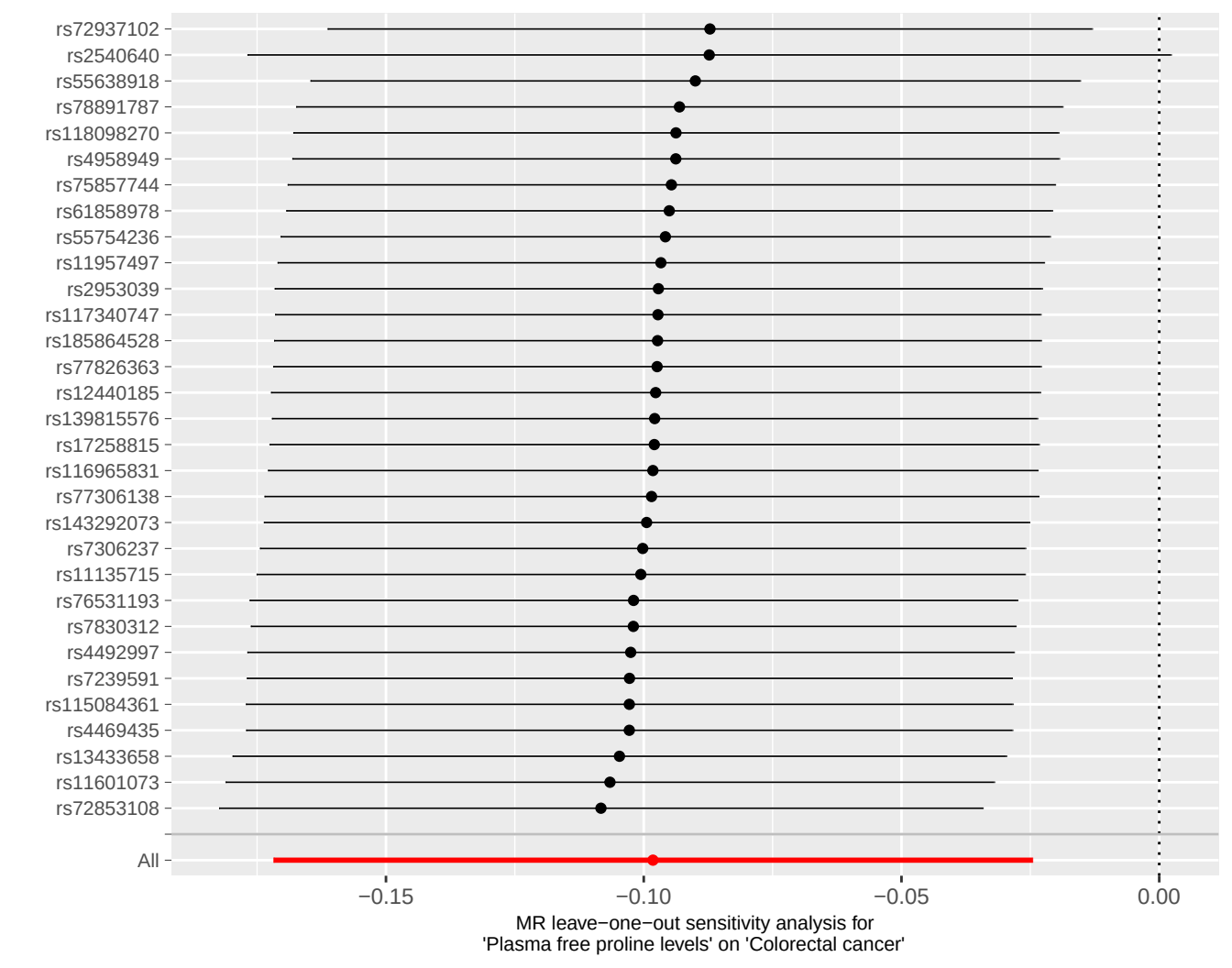
0.1
0.2
0.3
MR leave−one−out sensitivity analysis for
'Phosphate levels (UKB data field 30810)' on 'Colorectal cancer'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rs11135715
rs76531193
rs7830312
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rs7239591
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rs13433658
rs11601073
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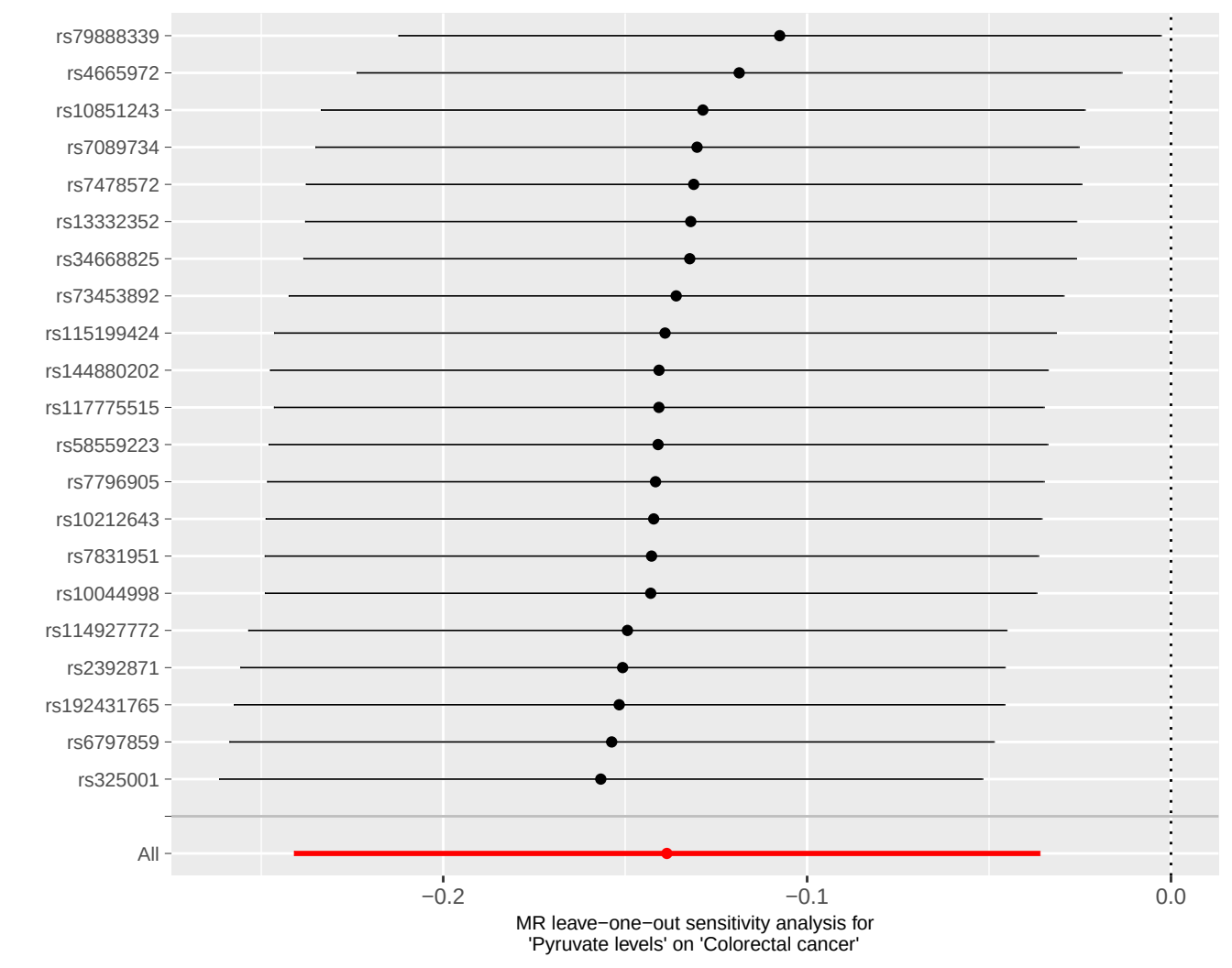
All
−0.15
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Plasma free proline levels' on 'Colorectal cancer'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rs2392871
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All
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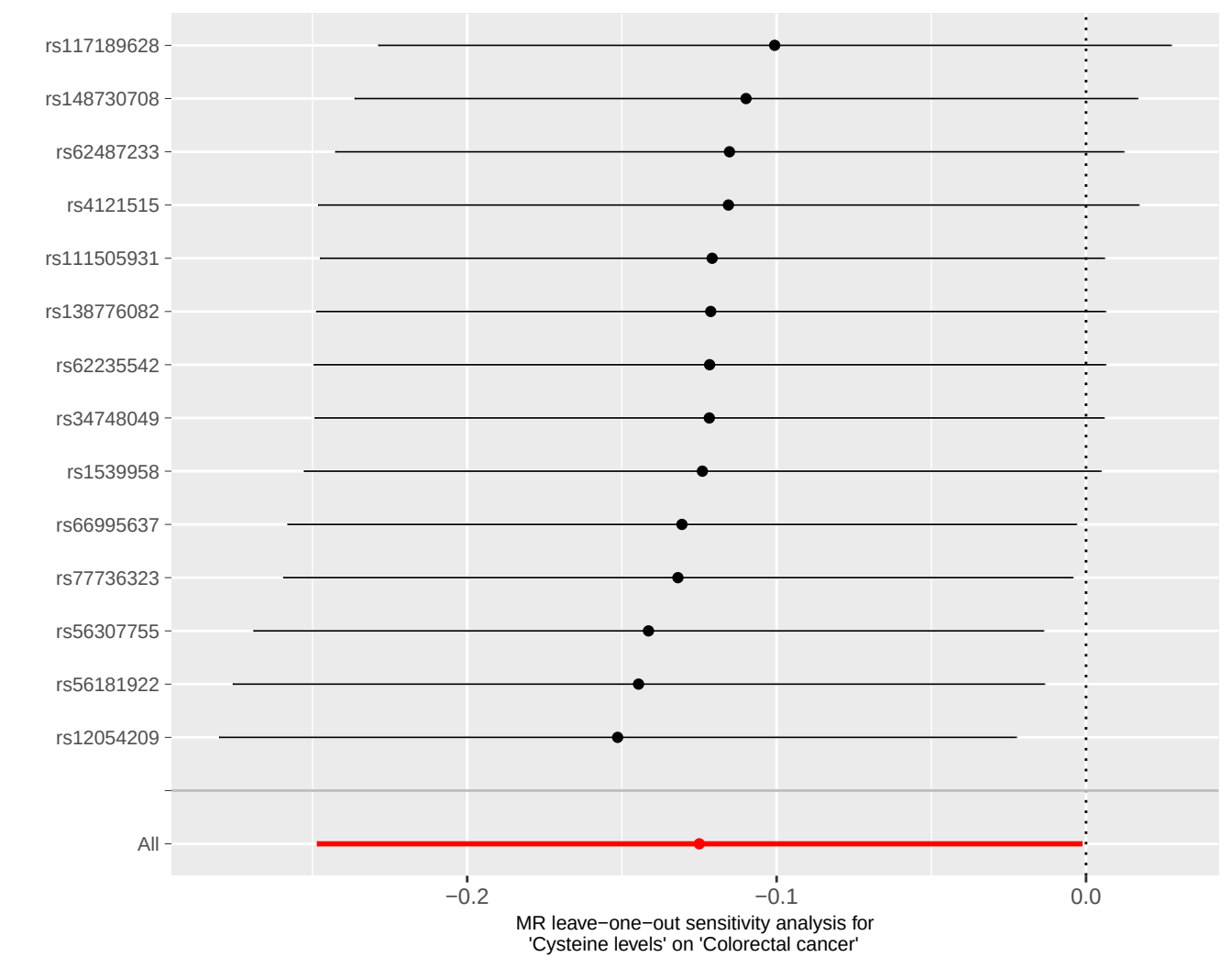
MR leave−one−out sensitivity analysis for
'Pyruvate levels' on 'Colorectal cancer'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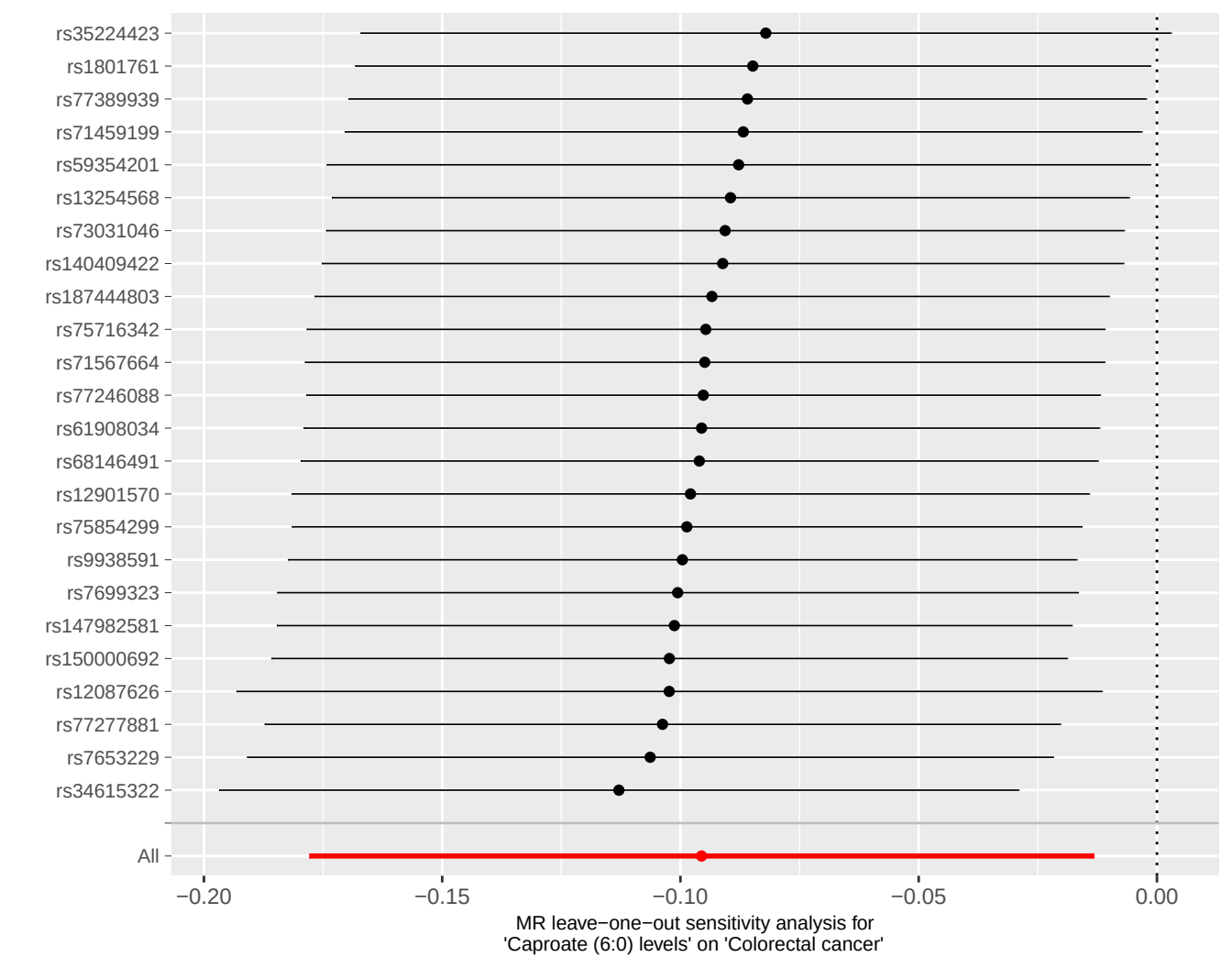
All
−0.2
−0.1
0.0
MR leave−one−out sensitivity analysis for
'Cysteine levels' on 'Colorectal cancer'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rs7653229
rs34615322
All
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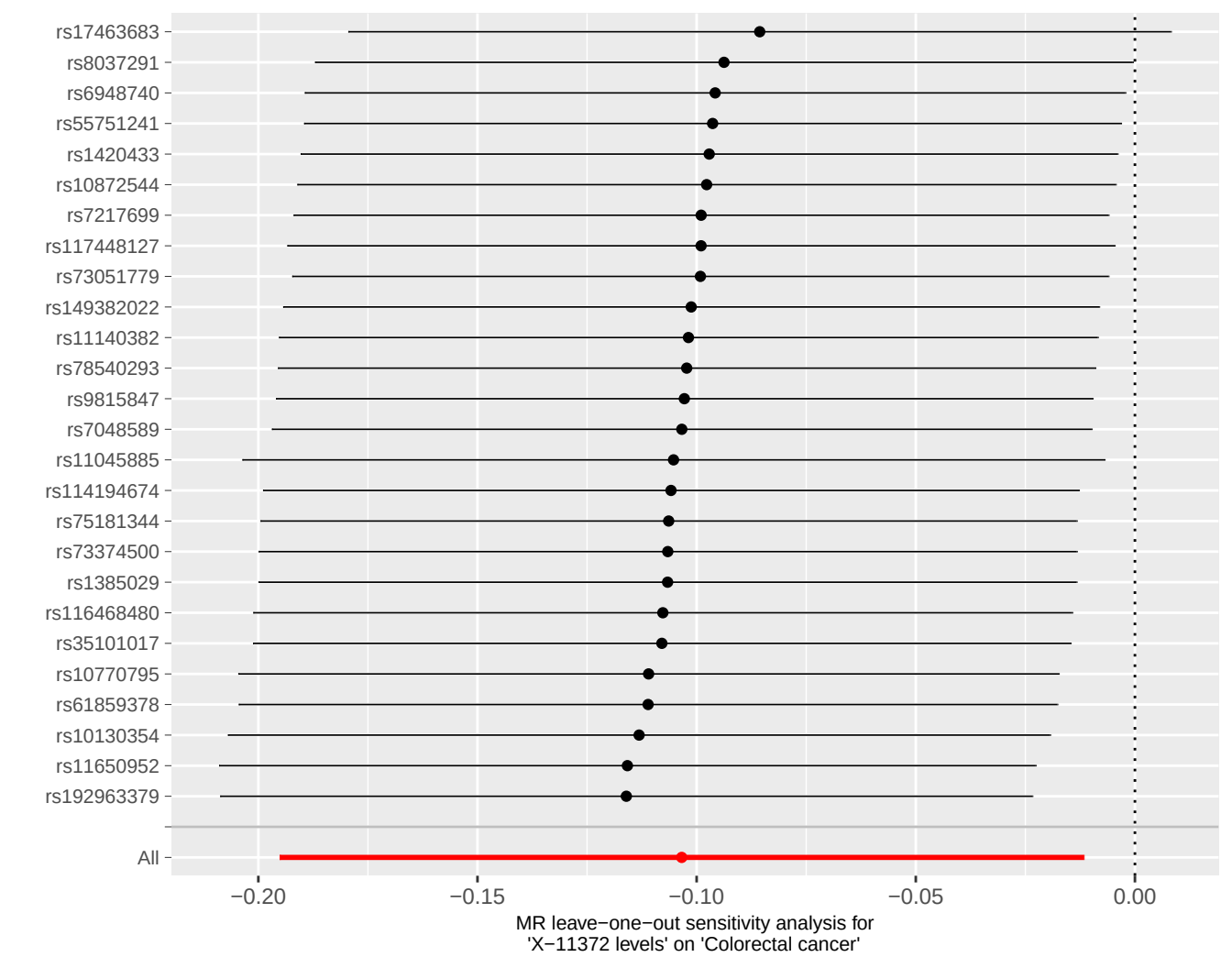
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Caproate (6:0) levels' on 'Colorectal cancer'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MR leave−one−out sensitivity analysis for
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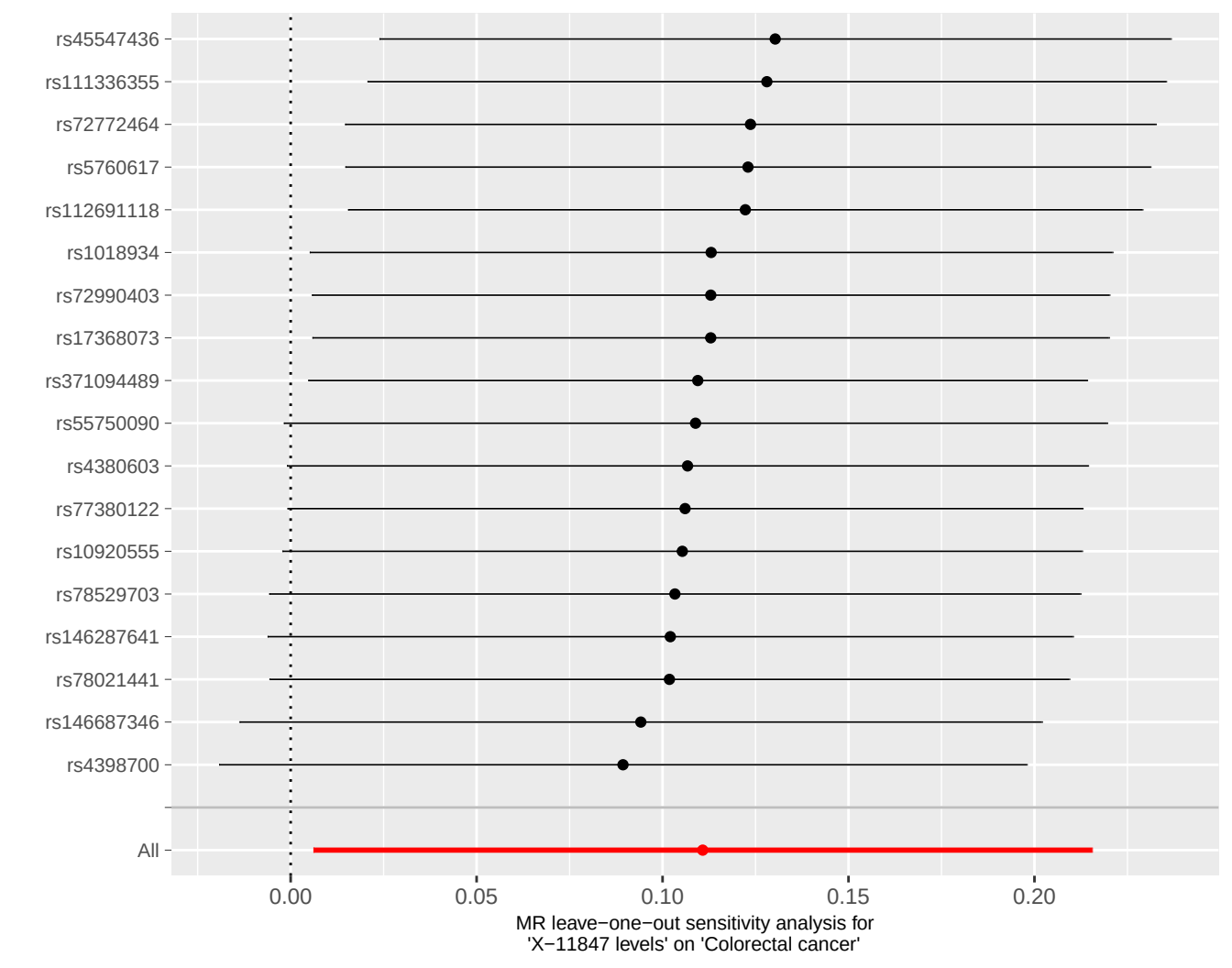
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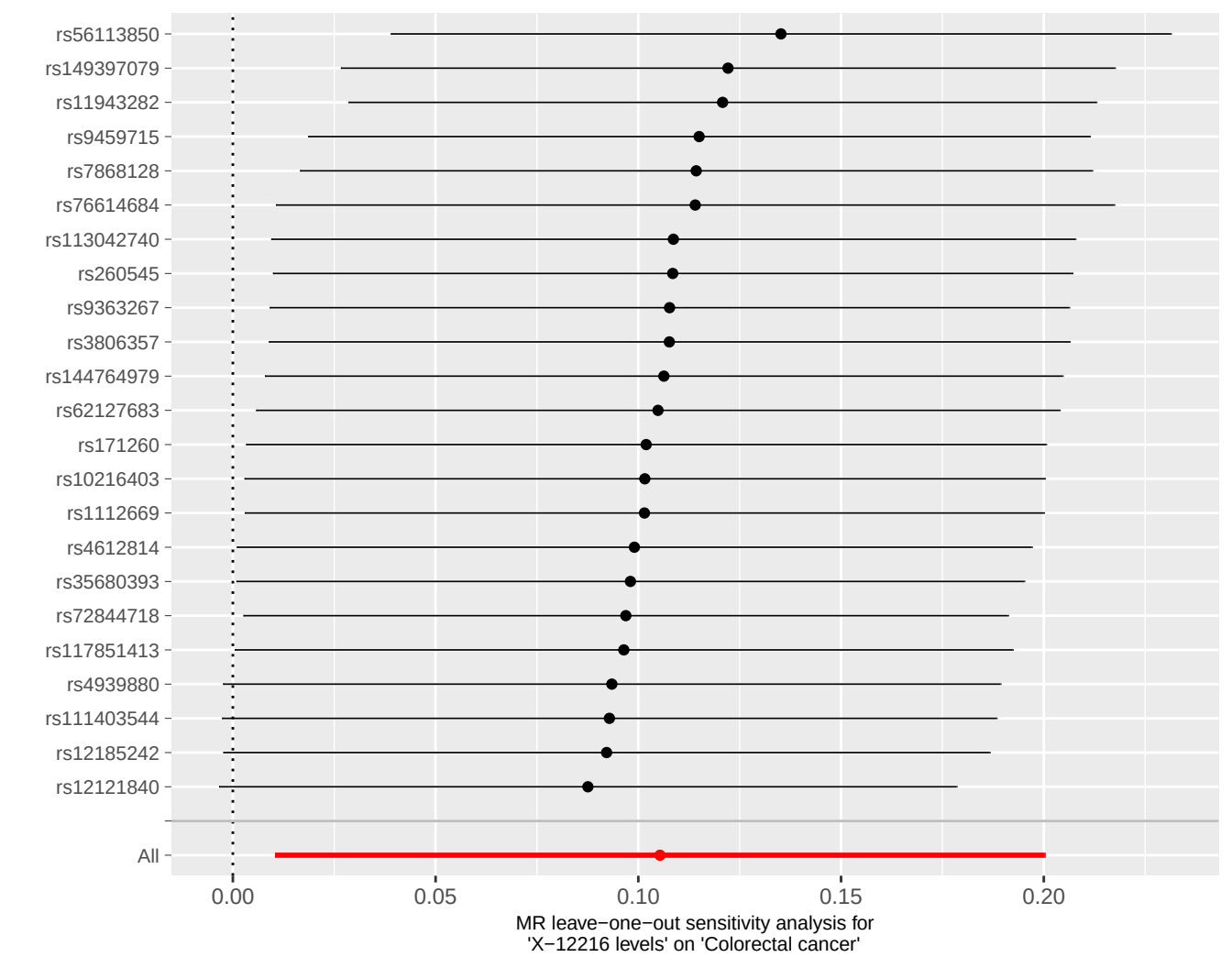
MR leave−one−out sensitivity analysis for
