Supplementary material

Socioeconomic Status, Individual Behaviors and Risk of Mental disorders: A Mendelian Randomization Study

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Supplementary Introduction for the Mendelian Randomization Approach

In recent years, the Mendelian randomization (MR) approach is widely applied to explore the risk factors of diseases (Smith and Ebrahim, 2003). The concept of MR was firstly attributed to Katan in 1986 and subsequently developed by the others, with instrumental variables (IVs) in econometrics introduced (Katan, 1986). In the MR framework, genetic variants are used as IVs to represent the exposure phenotypes of interest. When a certain phenotype is determined by the genotype, and the phenotype leads to the onset of a certain disease, then it can be considered that the genotype affects the disease through the phenotype (Thomas and Conti, 2004). Based on the random assortment at meiosis and fixed allocation at conception for genetic variants, MR design is less vulnerable to bias from confounders and reverse causality. Thus, genetic variations (single nucleotide polymorphisms, SNPs) can be used as IVs to infer causal relationships between phenotypes and the risk of diseases (Burgess et al., 2013). IVs must meet the following three assumptions in the MR framework: i) IVs are robustly associated with the exposure phenotype; ii) IVs are not associated with any potential confounders; iii) IVs influence the outcome only through the exposure phenotype (Emdin et al., 2017). The first assumption is known as the "relevance" assumption. The second (the "exclusiveness" assumption) and third (the "independence" assumption) assumptions are collectively known as independence from horizontal pleiotropy. Horizontal pleiotropy is also called "biological pleiotropy", which refers to an SNP associated with multiple exposure phenotypes and affecting the outcome independent of the risk factor but through other pathways. Violation of the fundamental assumptions can introduce bias in the MR analysis. To meet the first assumption, SNPs should be strongly associated with the exposure phenotype at genome-wide significance ($p < 5 \times 10^{8}$) with sufficient statistical strength (F-statistics > 10) (Burgess and Thompson, 2011). Whereas for the second and third assumptions, an array of sensitivity analysis methods have been established to evaluate any potential pleiotropy. For example, the intercept derived from MR-Egger regression can be used to detect horizontal pleiotropy. More detailed, the intercept with a $p > 0.05$ suggests the rejection of the "non-zero intercept" hypothesis, indicating no pleiotropy detected (Burgess and Thompson, 2017).

The present work performed a two-sample MR (TSMR) analysis based on summary-level statistics from genome-wide association studies (GWAS). The minimum information required for TSMR analysis includes SNP identification (ID), effect-allele (EA), effect size (BETA), and standard error (SE) of BETA. Other non-essential but useful information for MR analysis includes other-allele (OA), effect allele frequency (EAF), p-value, sample size (N), and so on. In our study, four models were used to estimate the causality including inverse weighted variance (IVW), MR-Egger regression, weighted median and weighted mode estimation. Detailed instructions for each of the models were presented in Table S6. Rigorous SNPs quality control and complementary statistical methods were conducted to detect and correct any potential pleiotropy.

Reference

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Table S1. Previous studies investigating associations between socioeconomic status/individual behaviors and mental disorders.