'X−11847 levels' on 'Colorectal cancer'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rs10216403
rs1112669
rs4612814
rs35680393
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rs4939880
rs111403544
rs12185242
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All
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MR leave−one−out sensitivity analysis for
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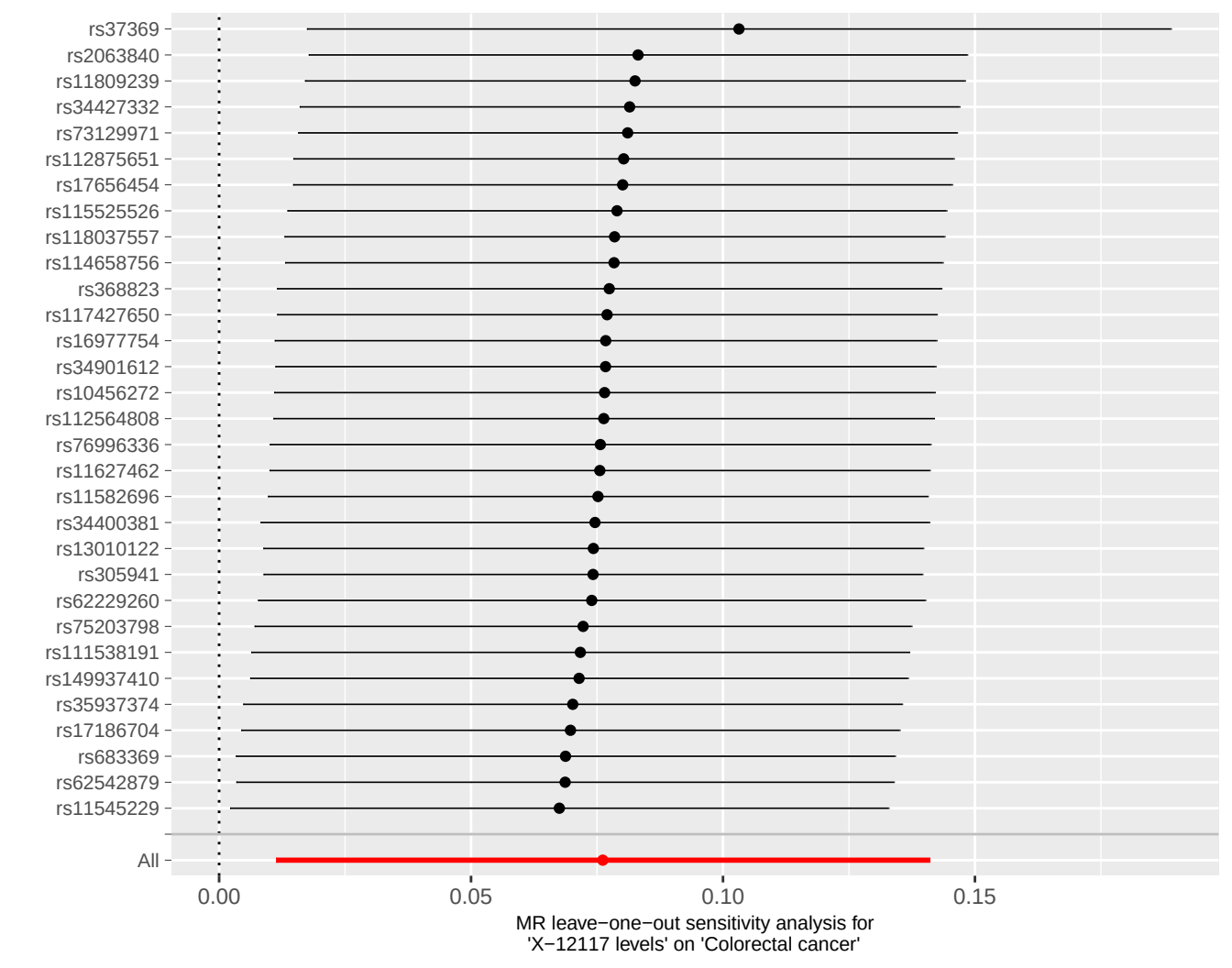
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rs305941
rs62229260
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rs149937410
rs35937374
rs17186704
rs683369
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All
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0.10
0.15
MR leave−one−out sensitivity analysis for
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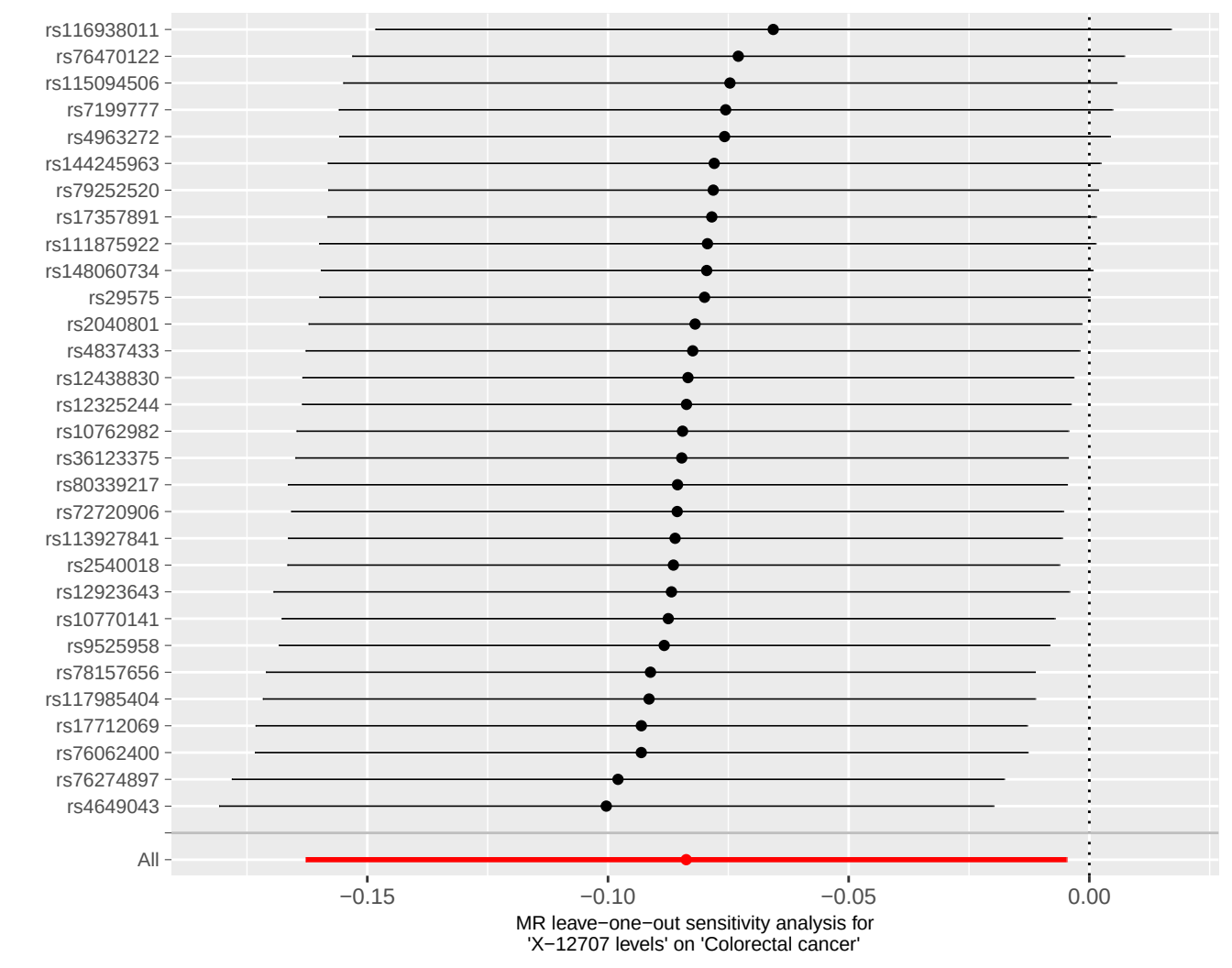
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rs2540018
rs12923643
rs10770141
rs9525958
rs78157656
rs117985404
rs17712069
rs76062400
rs76274897
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All
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−0.05
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MR leave−one−out sensitivity analysis for
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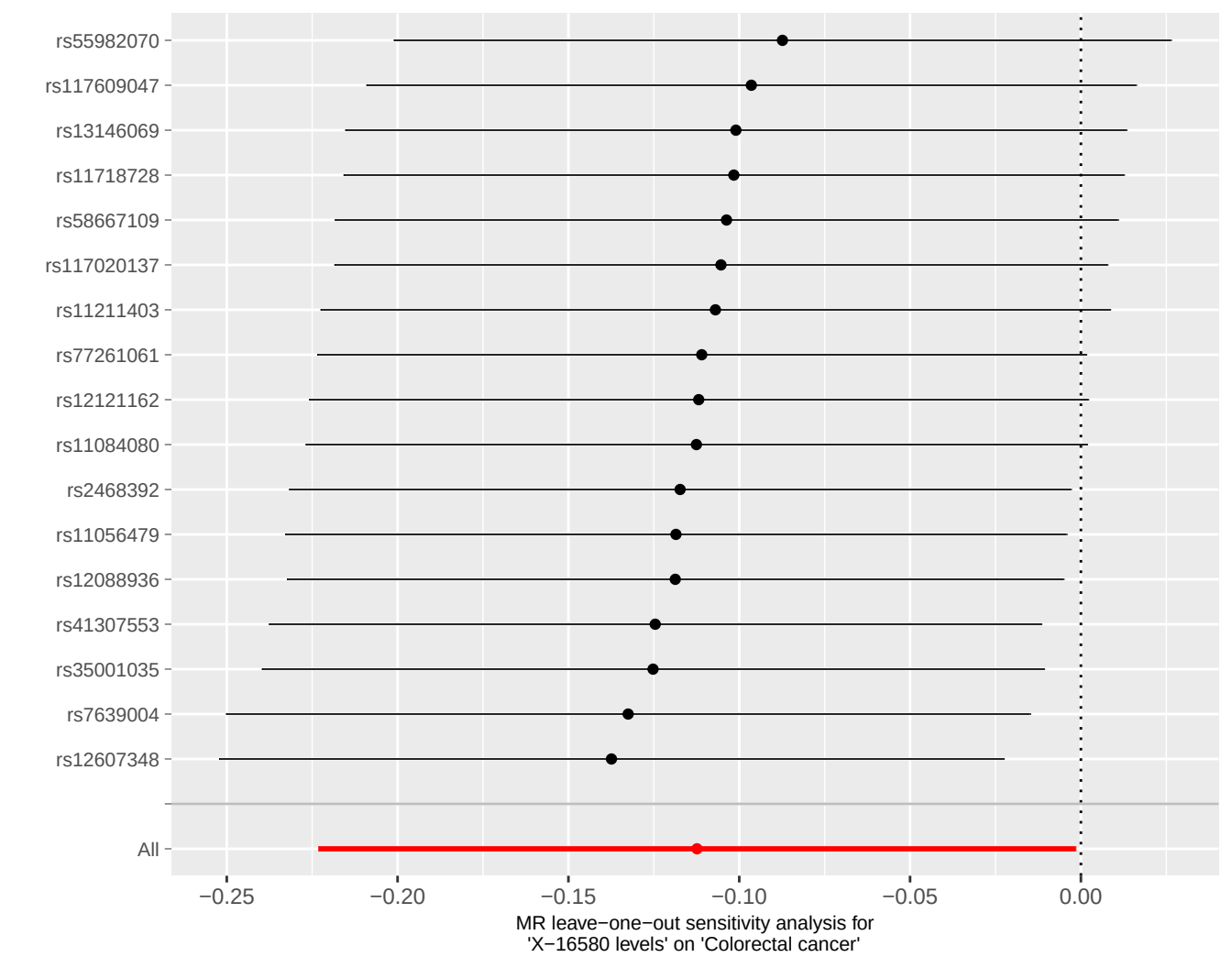
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rs2468392
rs11056479
rs12088936
rs41307553
rs35001035
rs7639004
rs12607348
All
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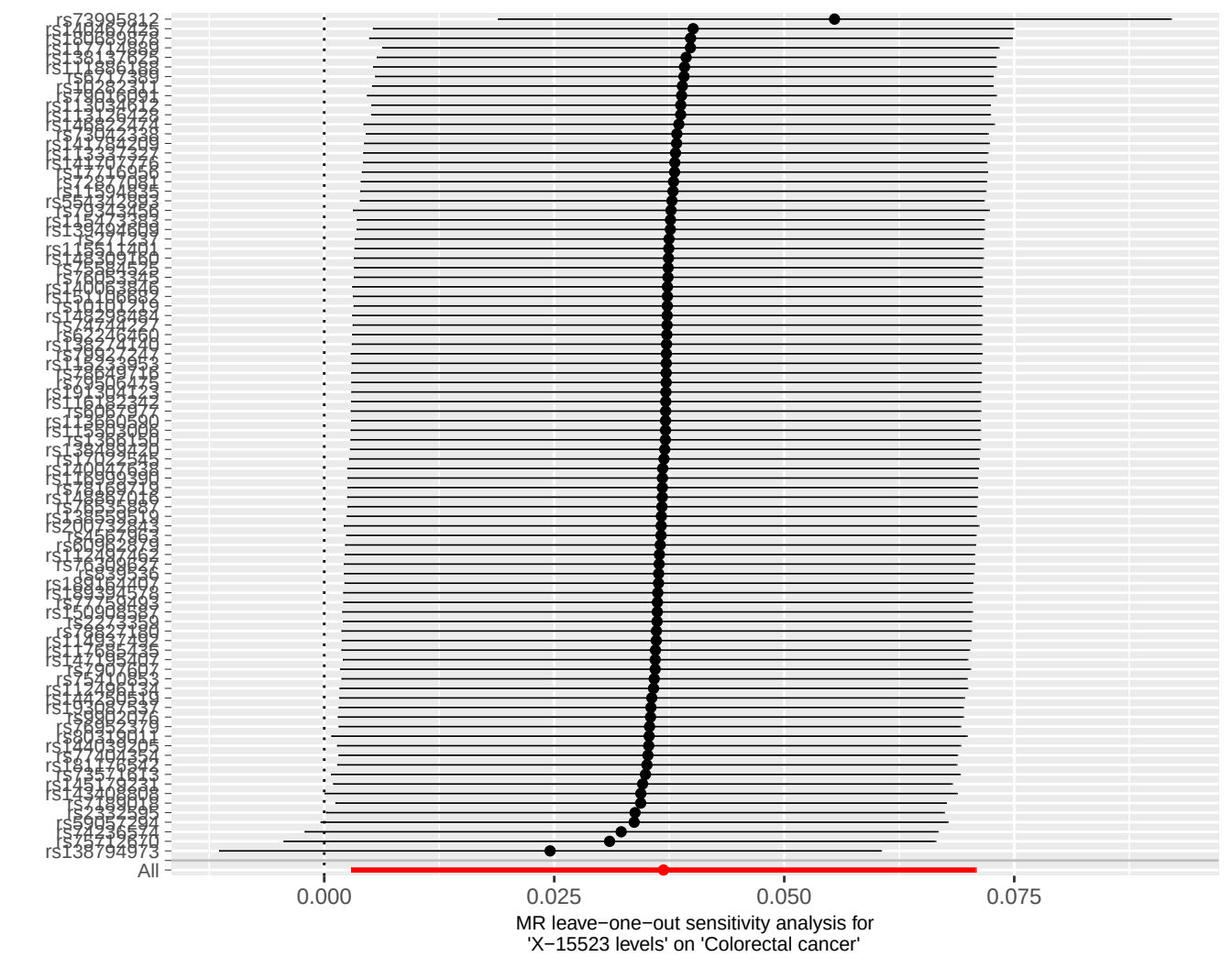
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'X−16580 levels' on 'Colorectal cancer'


All