Exposures	Mental disorders	Type of study	PMID	Primary Results
Education level	Major depressive disorder	Cohort study	25605025	Low educational level was associated with increased risk of major depressive disorder.
Educational attainment	Bipolar disorder	Case-control	16524631	Increased educational attainment was associated with increased risk of bipolar disorder.
Family income	Major depressive disorder	Cohort study	29450462	Low family income level was associated with increased risk of major depressive disorder.
Sugar-sweetened beverage consumption	Clinical depression or depressive symptoms	Meta-analysis	30419536	Regular consumption of sugar-sweetened beverage was associated with increased risk of depression.
Physical activity levels	Clinical depression or depressive symptoms	Meta-analysis	29690792	Higher physical activity level was associated with reduced risk of depression.
Physical activity level	Anxiety symptoms	Meta-analysis	31542132	Higher physical activity level was associated with reduced risk of anxiety symptoms.
Tobacco smoking behaviors	Bipolar disorder	Case-control	19267698	Bipolar disorder was associated with higher prevalence of tobacco smoking behaviors.
Smoking status (current, former and never)	Depression	Meta-analysis	24935795	Smoking was associated with increased risk of depression relative to both never smokers and former smokers
Smoking status (smoker or nonsmoker)	Schizophrenia	Meta-analysis	30102383	Smokers had an increased risk of schizophrenia compared with nonsmokers
Alcohol consumption (abstinence, light, moderate and heavy drinking)	Depressive symptoms	Meta-analysis	31837230	Light drinking was associated with lower risk of depressive symptoms while heavy drinking was not associated with depressive symptoms.
Sleep quality	Bipolar disorder	Cohort study	26228404	Poor sleep quality was associated with increased risk of bipolar disorder
Sedentary behaviors	Clinical depression or	Meta-analysis	25183627	Higher sedentary behavior at baseline was associated with

	depressive symptoms			higher risk of depression
Number of sexual partners	Depressive symptoms	Cohort study	21590465	Increased number of sexual partners was associated with increased risk of depressive symptoms.
Driving speed	Schizophrenia	Case-control	30219605	Patients with schizophrenia drove slower than healthy controls.
Age at first birth	Depressive symptoms	Cohort study	11989963	Delaying first birth was associated with decreased risk of depressive symptoms.

Table S2. Detailed description of exposure phenotypes in the present study.

Phenotypes	PMID	Sample size	Ancestry	Definition
Socioeconomic status				
Education attainment	30038396	1,131,881	European	Education attainment was measured as number of years of schooling completed. Mean education years 16.8 ± 4.2. (SSGAC: 10k lead SNPs in the sample including 23andMe; full GWAS data was available only from the sample excluding 23andMe.)
Total household income before tax	31844048	286,301 (Male 48.35%)	European	Using a 5-point scale corresponding to the total household income before tax: 1 being less than £18,000, 2 being £18,000-£29,999, 3 being £30,000-£51,999, 4 being £52,000-£100,000 and 5 being greater than £100,000. This 5-point scale was analyzed by treating the categories of income as a continuous variable. (UKB: top SNPs reported in the original GWAS; full GWAS data was no available.)
Dietary composition				
Relative carbohydrate intake	32393786	268,922 (Male 39.44%)	European	Carbohydrate included intake from all saccharides, while sugar included intake from mono- and disaccharides only. The four dietary composition phenotypes were measured as relative intake, which could be described as an "adjusted macronutrients density". Specifically, phenotype definition of the energy-corrected macronutrient intakes is given by $$corrected\ intake = \frac{energy\ from\ macronutrient}{total\ energy^{\beta}}$$ Here, the macronutrient and total energy intake was measured in the same unit (e.g., kilocalories). β is a correction factor and detailed estimated procedure was described by Meddens et al.
Relative fat intake	32393786	268,922 (Male 39.44%)	European	
Relative protein intake	32393786	268,922 (Male 39.44%)	European	
Relative sugar intake	32393786	235,391 (Male 43.32%)	European	
Habitual physical activity (UKB: top SNPs reported in the original GWAS; full GWAS data was not available.)				
Average acceleration	29899525	91,084	European	Average acceleration was derived from up to seven days of accelerometer wear (27.98±8.14 milli-gravities). Genetic variants used in our studied were obtained from a recent MR study (PMID: 32680943).