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0.050
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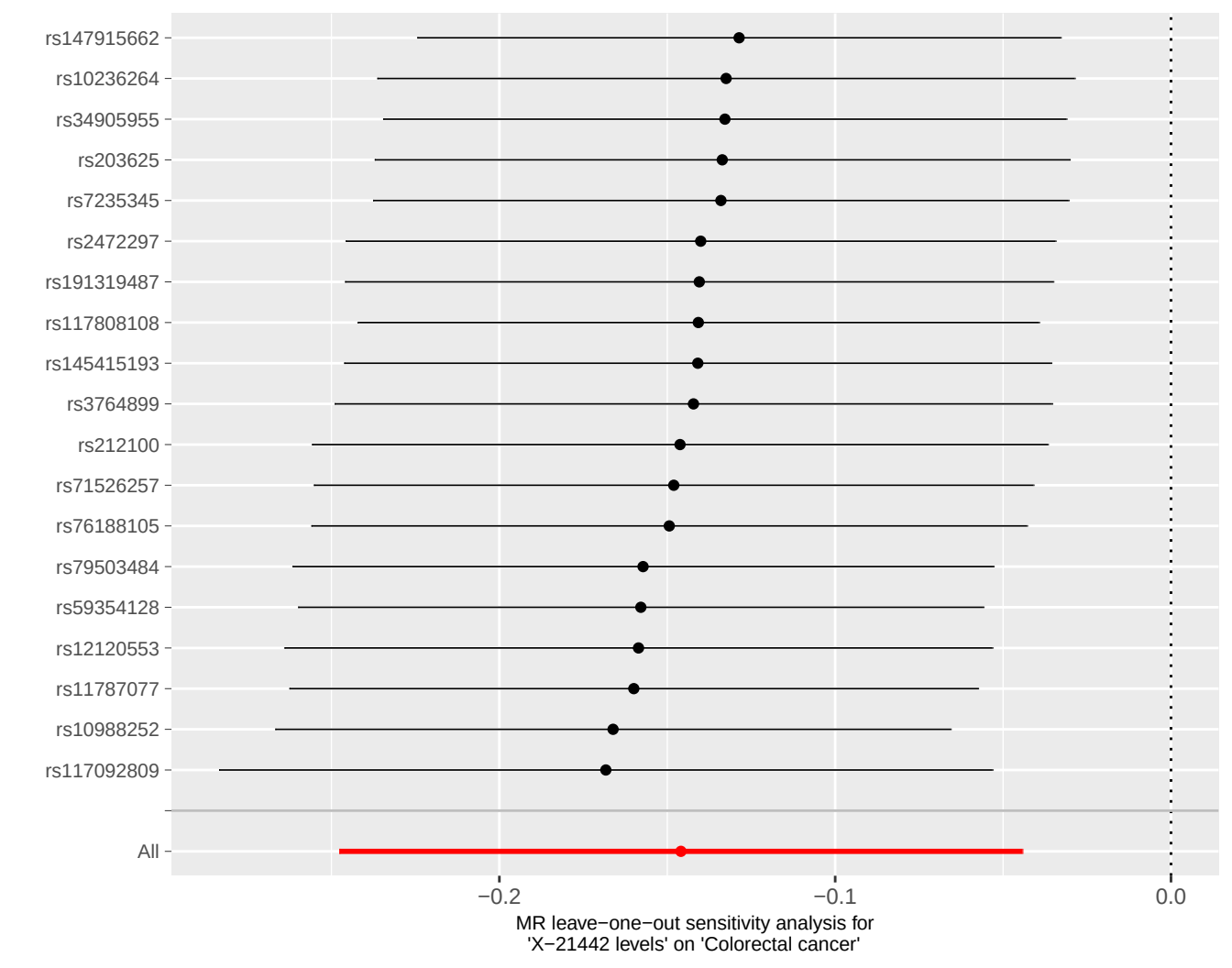
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rs76188105
rs79503484
rs59354128
rs12120553
rs11787077
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All
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MR leave−one−out sensitivity analysis for
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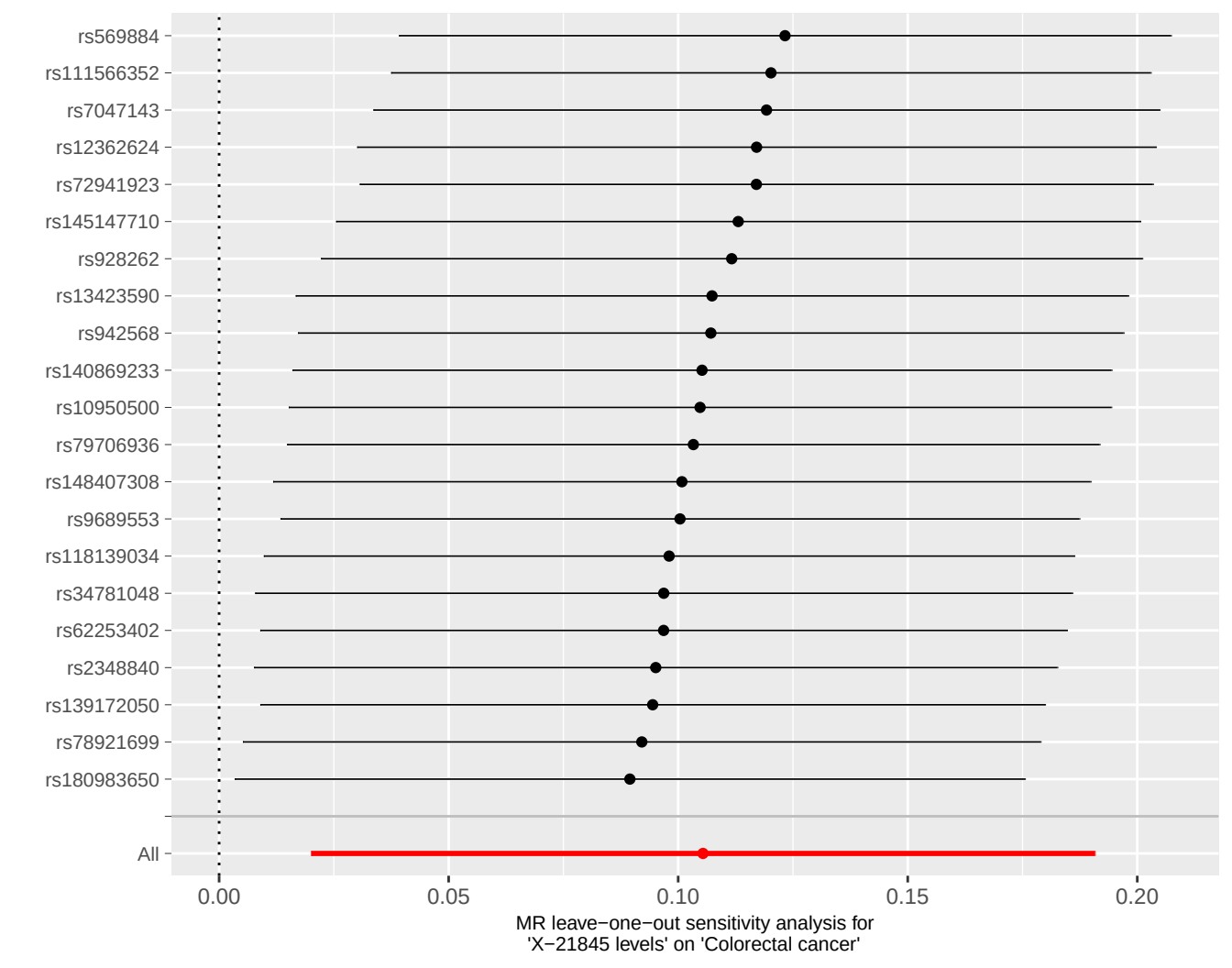
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rs148407308
rs9689553
rs118139034
rs34781048
rs62253402
rs2348840
rs139172050
rs78921699
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All
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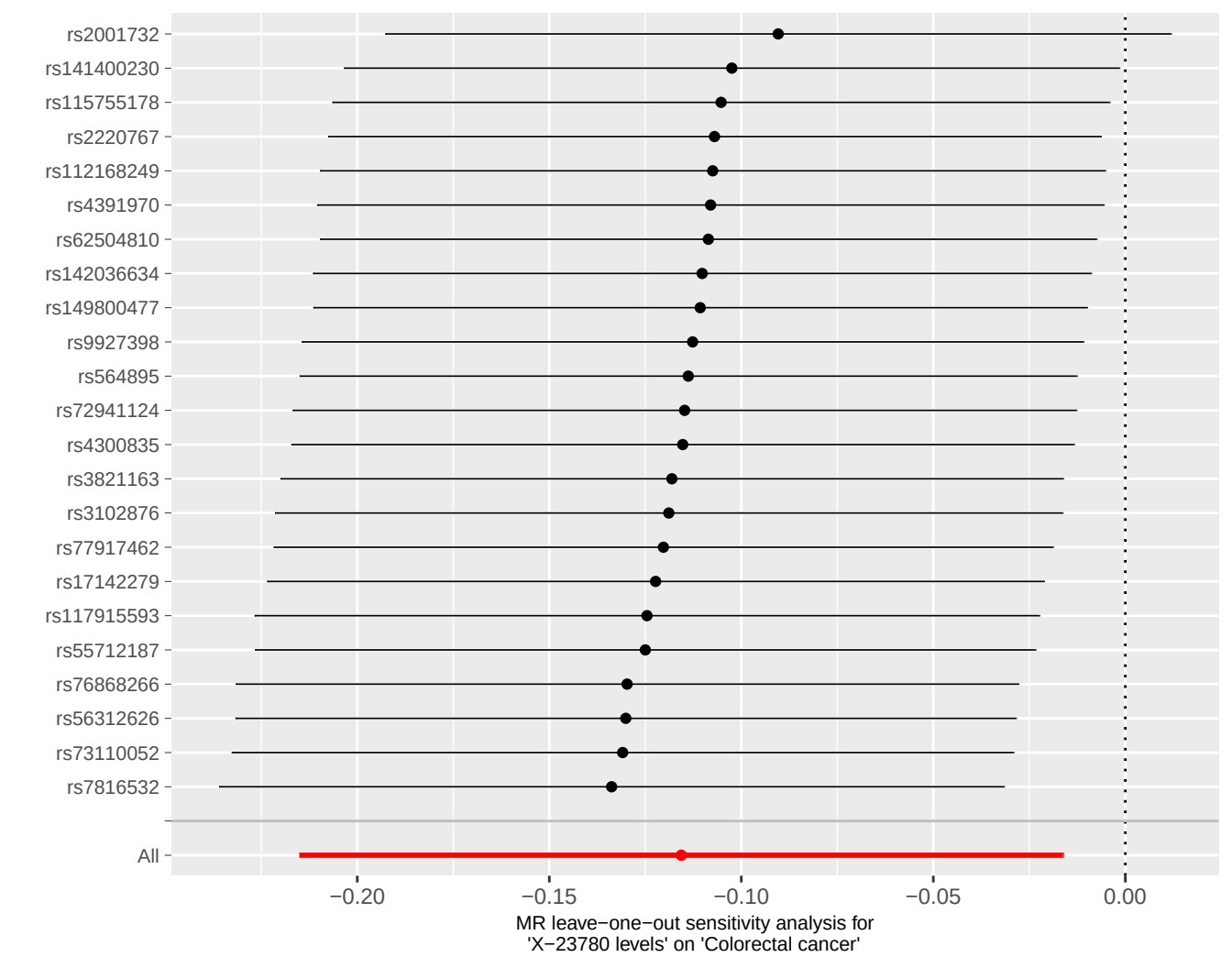
0.05
0.10
0.15
0.20
MR leave−one−out sensitivity analysis for
'X−21845 levels' on 'Colorectal cancer'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rs3102876
rs77917462
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rs117915593
rs55712187
rs76868266
rs56312626
rs73110052
rs7816532
All
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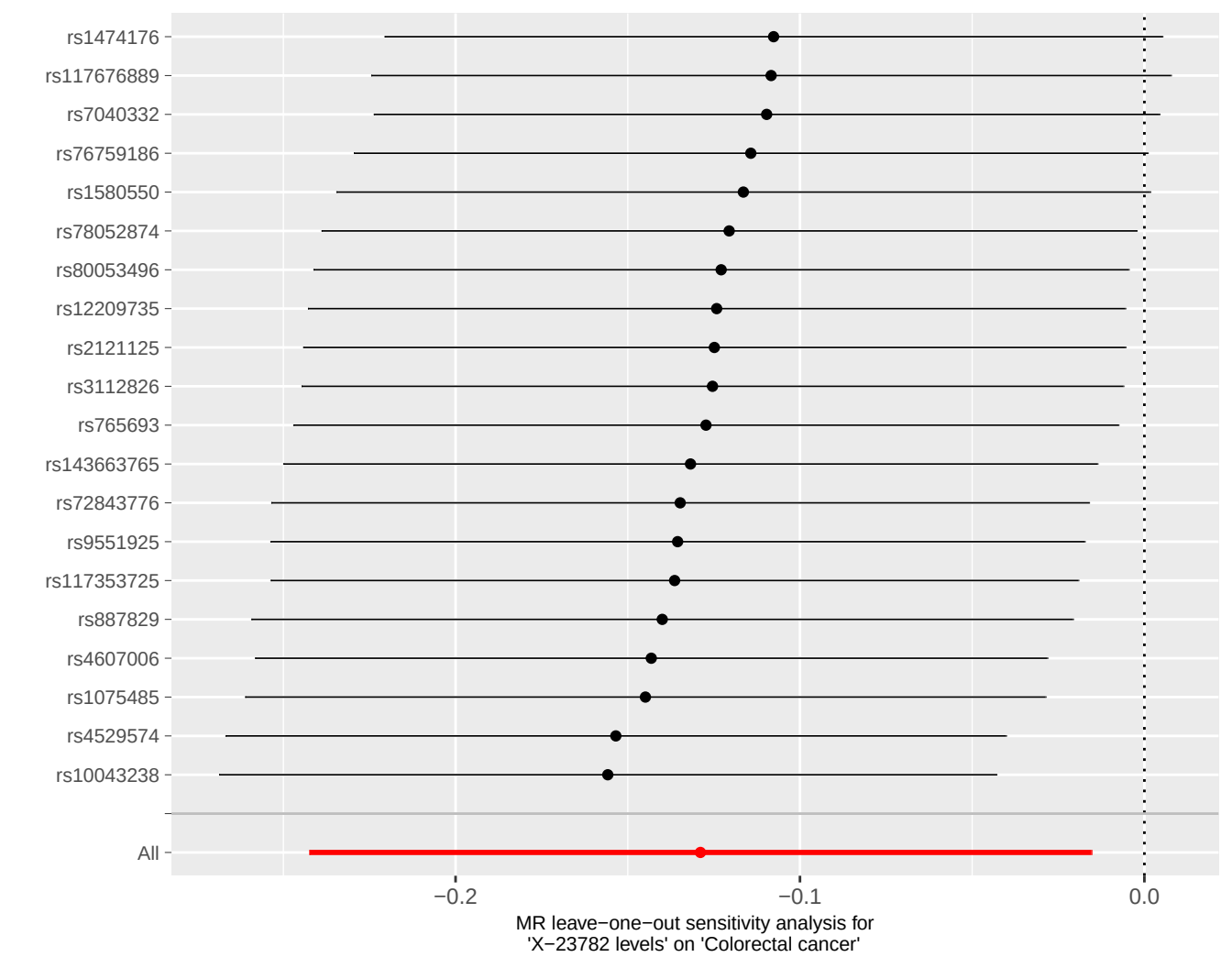
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'X−23780 levels' on 'Colorectal cancer'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rs9551925
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rs887829
rs4607006
rs1075485
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All
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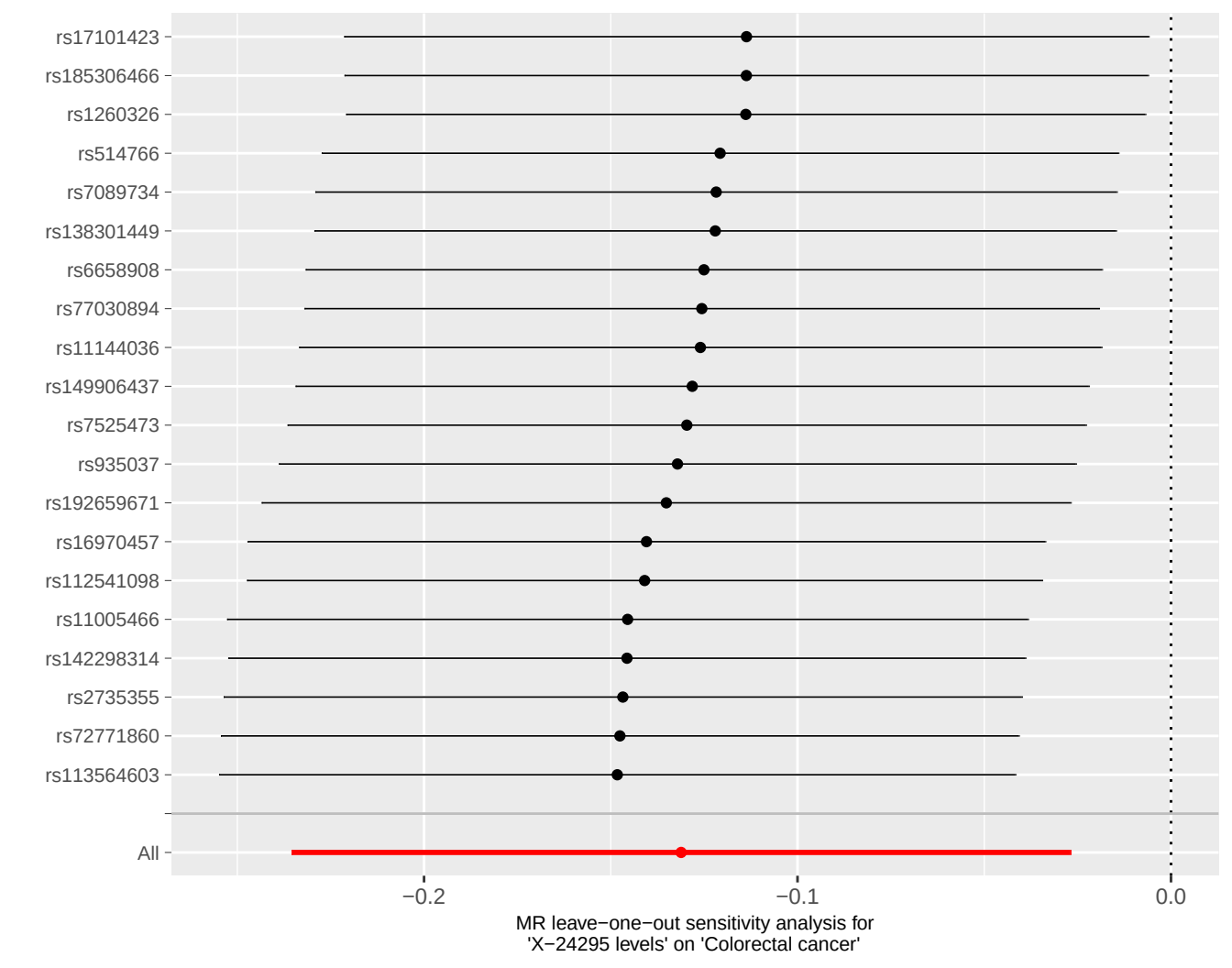
MR leave−one−out sensitivity analysis for
'X−23782 levels' on 'Colorectal cancer'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rs16970457
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rs2735355
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All
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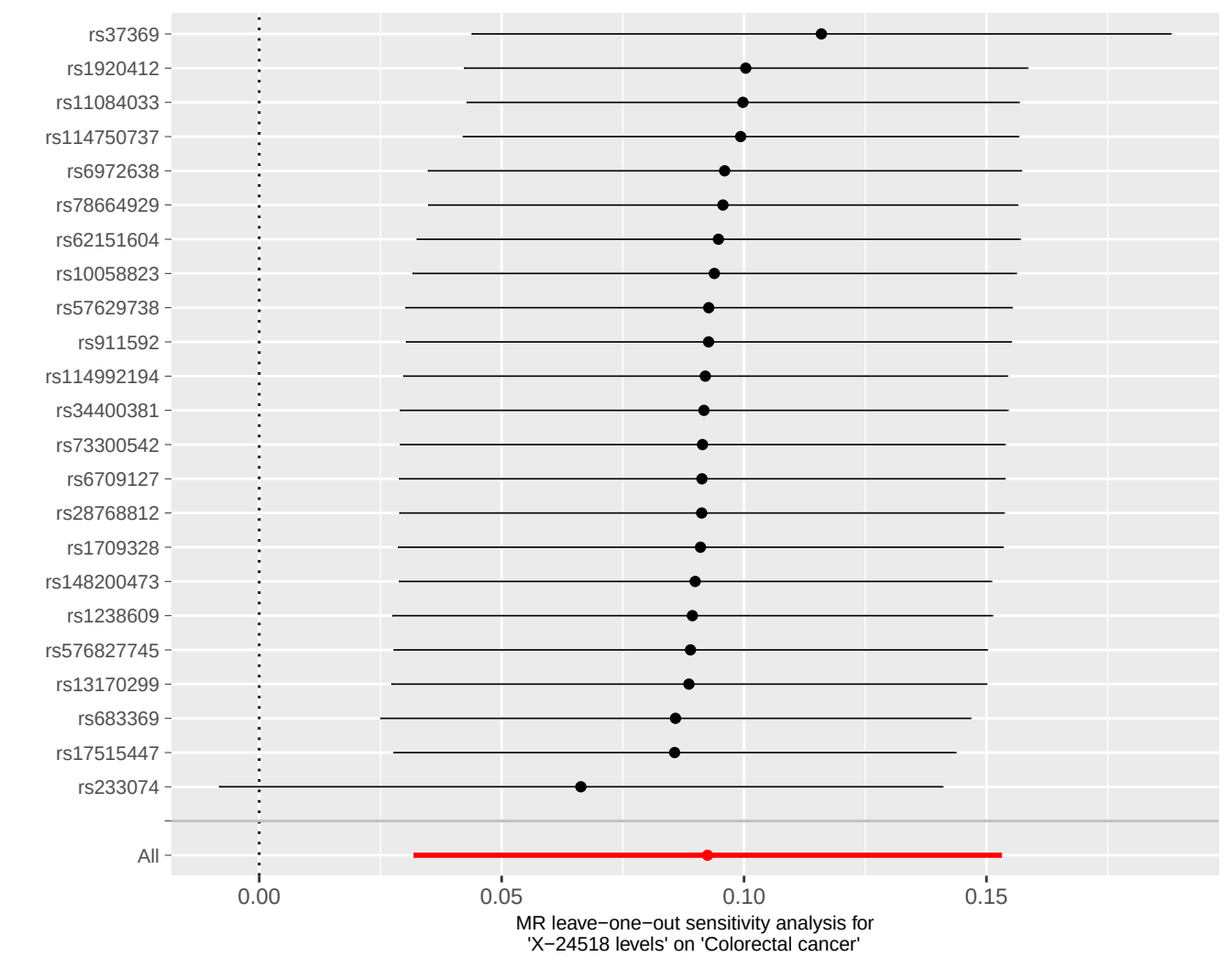
MR leave−one−out sensitivity analysis for
'X−24295 levels' on 'Colorectal cancer'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rs1709328
rs148200473
rs1238609
rs576827745
rs13170299
rs683369
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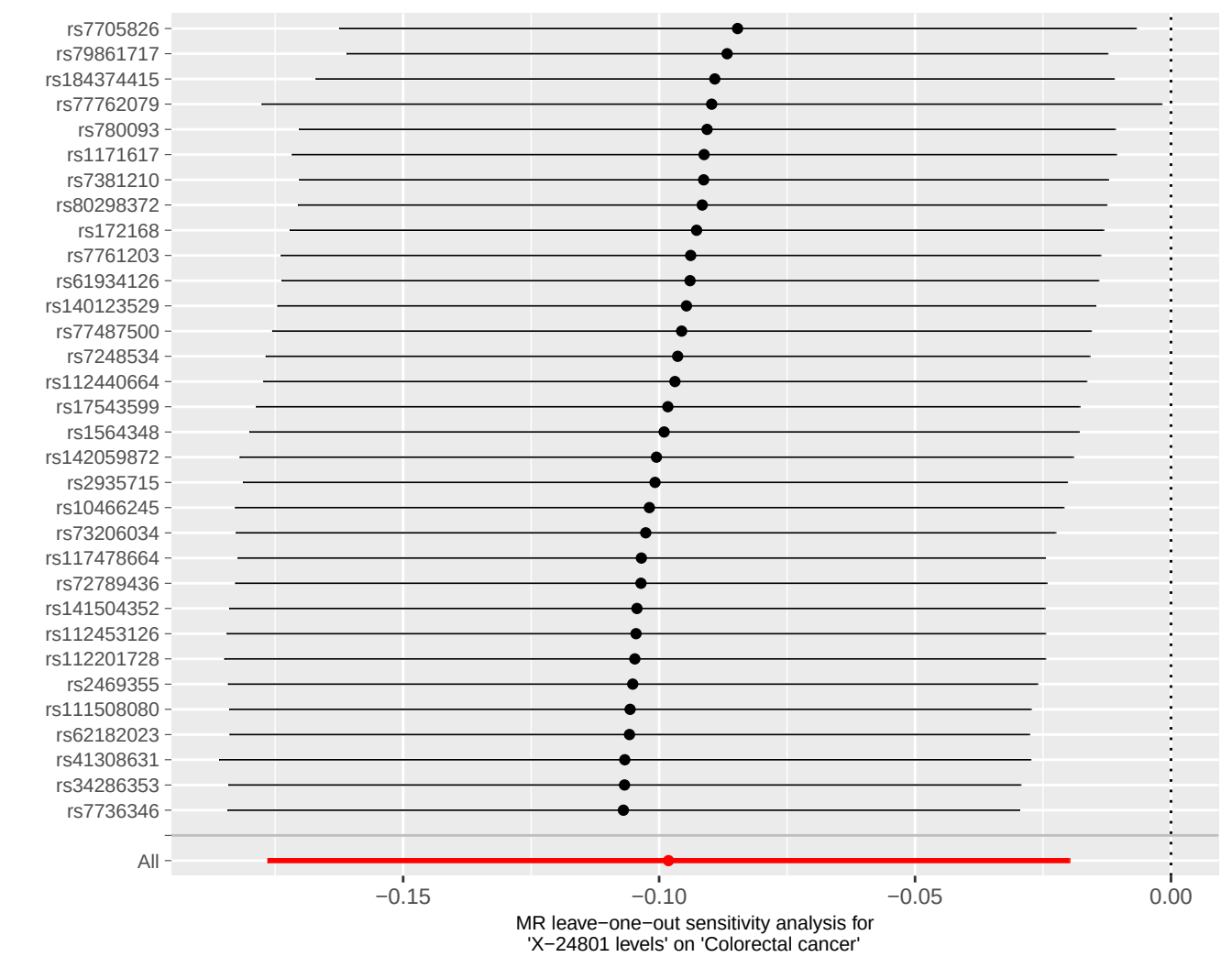
All
0.00
0.05
0.10
0.15
MR leave−one−out sensitivity analysis for
'X−24518 levels' on 'Colorectal cancer'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rs41308631
rs34286353
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All
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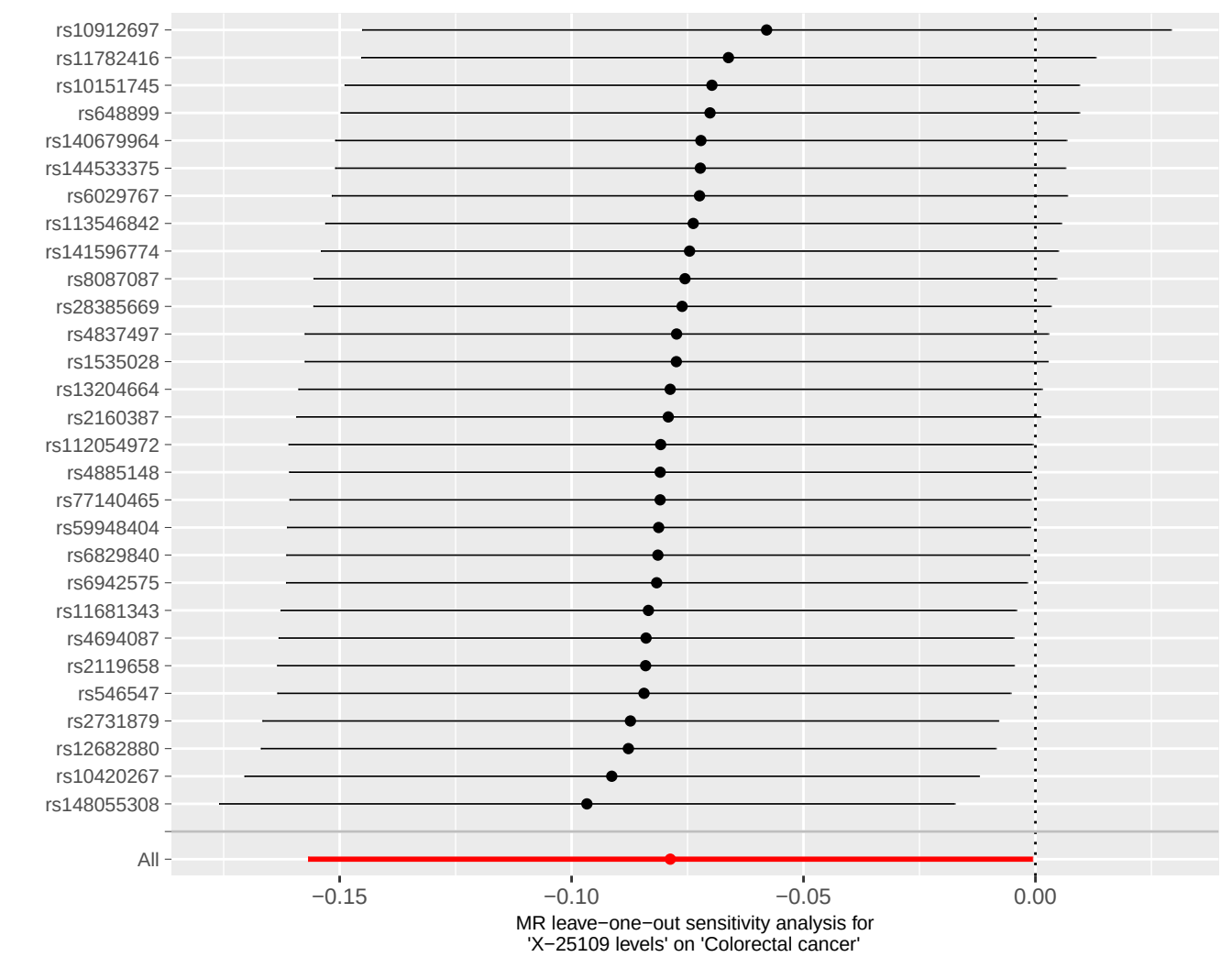
0.00
MR leave−one−out sensitivity analysis for
'X−24801 levels' on 'Colorectal cancer'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rs2731879
rs12682880
rs10420267
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All
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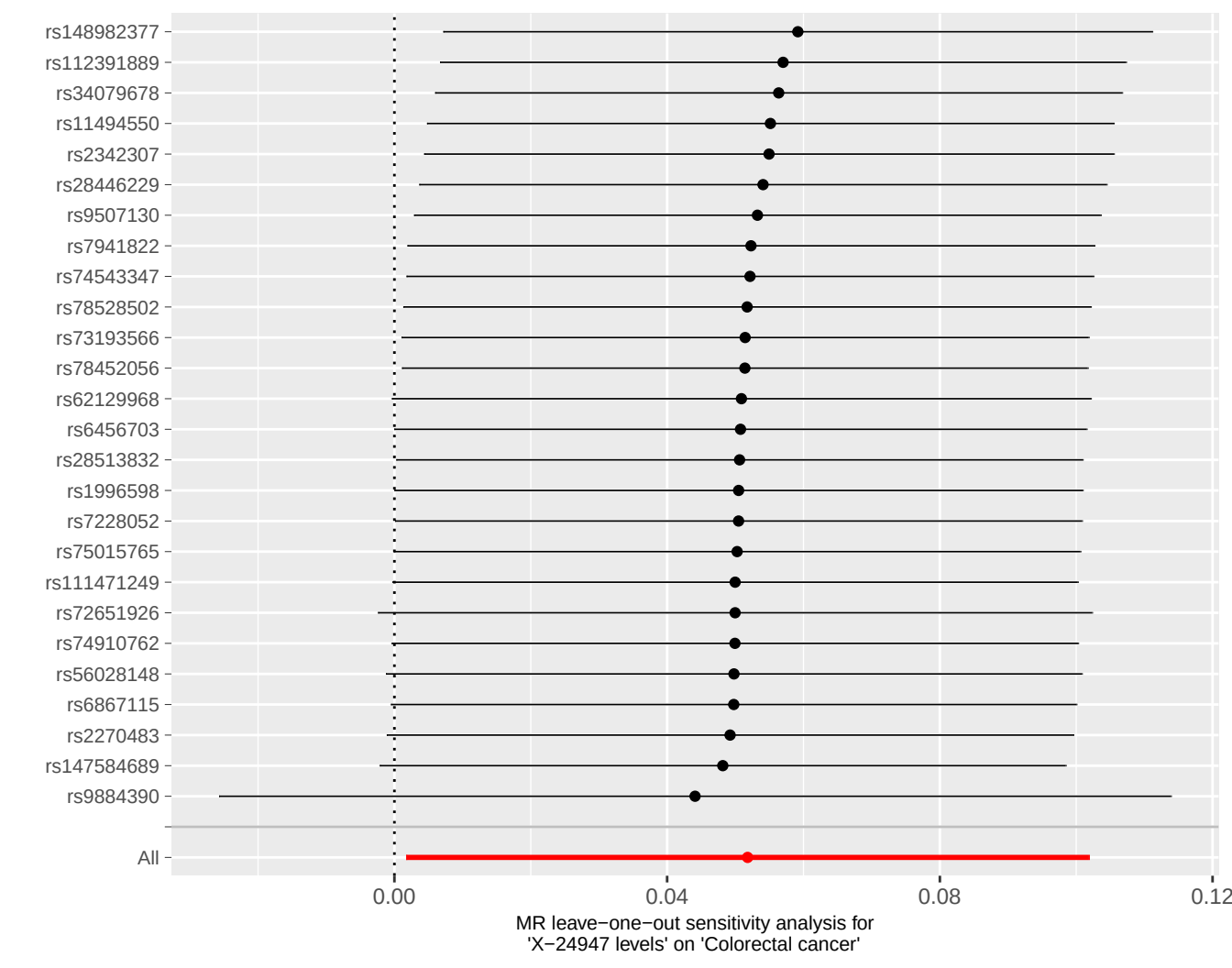
−0.05
0.00
MR leave−one−out sensitivity analysis for
'X−25109 levels' on 'Colorectal cancer'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rs7228052
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rs74910762
rs56028148
rs6867115
rs2270483
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All
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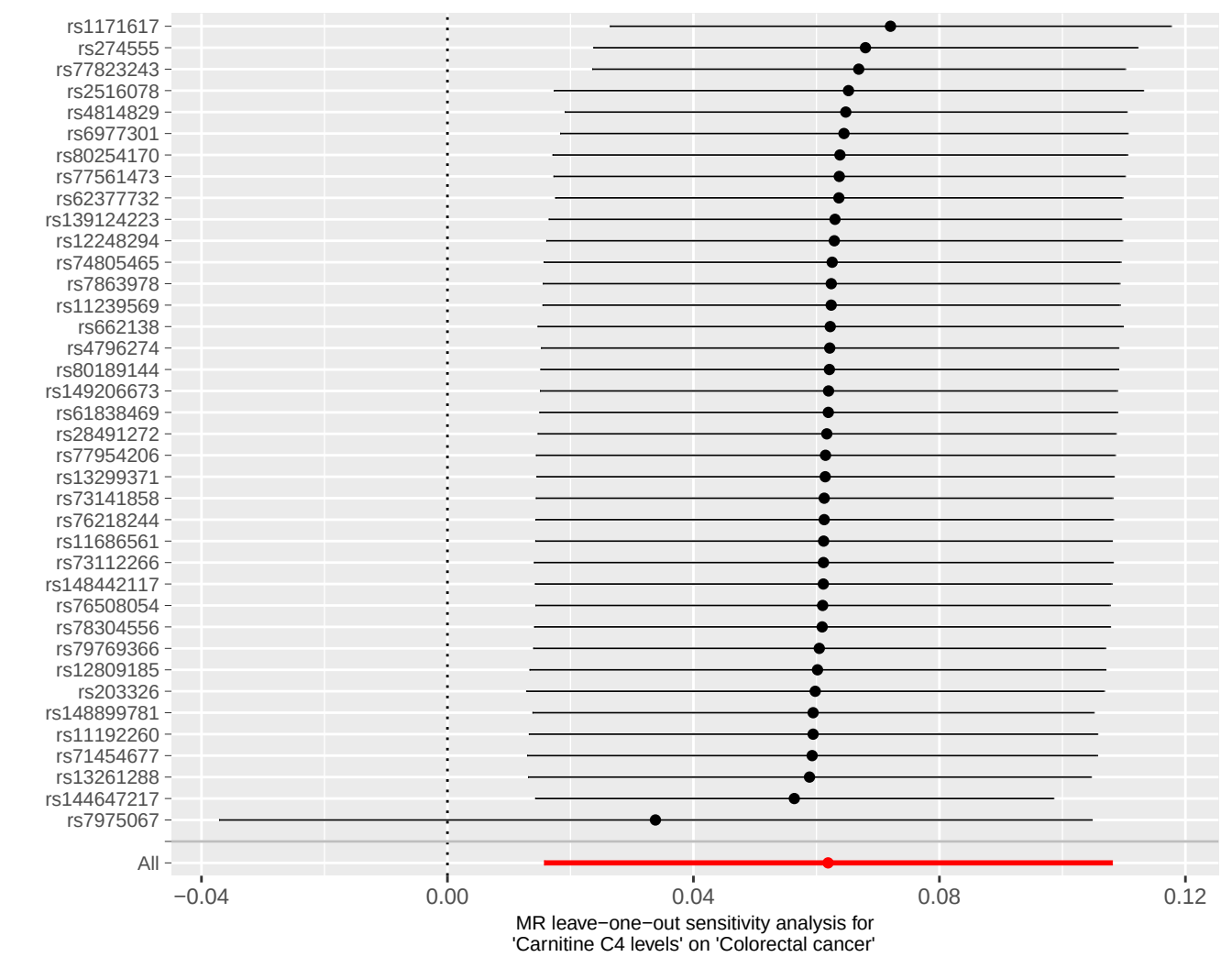
0.08
0.12
MR leave−one−out sensitivity analysis for
'X−24947 levels' on 'Colorectal cancer'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rs13261288