Moderate to vigorous physical activity (MVPA)	29899525	377,234	European	This is a self-reported phenotype measured as a continuous variable (metabolic-equivalent minutes per week: 1,650±2,084 minutes). Specifically, it was measured by taking the sum of total minutes/week of moderate physical activity (MPV) multiplied by four and the total minutes/week of VPA multiplied by eight, corresponding to their metabolic equivalents. Genetic variants proxied for MVPA were obtained from the full adjusted model without standard error (se) released. Hence, we calculated the standard error using the following formula: $se = 1/\sqrt{2N * EAF(1-EAF)}$, where N is the sample size and EAF is the effect allele frequency of SNP (PMID: 29892602).
Vigorous physical activity (VPA)	29899525	261,055 (98,060 cases vs. 162,995 controls)	European	This is a self-reported phenotype measured as a binary phenotype (98,060 cases with VPA for ≥ 3 days per week vs. 162,995 controls with VPA for 0 day per week). Participants were asked: "In a typical week, how many days did you do 10 minutes or more of vigorous physical activity? (These are activities that make you sweat or breathe hard such as fast cycling, aerobics, heavy lifting)". Genetic variants proxied for VPA were obtained from the full adjusted model without standard error (se) released. Hence, we calculated the standard error using the following formula: $se = \sqrt{[p \times (1-p)]}/\sqrt{2N \times EAF(1-EAF)}$, where p is the proportion of cases with VPA for ≥ 3 days per week, N is the sample size and EAF is the effect allele frequency of SNP (PMID: 29892602).
Smoking behaviors				
Age of initiation of regular smoking	30643251	341,427	European	Participants were asked "At what age did you begin smoking regularly?" or "what is your current age and how long have you smoked?".
Cigarettes per day	30643251	337,334	European	This phenotype was measured as the average number of cigarettes smoked per day. Participants were asked "How many cigarettes do you smoke per day?" or "How many cigarettes did you smoke per day?".
Smoking cessation	30643251	547,219	European	This phenotype was measured as binary variable with current smokers

				coded as “2” and former smokers coded as “1”. Participants were asked “Do you currently smoke? And have you ever smoked regularly?”, “Do you smoke? And have you smoked over 100 cigarettes in your entire life?”
Smoking initiation	30643251	1,232,091	European	This phenotype was measured as binary variable with ever being a regular smoker in their life (current or former) coded as “2” and never being a regular smoker in their life coded as “1”. Participants were asked “Have you smoked over 100 cigarettes over the course of your life?”, “Have you ever smoked every day for at least a month?” or “Have you ever smoked regularly?”.
Drinking behaviors				
Alcohol consumption per week	30643251	941,280	European	This phenotype was measured as the average number of drinks a participant reported drinking each week, aggregated across all types of alcohol. Participants were asked “In the past week, how many alcoholic beverages did you have?” or “Thinking about the past year, on the average how many drinks did you have each week?”.
AUDIT	30336701	121,604 (Male 43.8%)	European	The Alcohol Use Disorder Identification Test (AUDIT) total score was created by taking the sum of items 1-10 for all participants. (UKB + 23andMe: 10k SNPs; full GWAS data was not publicly available)
Sleeping behaviors				
Insomnia	30804565	1,331,010 (Male 48.98%; 397,956 cases vs. 933,054 controls)	European	UK biobank phenotype: Participants were asked “Do you have trouble falling asleep at night or do you wake up in the middle of the night?” and were able to choose one of the following four answers: “never/rarely”, “sometimes”, “usually”, or “prefer not to answer”. Insomnia cases were defined as participants who answered this question with “usually”, while participants answering “never/rarely” or “sometimes” were defined as controls. 23andMe phenotype:

				Insomnia cases affirmed at least one of the following questions: "Have you ever been diagnosed with, or treated for: Insomnia?"; “Have you ever been diagnosed with, or treated for, any of the following conditions: Insomnia but not Narcolepsy, Sleep apnea or Restless leg syndrome”; "Has a doctor ever told you that you have any of these conditions: Insomnia (difficulty getting to sleep or staying asleep)?"; "Have you ever been diagnosed by a doctor with any of the following neurological conditions: Sleep disturbance"; "Do you routinely have trouble getting to sleep at night?"; "What sleep disorders have you been diagnosed with? Please select all that apply: Insomnia, trouble falling or staying asleep"; "Have you ever taken these medications? Prescription sleep aids"; "In the last 2 years, have you taken any of these medications? Prescription sleep aids". (UKB + 23andMe: top SNPs reported in the original GWAS; full GWAS data was only available from the sample excluding 23andMe.)
Long sleep duration	30846698	339,926 (Male 43.9%; 34,184 case vs. 305,742 controls)	European	Long sleep duration was defined as sleeping for 9h or more relative to 7-8h sleep duration (set as controls).
Short sleep duration	30846698	411,934 (Male 46.9%; 106,192 cases vs. 305,742 controls).	European	Short sleep duration was defined as sleeping for 6h or less relative to 7-8h sleep duration (set as controls).
Sleep duration	30846698	446,118 (Male 45.9%)	European	Sleep duration was treated as a continuous variable. Participants were asked: About how many hours sleep do you get in every 24h? (please include naps), with responses in hour increments. Extreme responses of

				less than 3 h or more than 18h were excluded and “Do not know” or “Prefer not to answer responses” were set to missing. Mean sleep duration was 7.2±1.1 hours.
Leisure sedentary behaviors (UKB: top SNPs reported in the original GWAS; full GWAS data was not publicly available**)**				
Computer use time	32317632	422,218 (Male 45.7%)	European	Participants were asked “In a typical day, how many hours do you spend using the computer?”. Average time using the computer was 1.0 ± 1.2h.
Television watching time	32317632	422,218 (Male 45.7%)	European	Participants were asked “In a typical day, how many hours do you spend watching TV?”. Average time watching TV was 2.8 ± 1.5h.
Drive time	32317632	422,218 (Male 45.7%)	European	Participants were asked “In a typical day, how many hours do you spend driving?”. Average time driving was 0.9 ± 1.0h.
Risky behaviors (SSGAC: top SNPs reported in the original GWAS; full GWAS data for adventurousness was not available**)**				
Adventurousness	30643258	557,923	European	Participants were asked “if forced to choose, would you consider yourself to be more cautious or more adventurous? 1) Very cautious /2) Somewhat cautious /3) Neither /4) Somewhat adventurous /5) Very adventurous”.
Automobile speeding propensity	30643258	404,291	European	Participants were asked “How often do you drive faster than the speed limit on the motorway?”. Response options: 1) Never/rarely, 2) Sometimes, 3) Often, 4) Most of the time, and also 5) Do not drive on the motorway. Average normalized automobile speeding propensity was 0.04 ± 0.82. Those not driving on the motorway were dropped.
General risk to tolerance	30643258	939,908	European	The UKB measurement of general risk tolerance was based on the question “Would you describe yourself as someone who takes risks? Yes/No”. The 23andMe measurement was based on a question about overall comfort taking risks, with five response options ranging from “very comfortable’” to “very uncomfortable”.
Number of sexual partners	30643258	370,711	European	Participants were asked “About how many sexual partners have you had in your lifetime?”. If respondents reported more than 99 lifetime sexual partners, they were asked to confirm their responses. Average number of

				sexual partners was 0.03 ± 0.94.
Reproductive behaviors (SSGAC: top SNPs reported in the original GWAS; full GWAS data was only available from the sample excluding 23andMe.)				
Age at first birth (AFB)	27798627	251,151 (Male 20.33%)	European	Age at first birth (AFB): Self-reported age when subjects had their first child. In most cohorts this was asked directly like "How old were you when you had your first child?". Besides, it could also be calculated based on survey questions such as the date of birth of the subject and date of birth of the first child. The average age was 26.8 ± 4.78 years. Number of children ever born (NEB): Self-reported number of children. Participants were asked directly (e.g. "How many children do you have?" or "How many natural (biological) children have you ever had, that is, all children who were born alive?", or "How many children have you had - not counting any step, adopted, or foster children, or any who were stillborn?") . Besides, it could also be calculated based on survey questions such as pregnancy histories and outcomes, number of deliveries and so on. The average number was 2.3 ± 1.43 children. Standard error (se) of estimated genetic effect on AFB and NEB was not released by Barban et al. As AFB and NEB were analyzed as continuous variables, standard error was calculated using the following formula: $se = 1/\sqrt{2N * EAF(1-EAF)}$, where N is the sample size and EAF is the effect allele frequency of SNP (PMID: 29892602).
Number of children ever born (NEB)	27798627	343,072 (Male 31.57%)	European	