rs144647217
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All
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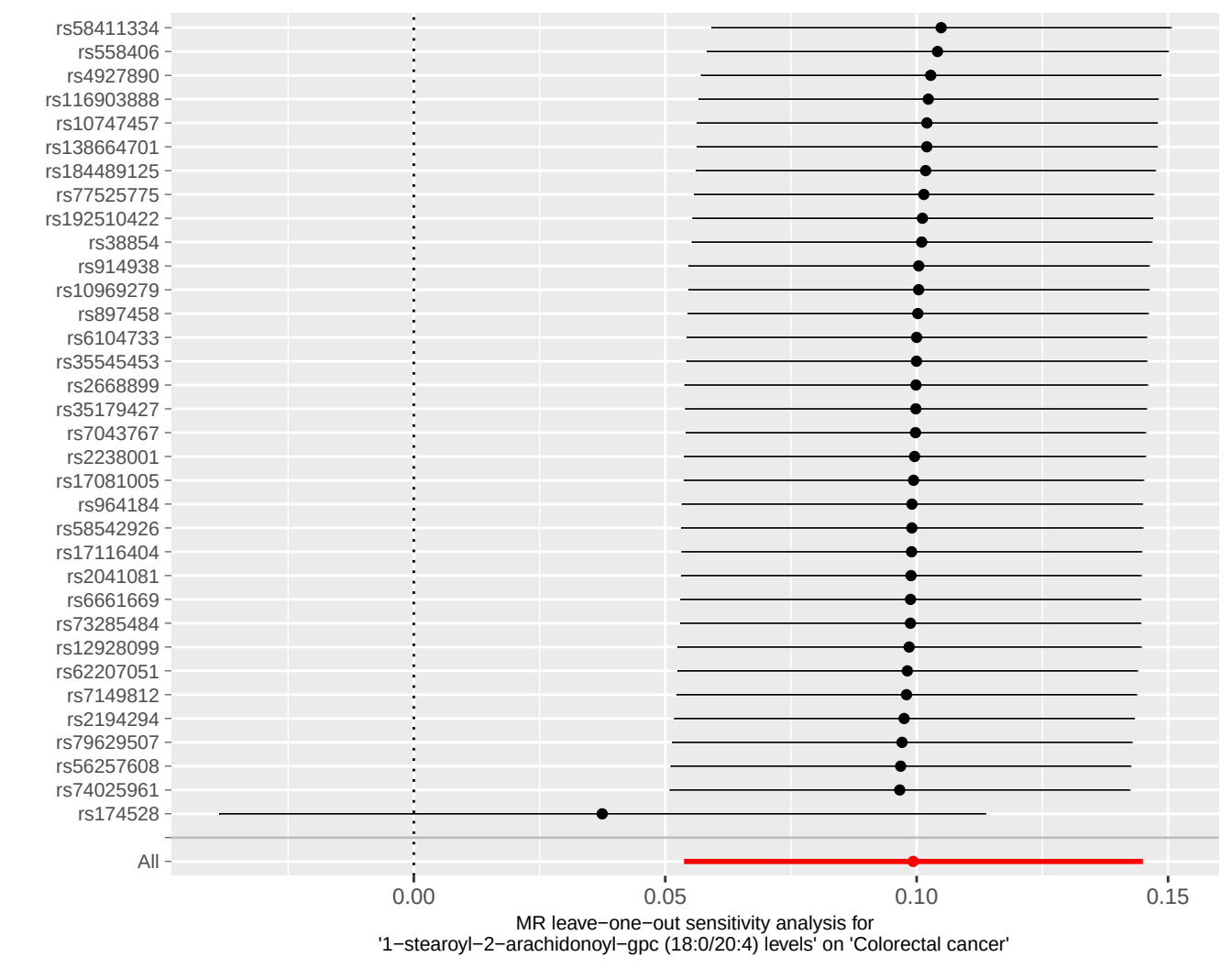
0.00
0.04
0.08
0.12
MR leave−one−out sensitivity analysis for
'Carnitine C4 levels' on 'Colorectal cancer'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rs6661669
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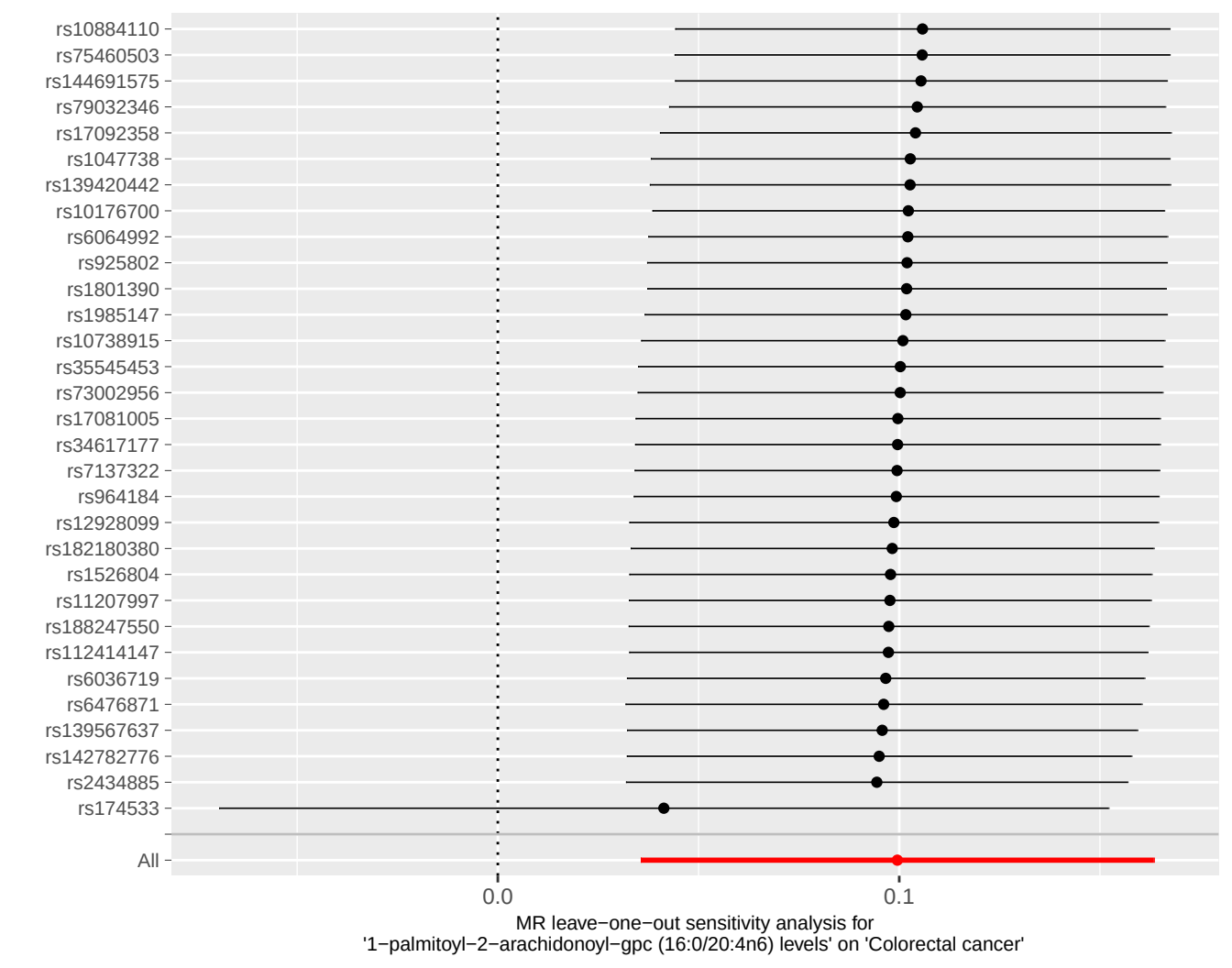
rs12928099
rs62207051
rs7149812
rs2194294
rs79629507
rs56257608
rs74025961
rs174528
All
0.00
0.05
0.10
0.15
MR leave−one−out sensitivity analysis for
'1−stearoyl−2−arachidonoyl−gpc (18:0/20:4) levels' on 'Colorectal cancer'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rs174533
All
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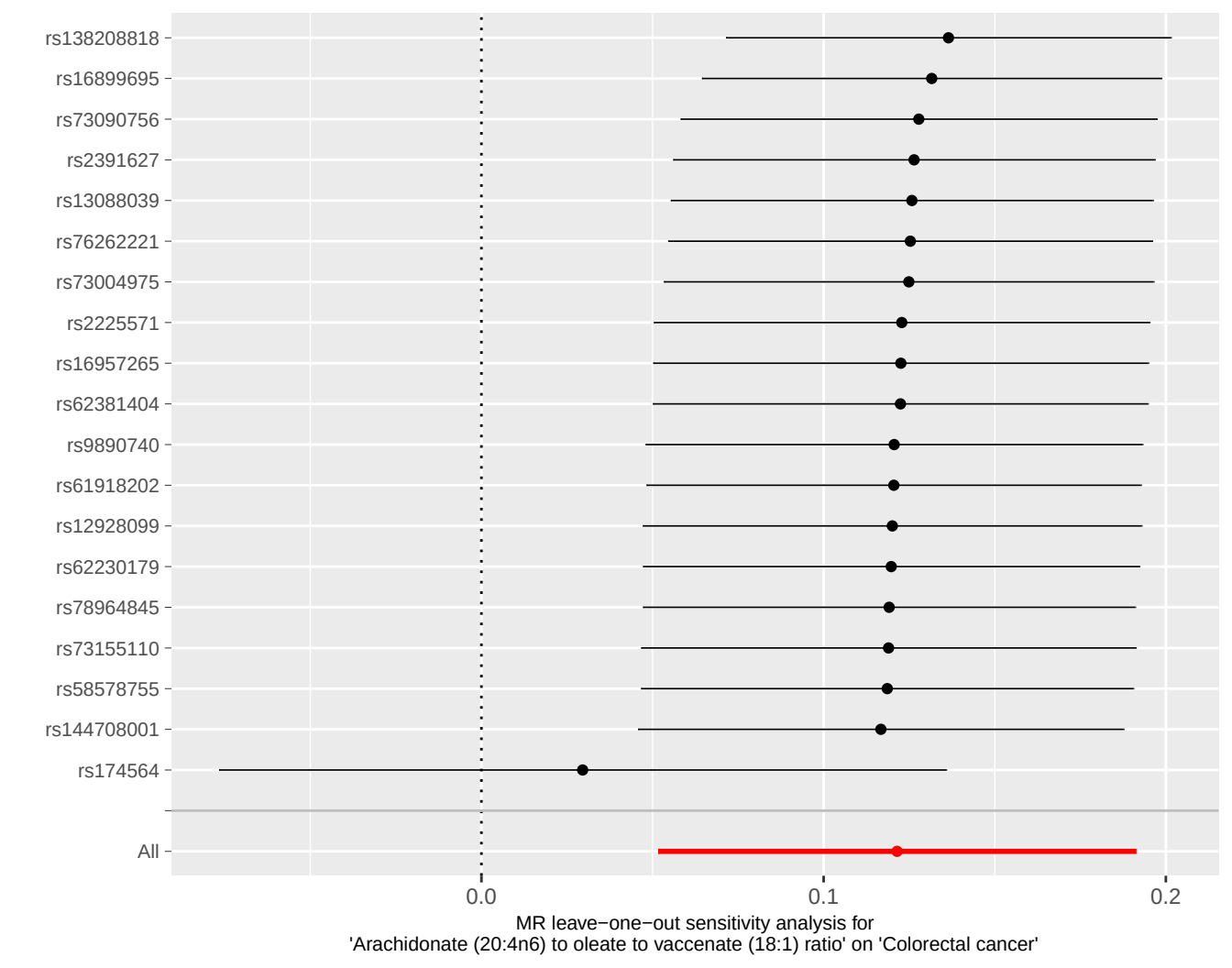
MR leave−one−out sensitivity analysis for
'1−palmitoyl−2−arachidonoyl−gpc (16:0/20:4n6) levels' on 'Colorectal cancer'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rs58578755
rs144708001
rs174564
All
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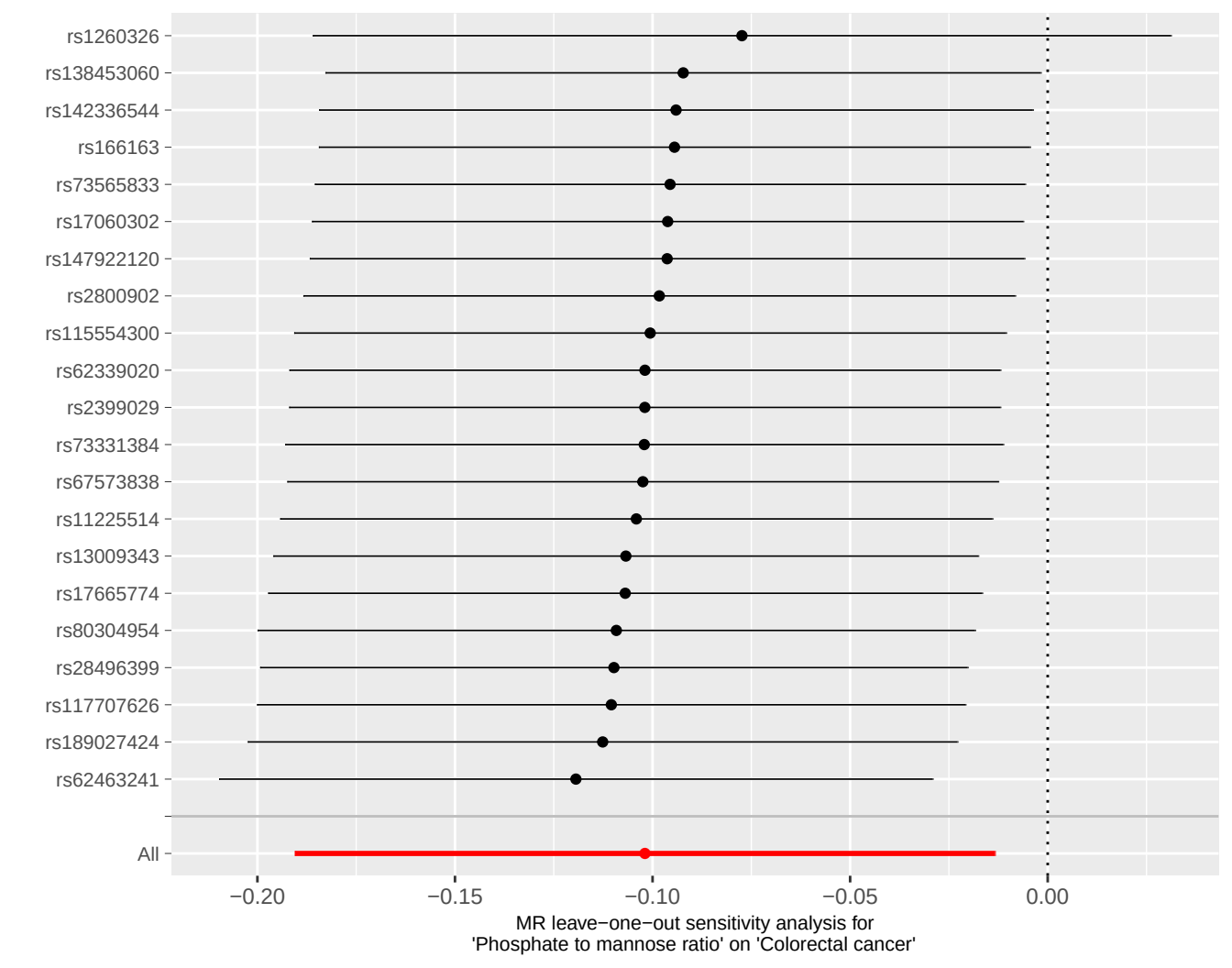
0.2
MR leave−one−out sensitivity analysis for
'Arachidonate (20:4n6) to oleate to vaccenate (18:1) ratio' on 'Colorectal cancer'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rs67573838
rs11225514
rs13009343
rs17665774
rs80304954
rs28496399
rs117707626
rs189027424
rs62463241
All
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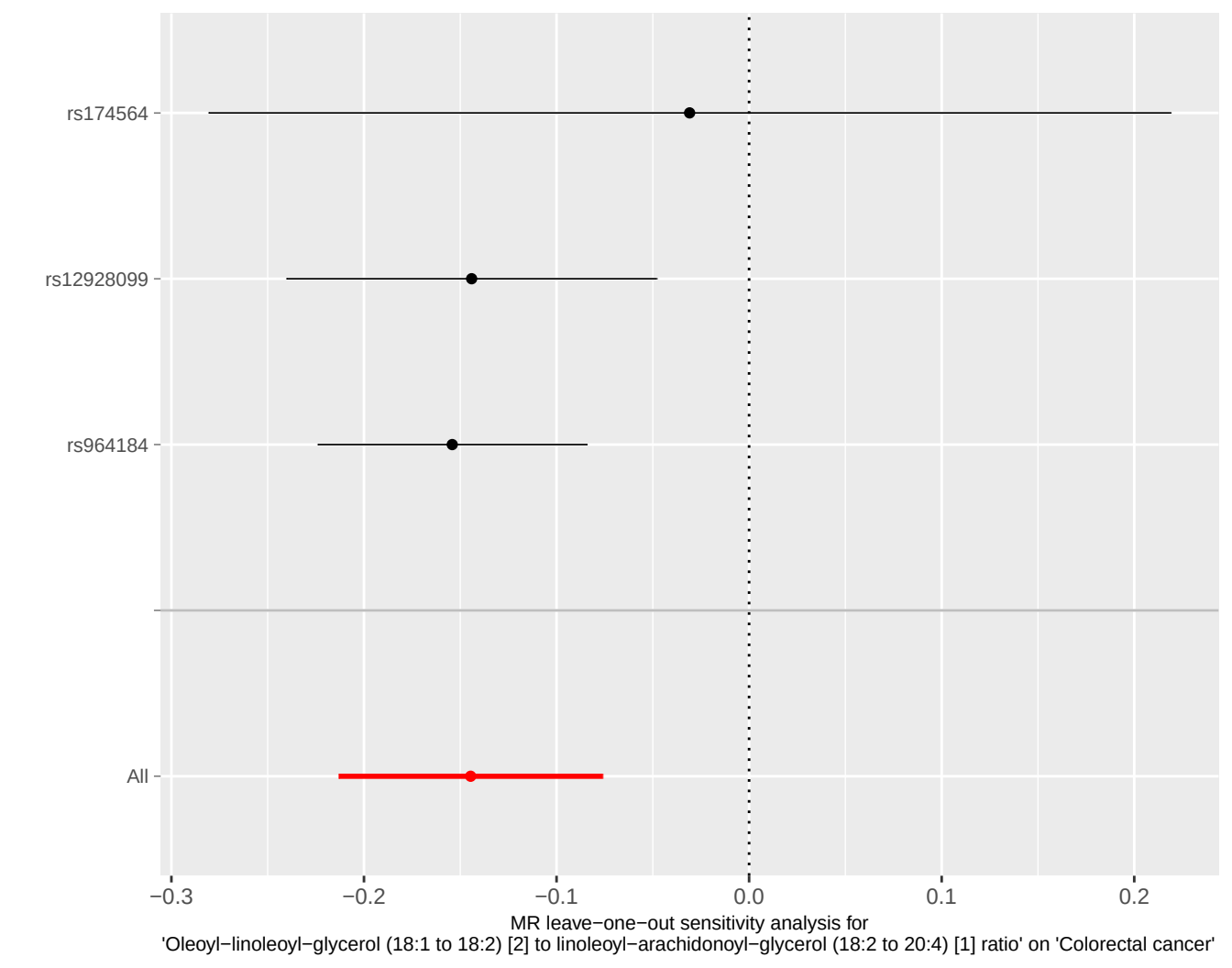
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Phosphate to mannose ratio' on 'Colorectal cancer'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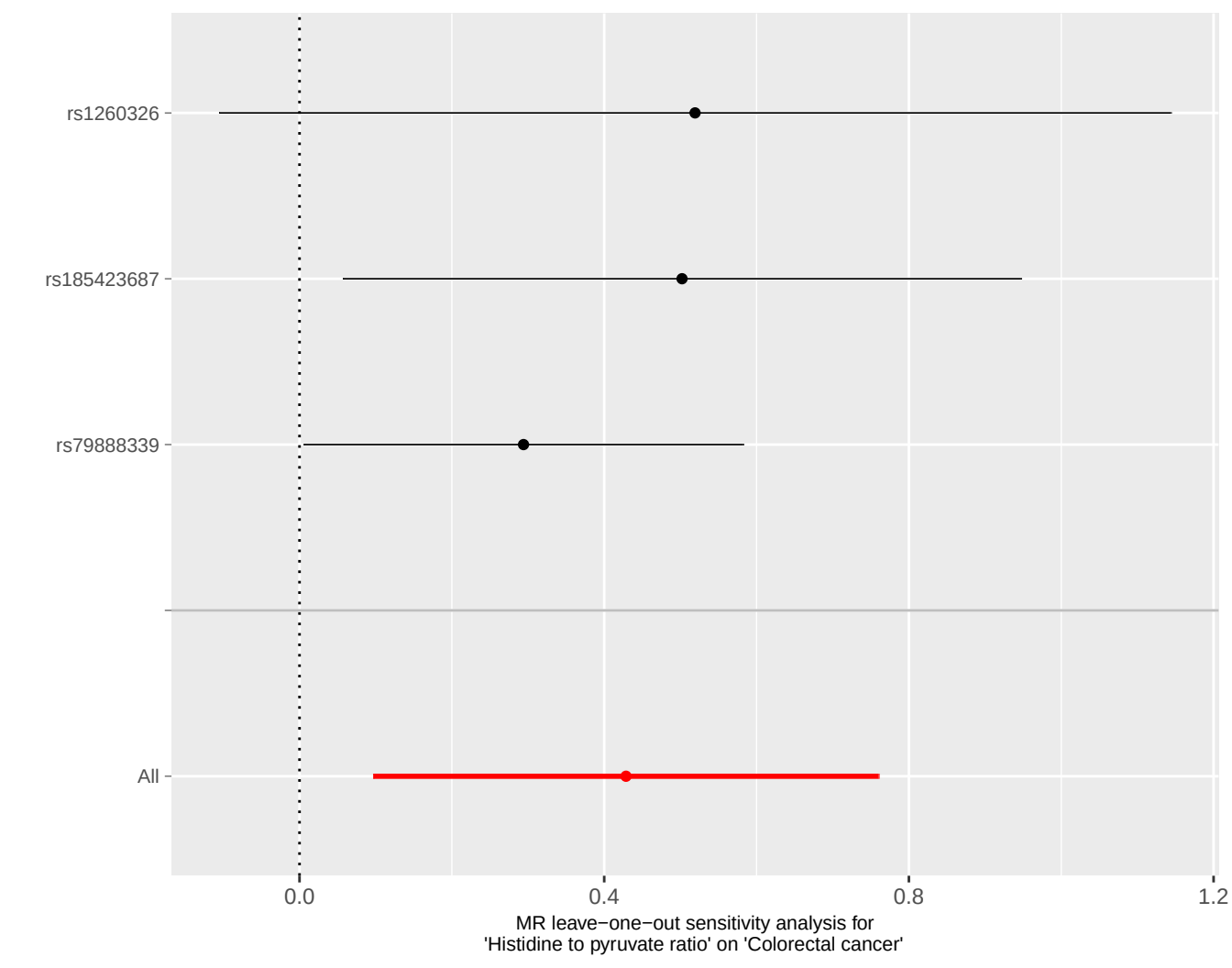
rs12928099
rs964184
All
−0.3
−0.2
−0.1
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Oleoyl−linoleoyl−glycerol (18:1 to 18:2) [2] to linoleoyl−arachidonoyl−glycerol (18:2 to 20:4) [1] ratio' on 'Colorectal cancer'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rs185423687
rs79888339
All
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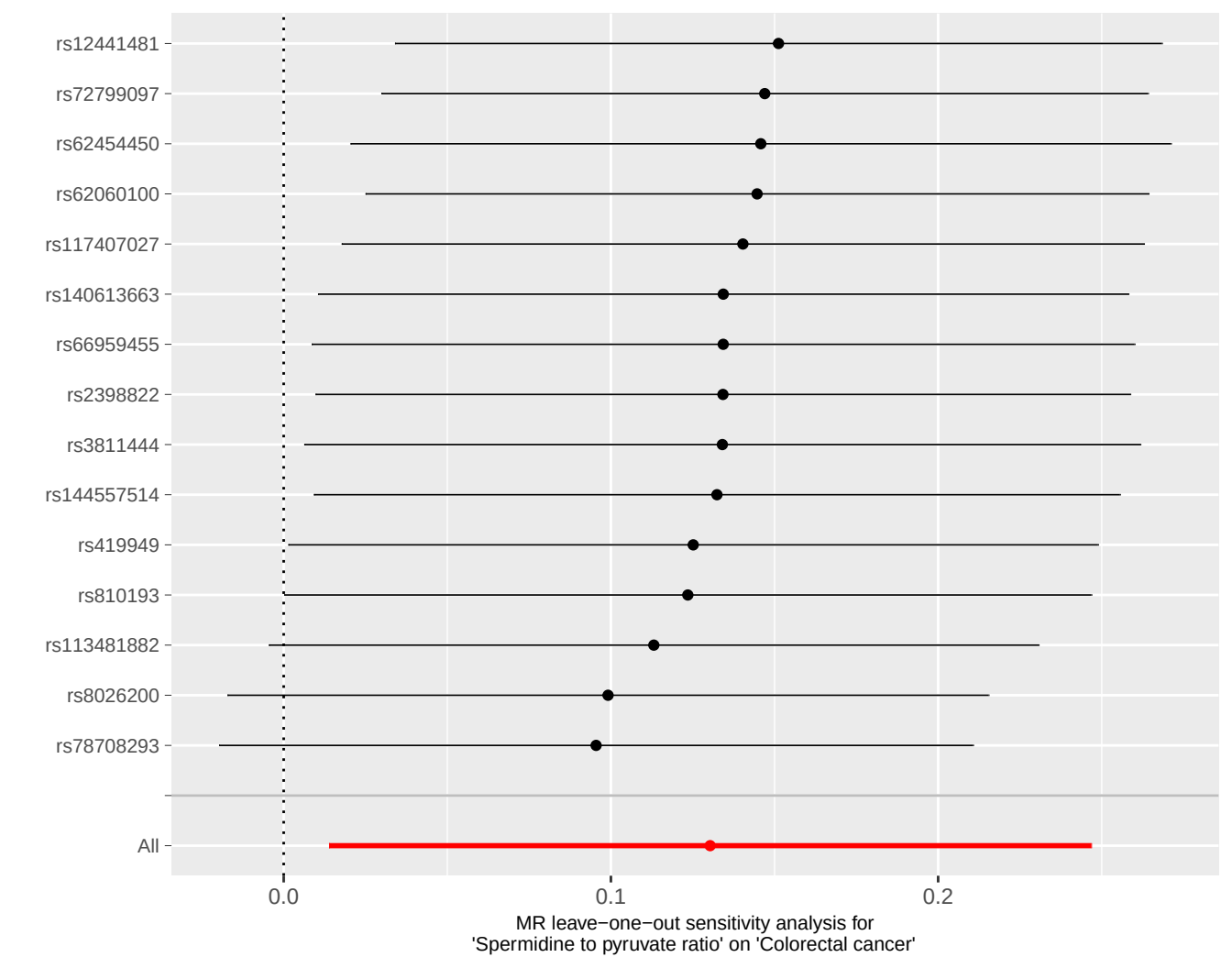
0.4
0.8
1.2
MR leave−one−out sensitivity analysis for
'Histidine to pyruvate ratio' on 'Colorectal cancer'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rs144557514
rs419949
rs810193
rs113481882
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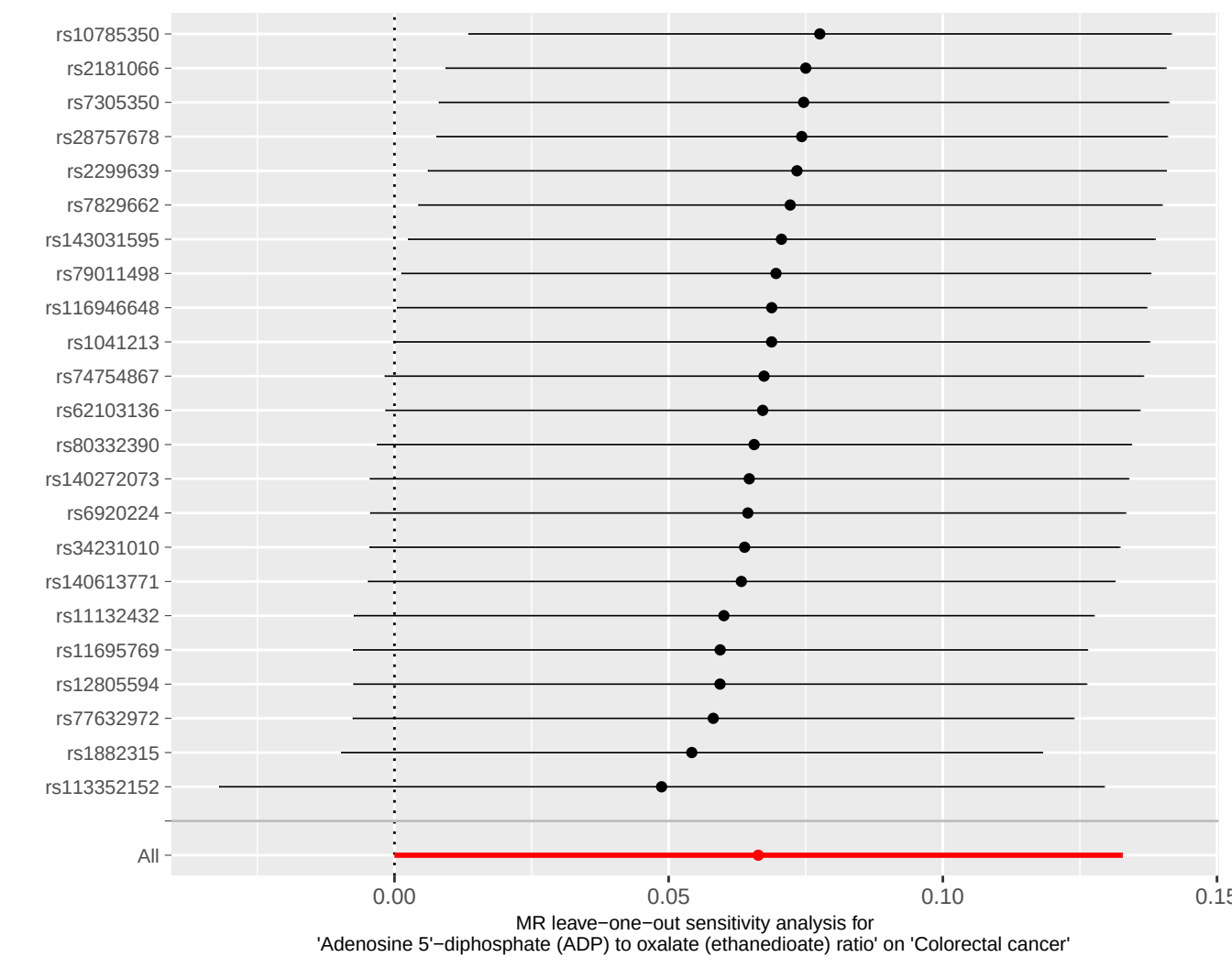
All
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Spermidine to pyruvate ratio' on 'Colorectal cancer'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rs6920224
rs34231010
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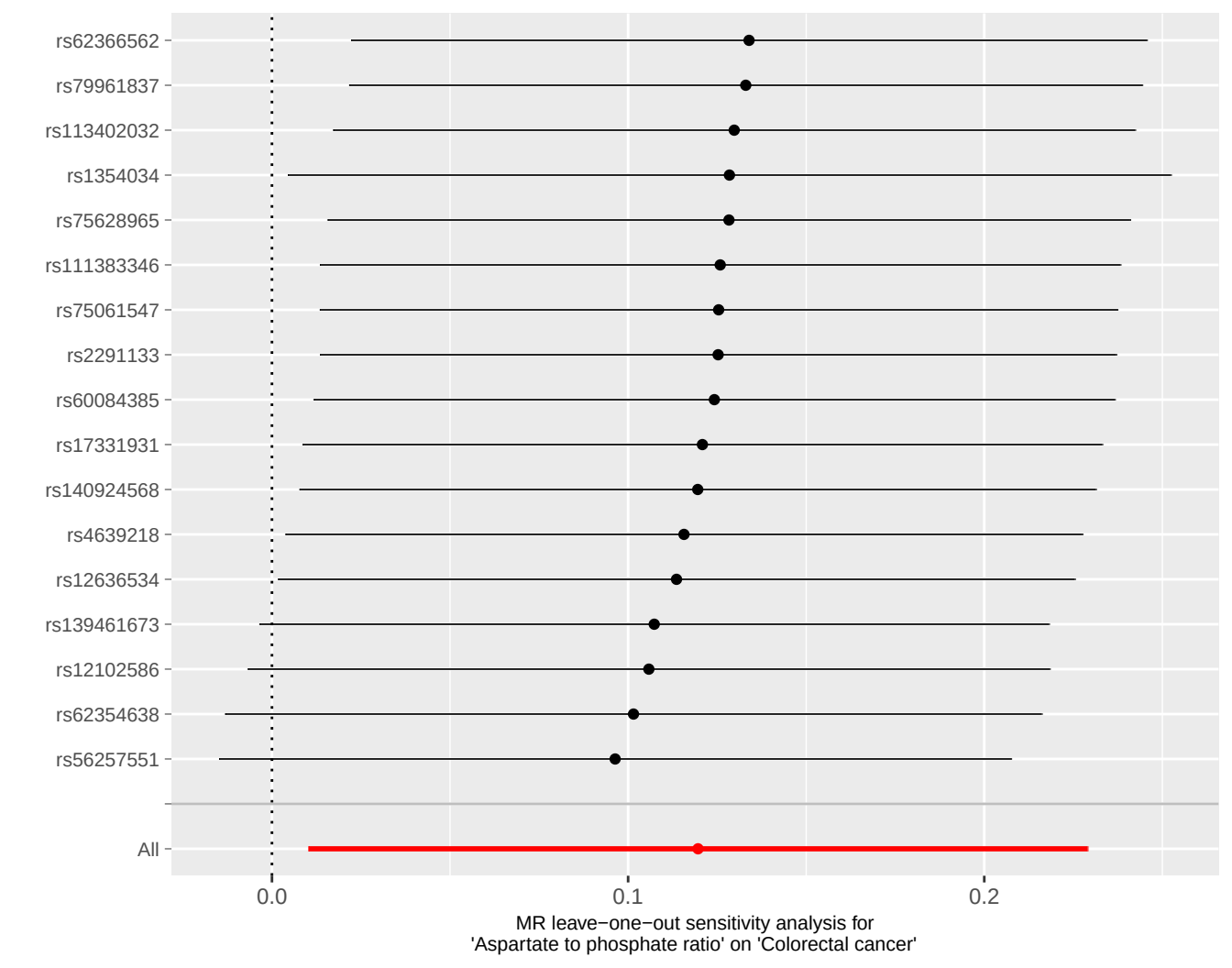
rs11132432
rs11695769
rs12805594
rs77632972
rs1882315
rs113352152
All
0.00
0.05
0.10
0.15
MR leave−one−out sensitivity analysis for
'Adenosine 5'−diphosphate (ADP) to oxalate (ethanedioate) ratio' on 'Colorectal cancer'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rs140924568
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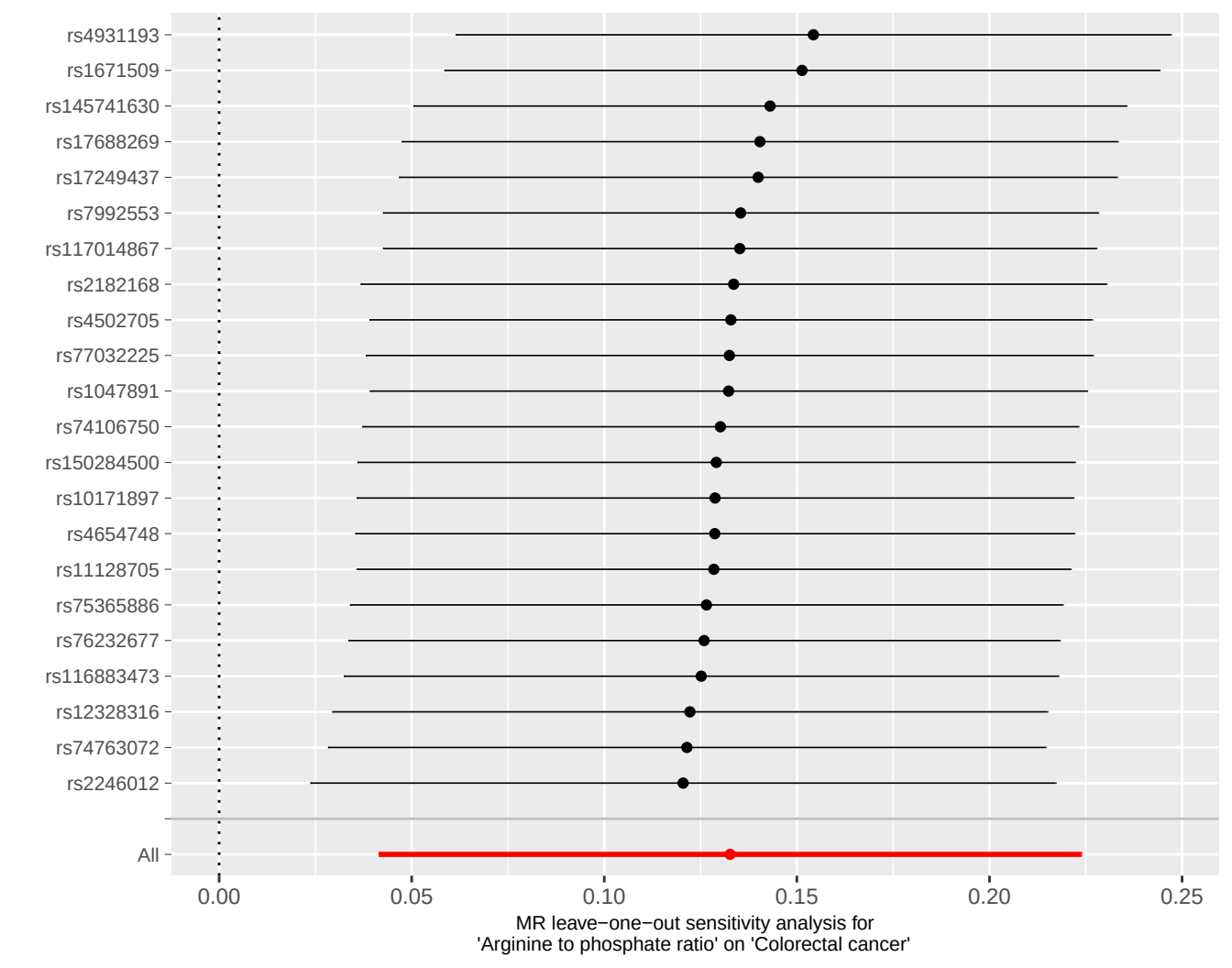
rs12636534
rs139461673
rs12102586
rs62354638
rs56257551
All
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Aspartate to phosphate ratio' on 'Colorectal cancer'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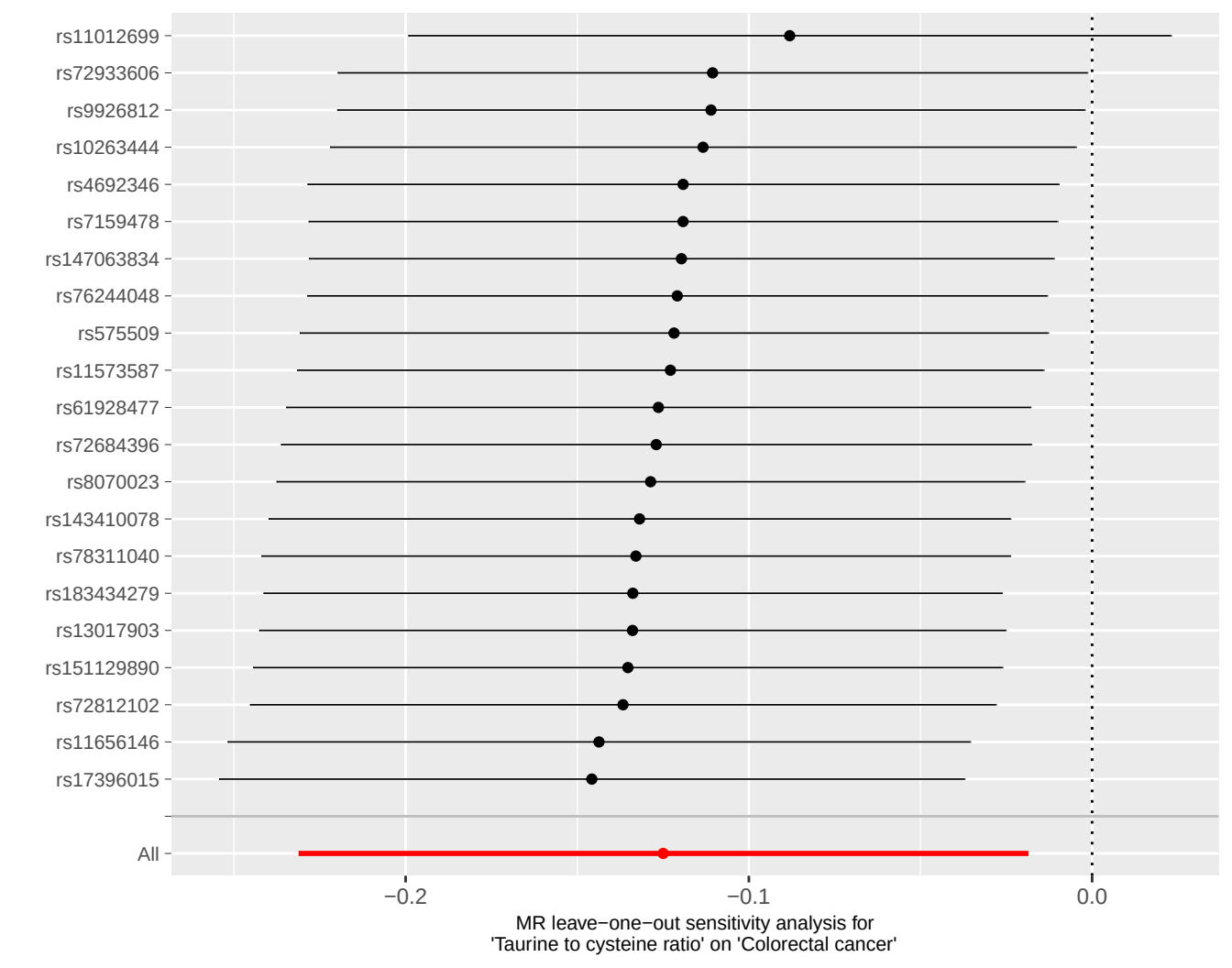
rs10171897
rs4654748
rs11128705