SSGAC, Social Science Genetic Association Consortium; SNP, single nucleotide polymorphism; GWAS, genome-wide association study; UKB, United Kingdom Biobank;

Table S3. Detailed descriptions for GWAS meta-analysis of 3 mental disorders.

Mental disorders	Bipolar disorder	Major depressive disorder	Schizophrenia
Samples	PGC1 and PGC2 (totally 32 samples)	PGC29, deCODE, Generation Scotland, GERA, and iPSYCH (totally 33 samples)	PGC1, new CC and East Asia (totally 49 samples)
Total sample sizes	20,352 cases/31,358 controls	45,396 cases/97,250 controls	34,241 cases/45,604 controls
Percentage of European	100%	100%	93.5%
Diagnosis criteria	Using structured diagnostic instruments, a lifetime diagnosis of bipolar disorder was established on the basis of international consensus criteria (DSM-IV or ICD-9/10). Assessments came from trained interviewers, clinician-administered checklists or medical record review.	Cases ascertainment included structured diagnostic interviews, national inpatient electronic records and Kaiser Permanente Northern California Healthcare electronic medical records (1995-2013). Lifetime major depressive disorder was diagnosed according to DSM-III/IV or ICD-9/10.	Diagnosis of schizophrenia was established on the basis of DSM-IV or ICD-10. All participating cohorts were further included for GWAS meta-analysis based on a questionnaire covering assessment protocol and associated quality control procedures.

GWAS, genome-wide association study; PGC, Psychiatric Genomics Consortium. New CC, case-control samples not part of a discovery portion of a prior PGC mega-analysis; iPSYCH, Integrative Psychiatric Research; DSM, Diagnostic and Statistical Manual of Mental Disorders; ICD, International Classification of Diseases.

Table S4. Details of SNPs filtering procedures.

Exposure phenotypes	Number of SNPs available[1]	SNP filtering (number of SNPs remained[2])									
		Step 1	BIP			MDD			SCZ		
			Step 2	Step 3	Step 4	Step 2	Step 3	Step 4	Step 2	Step 3	Step 4
Socioeconomic status											
Educational attainment	393	386	385	371	364	385	371	369	380	367	347
Total household income before tax	27	25	25	24	21	25	24	24	24	23	19
Dietary composition											
Relative carbohydrate intake	11	7	6	6	5	6	6	6	6	6	6
Relative fat intake	4	3	3	3	3	3	3	3	3	3	3
Relative protein intake	7	7	7	7	5	7	7	7	7	7	5
Relative sugar intake	8	5	5	4	4	5	4	4	5	4	4
Habitual physical activity											
Average acceleration	8	8	8	7	7	8	7	7	8	7	5
Moderate to vigorous physical activity	7	6	5	5	4	5	5	4	5	5	4
Vigorous physical activity	4	4	4	4	3	4	4	4	4	4	3
Smoking behaviors											
Age of initiation of regular smoking	9	9	9	7	7	9	7	7	9	7	6
Number of cigarettes per day	38	37	37	37	34	37	37	37	35	35	27
Smoking cessation	15	14	14	14	13	14	14	13	13	13	11
Smoking initiation	202	195	195	188	184	195	188	183	190	183	174
Drinking behaviors											
Alcohol consumption per week	71	66	66	64	62	66	65	63	64	63	56
Alcohol Use Disorder Identification Test (AUDIT)	6	3	3	3	3	3	3	3	3	3	3
Sleeping behaviors											
Insomnia	158	155	155	148	146	155	148	147	152	145	135
Long sleep duration	8	8	7	7	7	7	7	7	7	7	7
Short sleep duration	25	21	21	19	4	21	19	17	21	19	16