rs75365886
rs76232677
rs116883473
rs12328316
rs74763072
rs2246012
All
0.00
0.05
0.10
0.15
0.20
0.25
MR leave−one−out sensitivity analysis for
'Arginine to phosphate ratio' on 'Colorectal cancer'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rs72684396
rs8070023
rs143410078
rs78311040
rs183434279
rs13017903
rs151129890
rs72812102
rs11656146
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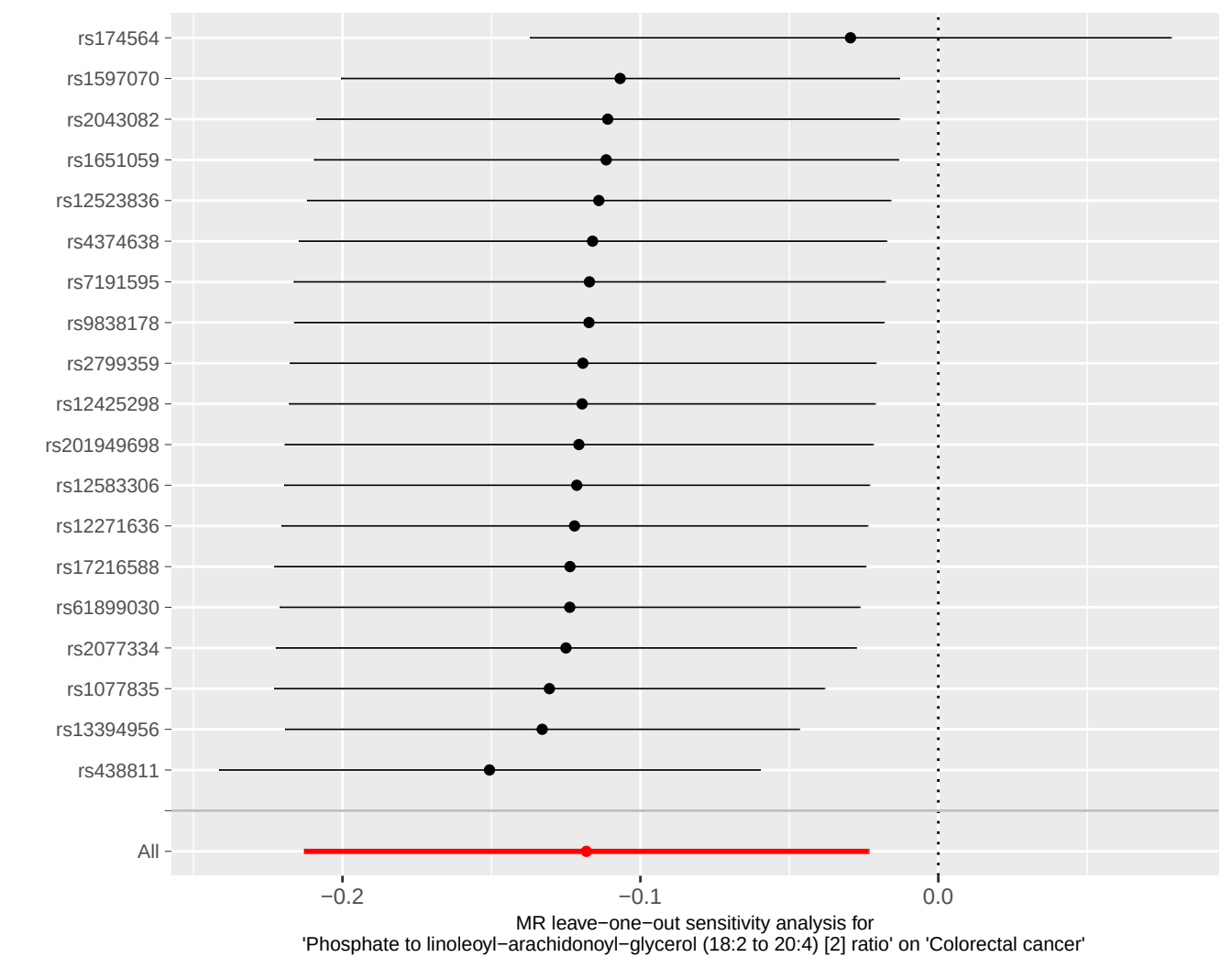
All
−0.2
−0.1
0.0
MR leave−one−out sensitivity analysis for
'Taurine to cysteine ratio' on 'Colorectal cancer'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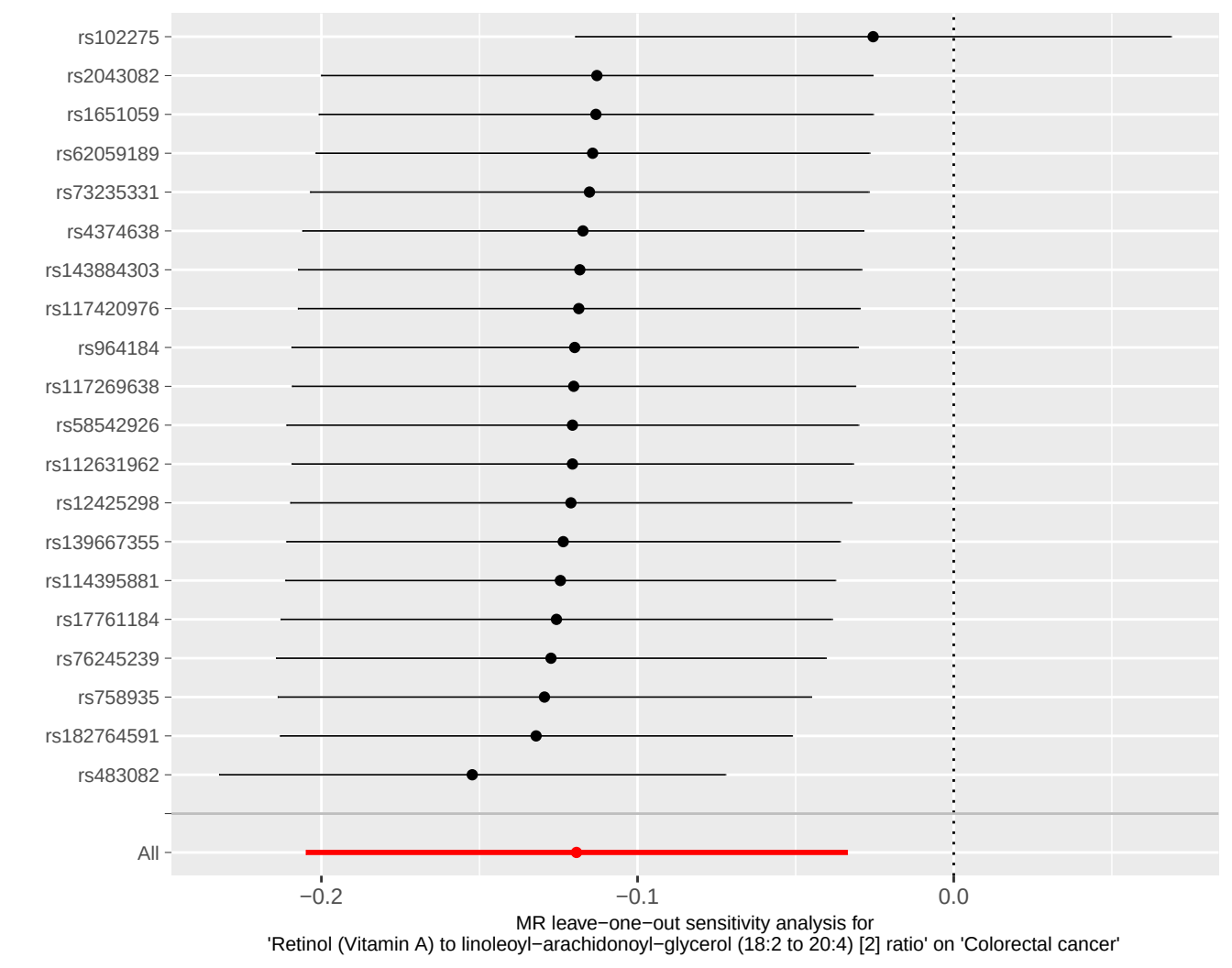
rs12583306
rs12271636
rs17216588
rs61899030
rs2077334
rs1077835
rs13394956
rs438811
All
−0.2
−0.1
0.0
MR leave−one−out sensitivity analysis for
'Phosphate to linoleoyl−arachidonoyl−glycerol (18:2 to 20:4) [2] ratio' on 'Colorectal cancer'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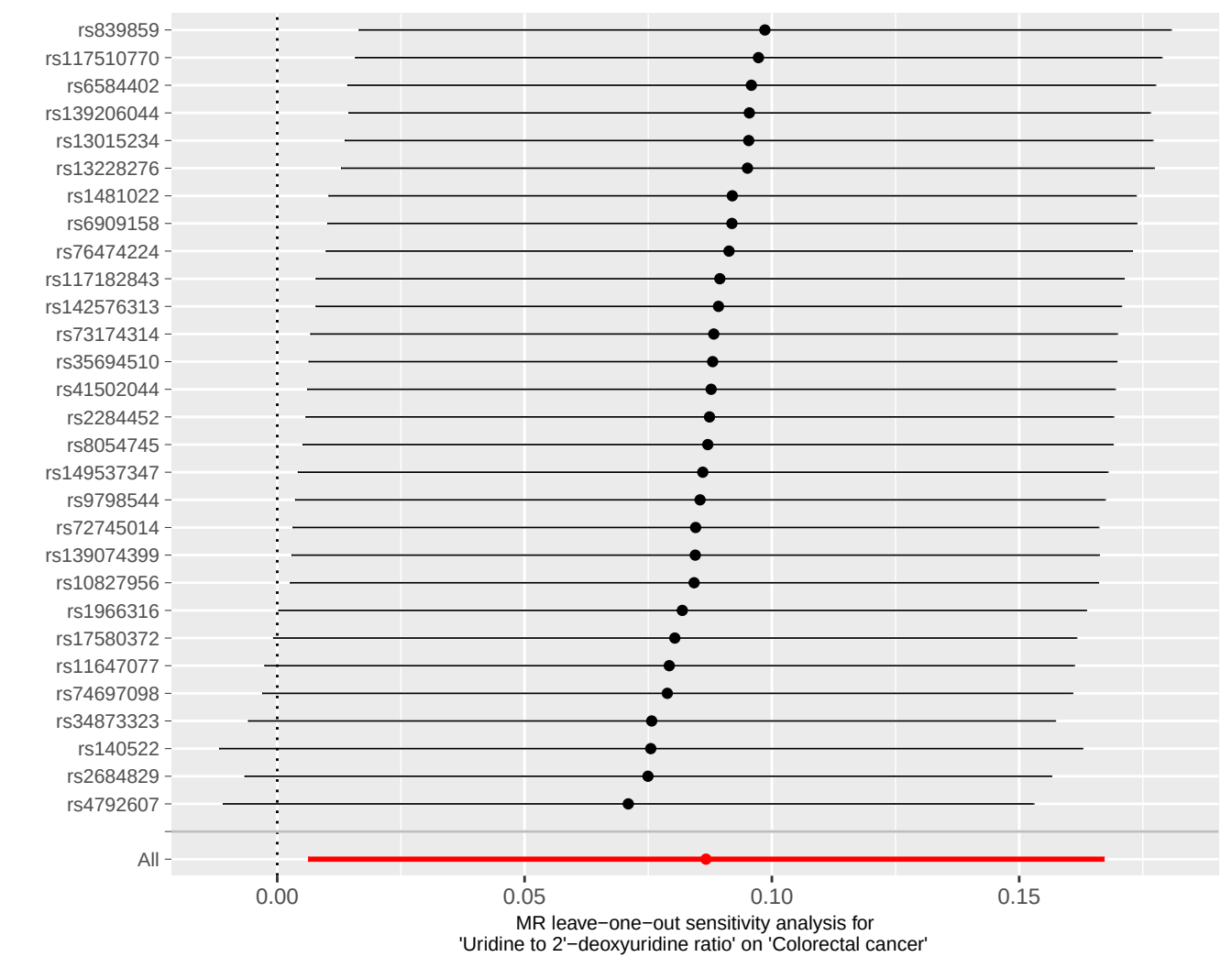
rs112631962
rs12425298
rs139667355
rs114395881
rs17761184
rs76245239
rs758935
rs182764591
rs483082
All
−0.2
−0.1
0.0
MR leave−one−out sensitivity analysis for
'Retinol (Vitamin A) to linoleoyl−arachidonoyl−glycerol (18:2 to 20:4) [2] ratio' on 'Colorectal cancer'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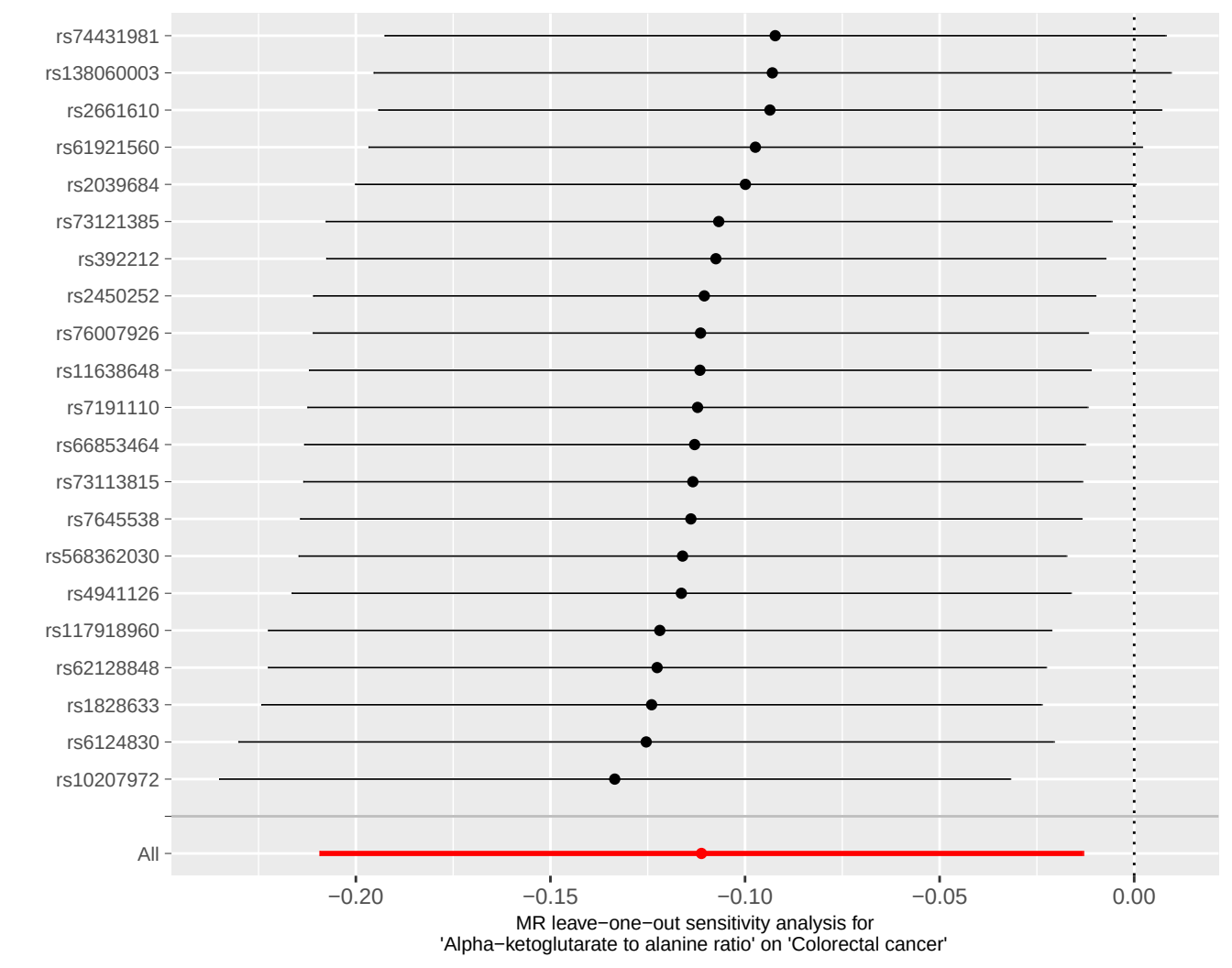
rs72745014
rs139074399
rs10827956
rs1966316
rs17580372
rs11647077
rs74697098
rs34873323
rs140522
rs2684829
rs4792607
All
0.00
0.05
0.10
0.15
MR leave−one−out sensitivity analysis for
'Uridine to 2'−deoxyuridine ratio' on 'Colorectal cancer'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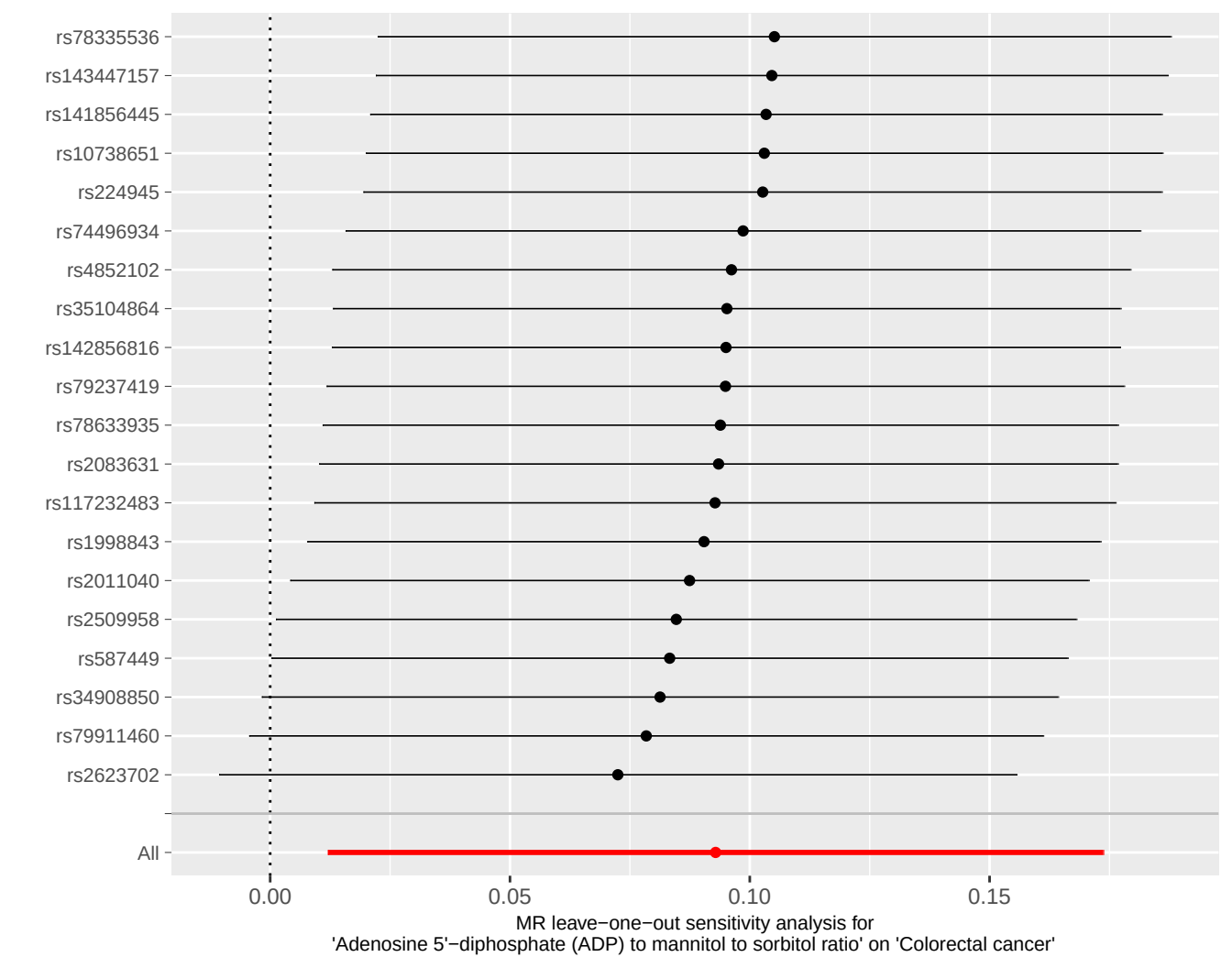
rs66853464
rs73113815