Sleep duration	63	61	60	56	54	60	56	54	59	55	50
Leisure sedentary behaviors											
Computer use time	22	20	20	20	16	20	20	19	19	19	18
Television watching time	95	91	89	84	81	90	85	85	87	82	79
Drive time	4	4	4	4	3	4	4	4	3	3	3
Risky behaviors											
Adventurousness	108	103	102	97	96	102	97	97	102	97	90
Automobile speeding propensity	31	28	28	28	24	28	28	28	27	27	27
General risk tolerance	80	73	71	68	66	71	68	67	67	64	59
Number of sexual partners	77	73	73	71	68	73	71	69	69	67	62
Reproductive behaviors											
Age at first birth	9	9	9	9	9	9	9	9	9	9	7
Number of children ever born	2	2	2	2	2	2	2	2	2	2	2

SNP, single nucleotide polymorphisms; BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.

[1] Number of independent SNPs ($p < 5 \times 10^{-8}$) within each phenotype at a cut-off of linkage disequilibrium $r^2 \leq 0.001$.

[2] SNPs filtering steps:

Step 1, we excluded SNPs associated with more than one phenotype.

Step 2, we extracted exposure-SNPs from the outcomes and excluded the SNPs meeting the following items: 1) SNPs associated with outcomes at genome-wide significance; 2) SNPs absent in the outcome GWAS data without appropriate proxies available.

Step 3, we harmonized the SNPs of from exposure and outcome to exclude SNPs being palindromic with intermediate allele frequencies based on the allele frequency over 0.42 using the harmonization function in the "Two-sample MR" R package.

Step 4, we conducted MR-PRESSO to exclude SNPs with potential pleiotropy using "MR-PRESSO" R package.

Table S5. List of genetic variants associated with more than one phenotype.

SNPs	Exposures
rs1008078	educational attainment, smoking initiation
rs10189857	educational attainment, television watching time
rs1104608	relative carbohydrate intake, alcohol consumption per week
rs11076962	educational attainment, smoking initiation
rs11128203	smoking initiation, automobile speeding propensity
rs11588857	educational attainment, total household income before tax
rs11940694	alcohol consumption per week, Alcohol Use Disorder Identification Test
rs12151248	educational attainment, total household income before tax
rs12567114	short sleep duration, sleep duration
rs1260326	alcohol consumption per week, Alcohol Use Disorder Identification Test
rs13107325	alcohol consumption per week, television watching time, short sleep duration
rs1531518	general risk tolerance, number of sexual partners
rs17005118	insomnia, short sleep duration
rs205024	short sleep duration, sleep duration
rs2239030	adventurousness, general risk tolerance
rs2279829	smoking initiation, number of sexual partners
rs2472297	relative carbohydrate intake, alcohol consumption per week
rs42210	educational attainment, television watching time
rs429358	moderate to vigorous physical activity, insomnia
rs4702	insomnia, number of sexual partners
rs55745410	adventurousness, general risk tolerance
rs56113850	number of cigarettes per day, smoking cessation
rs58400863	smoking initiation, general risk tolerance
rs62062288	alcohol Use Disorder Identification Test, automobile speeding propensity
rs62519839	adventurousness, general risk tolerance
rs67361341	adventurousness, general risk tolerance

rs6874731	smoking initiation, general risk tolerance
rs7012814	relative fat intake, Relative sugar intake
rs72780746	smoking initiation, number of sexual partners
rs8097672	relative carbohydrate intake, relative sugar intake
rs838144	relative carbohydrate intake, relative sugar intake
rs9372625	computer use time, automobile speeding propensity
rs9556958	educational attainment, adventurousness
rs984409	computer use time, television watching time

SNP, single nucleotide polymorphisms.

Table S6. Descriptions of the Mendelian randomization (MR) methods.