rs7645538
rs568362030
rs4941126
rs117918960
rs62128848
rs1828633
rs6124830
rs10207972
All
−0.20
−0.15
−0.10
−0.05
0.00
MR leave−one−out sensitivity analysis for
'Alpha−ketoglutarate to alanine ratio' on 'Colorectal cancer'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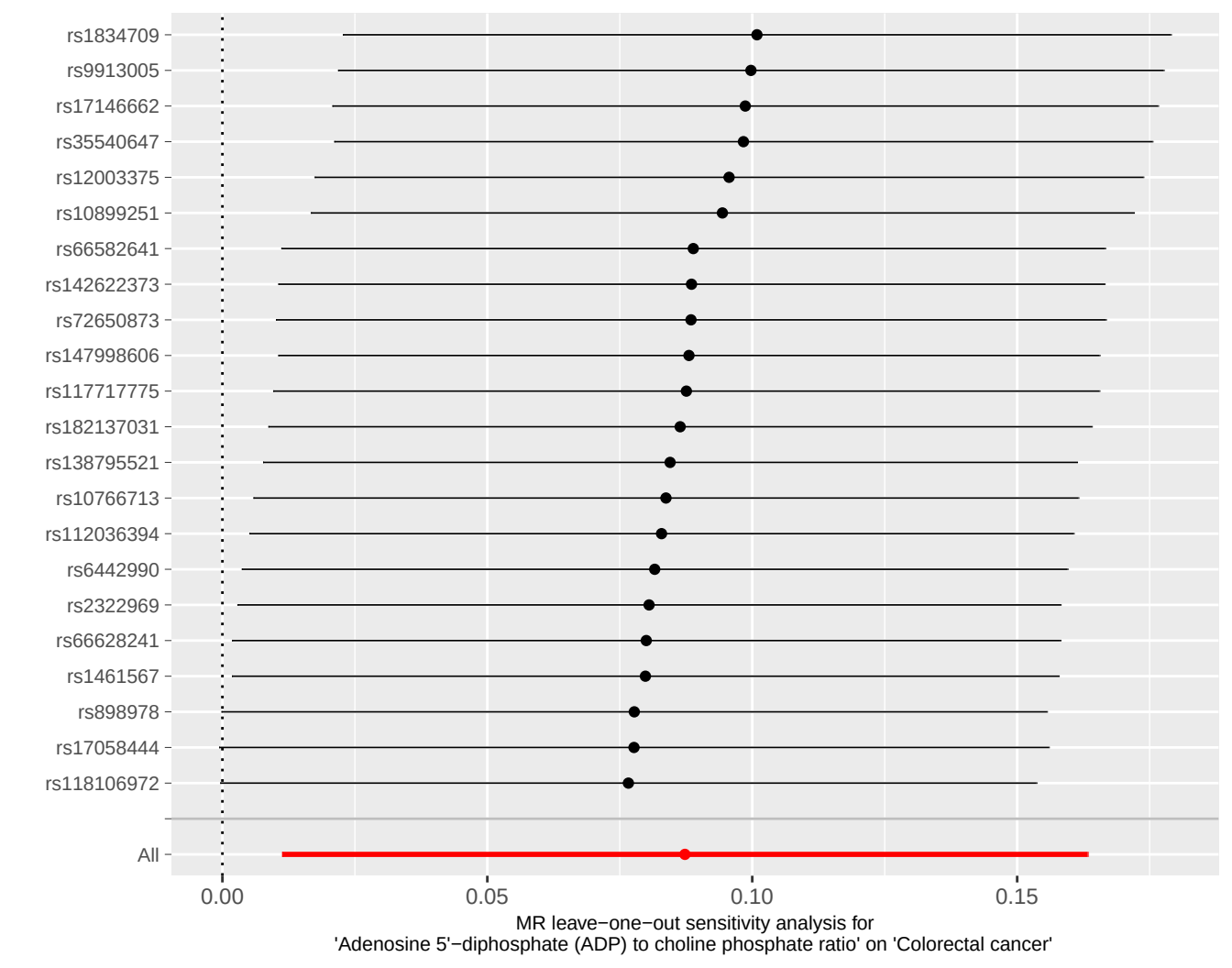
rs78633935
rs2083631
rs117232483
rs1998843
rs2011040
rs2509958
rs587449
rs34908850
rs79911460
rs2623702
All
0.00
0.05
0.10
0.15
MR leave−one−out sensitivity analysis for
'Adenosine 5'−diphosphate (ADP) to mannitol to sorbitol ratio' on 'Colorectal cancer'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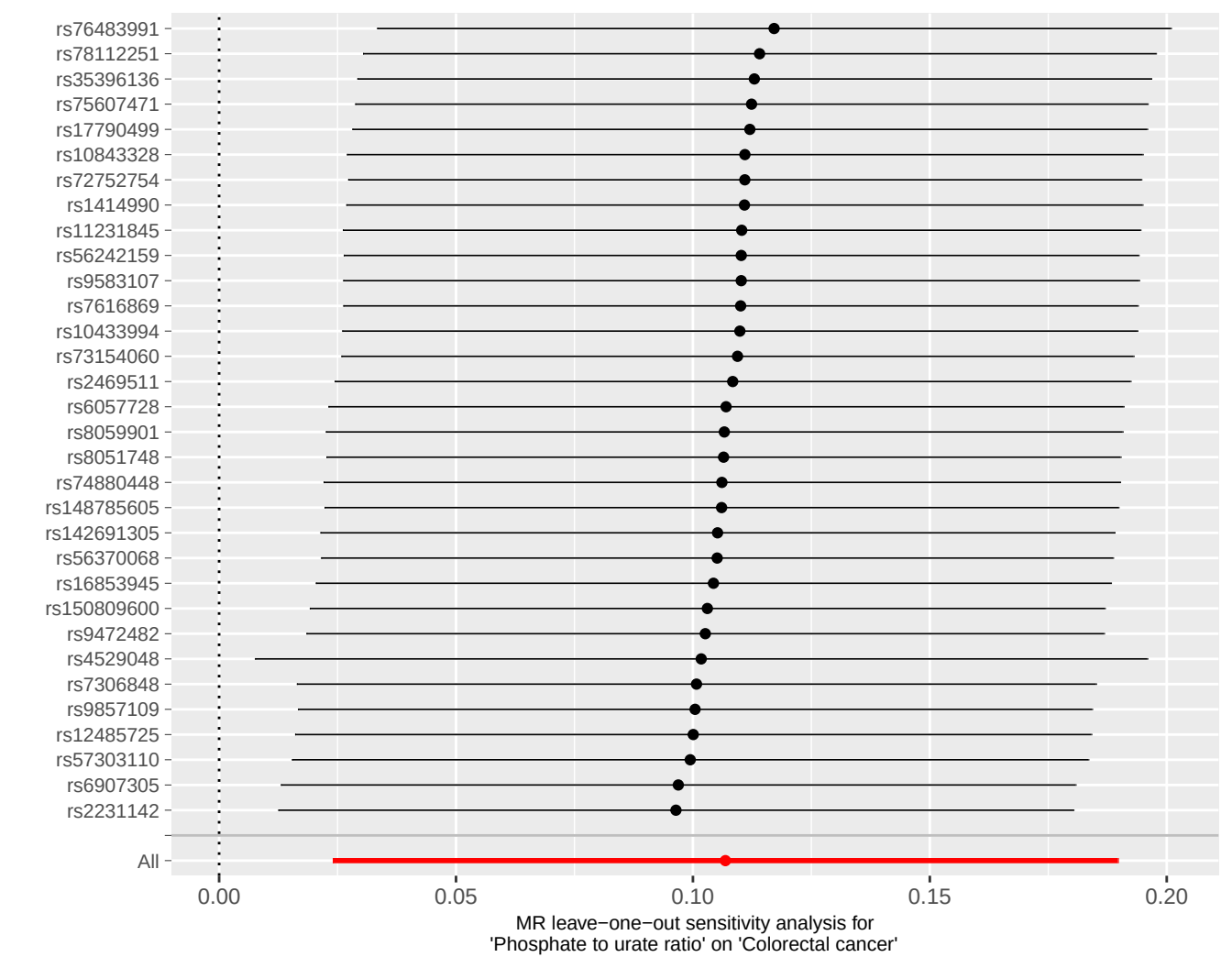
rs138795521
rs10766713
rs112036394
rs6442990
rs2322969
rs66628241
rs1461567
rs898978
rs17058444
rs118106972
All
0.00
0.05
0.10
0.15
MR leave−one−out sensitivity analysis for
'Adenosine 5'−diphosphate (ADP) to choline phosphate ratio' on 'Colorectal cancer'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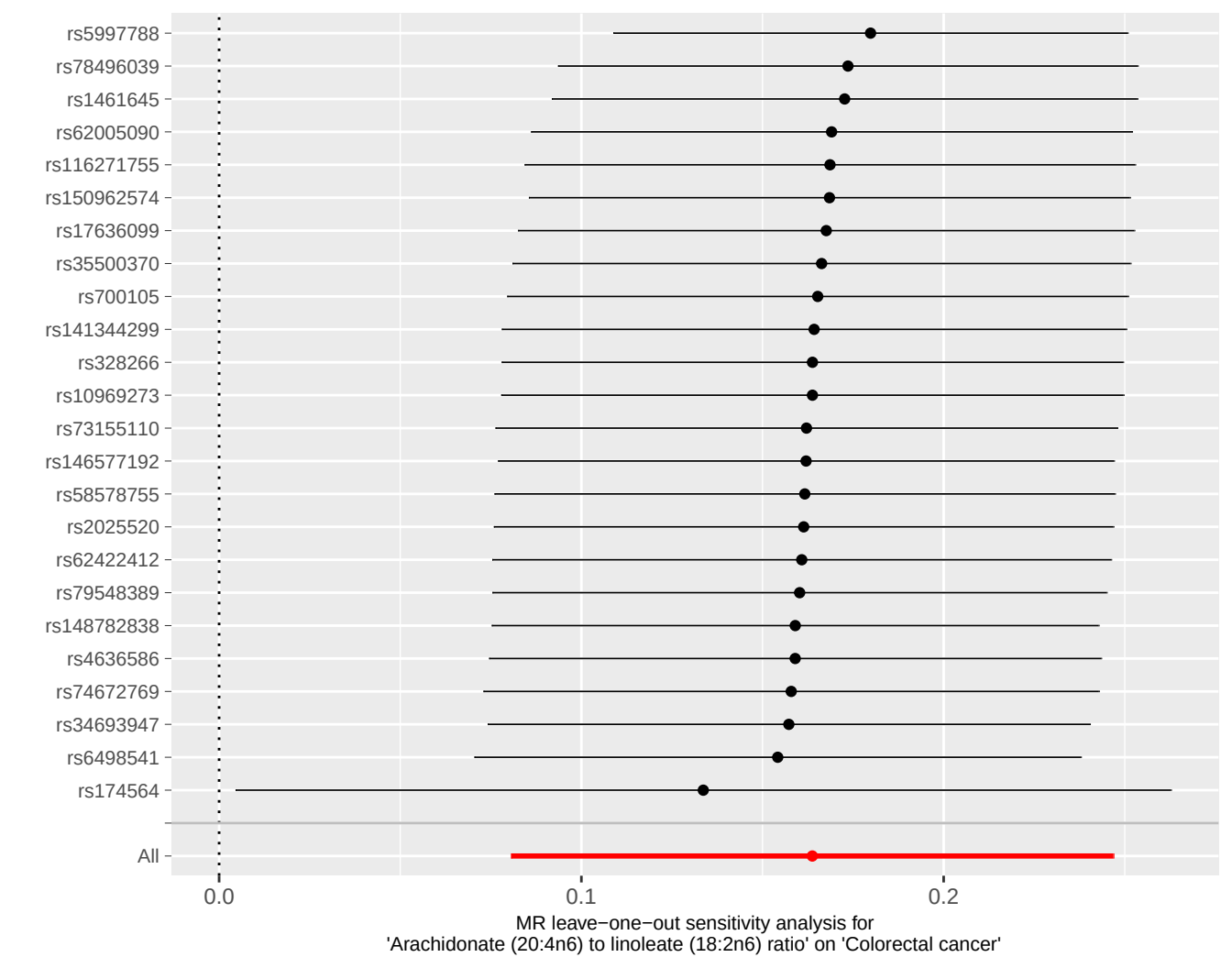
rs10433994
rs73154060
rs2469511
rs6057728
rs8059901
rs8051748
rs74880448
rs148785605
rs142691305
rs56370068
rs16853945
rs150809600
rs9472482
rs4529048
rs7306848
rs9857109
rs12485725
rs57303110
rs6907305
rs2231142
All
0.00
0.05
0.10
0.15
0.20
MR leave−one−out sensitivity analysis for
'Phosphate to urate ratio' on 'Colorectal cancer'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rs328266
rs10969273
rs73155110
rs146577192
rs58578755
rs2025520
rs62422412
rs79548389
rs148782838
rs4636586
rs74672769
rs34693947
rs6498541
rs174564
All
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Arachidonate (20:4n6) to linoleate (18:2n6) ratio' on 'Colorectal cancer'