Mendelian randomization methods	Intercept	Breakdown levels	Assumptions and comments
Inverse variance weighted (IVW)	Zero	0%	Instrumental variants (IVs) should meet the Instrument Strength Independent of Direct Effects (InSIDE) assumption. The method assumes that all the variants are valid. Even one invalid IV can bias the effect estimate. This method is the most powerful and precise.
MR-Egger regression	Non-zero	100%	IVs should meet the InSIDE assumption. This method allows all IVs are invalid but it is substantially less efficient than IVW and median-based methods. A non-zero intercept derived from Egger regression can be used to determine whether there is directional pleiotropy detected.
Weighted median	Zero	50%	This method allows no more than 50% of invalid IVs and the efficiency is similar to that of IVW.
Weighted-mode based estimation	Zero	50-100%	This method allows more than 50% of invalid IVs. The efficiency is smaller the IVW and weighted median methods, but is larger than that of MR Egger regression.

Table S7. Mendelian randomization estimates for the association of socioeconomic status/individual behaviors with 3 mental disorder derived from different models.

Exposures	Outcomes	Number of SNPs	Number of proxies[1]	Inverse variance weighted		MR-Egger		Weighted median		Weighted mode	
				OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Educational attainment	BIP	364	0	1.53 (1.28, 1.82)	2.91E-06	1.06 (0.55,1.74)	0.87	1.38 (1.10,3.01)	4.64E-03	1.11 (0.60,1.81)	0.75
Total household income before tax	BIP	21	3	1.06 (0.61, 1.83)	0.85	0.31 (2.46E-04, 399.18)	0.75	1.12 (0.52, 2.40)	0.78	1.04 (0.25, 4.36)	0.95
Relative carbohydrate intake	BIP	5	0	1.29 (0.64, 2.62)	0.48	0.92 (8.81E-05, 9.63E+03)	0.99	1.66 (0.65, 4.22)	0.29	1.78 (0.48, 6.64)	0.44
Relative fat intake	BIP	3	0	0.70 (0.30, 1.61)	0.40	1.01 (0.17, 5.98)	0.99	1.05 (0.57, 1.96)	0.87	1.06 (0.52, 2.17)	0.89
Relative protein intake	BIP	5	0	1.76 (0.78, 3.95)	0.17	7.65 (0.06, 910.90)	0.47	2.21 (0.97, 5.05)	0.06	2.11 (0.73, 6.06)	0.24
Relative sugar intake	BIP	4	0	0.71 (0.33, 1.55)	0.39	3.77E-08 (9.61E-21, 1.48E+05)	0.37	0.63 (0.25, 1.58)	0.33	0.60 (0.16, 2.23)	0.50
Average acceleration	BIP	7	1	1.04 (0.98, 1.12)	0.21	0.97 (0.71, 1.31)	0.85	1.04(0.97,1.11)	0.24	1.03 (0.92, 1.14)	0.64
Moderate to vigorous physical activity	BIP	4	0	3.64 (0.89, 14.80)	0.07	3.65E+08 (1.38, 9.68E+16)	0.18	2.02 (0.51, 8.06)	0.32	1.29 (0.17, 9.58)	0.82
Vigorous physical activity	BIP	3	0	0.94 (0.63, 1.39)	0.75	2.45 (0.23, 26.55)	0.59	1.03 (0.63, 1.71)	0.90	1.11 (0.60, 2.10)	0.77
Age of initiation of regular smoke	BIP	7	0	0.64 (0.33, 1.24)	0.19	0.78 (0.03, 17.83)	0.88	0.68 (0.29, 1.56)	0.36	0.43 (0.12, 1.49)	0.23
Number of cigarettes per day	BIP	34	0	1.23 (0.90, 1.68)	0.19	1.29 (0.76, 2.21)	0.35	1.29 (0.98, 1.71)	0.07	1.32 (0.99, 1.75)	0.07
Smoking cessation	BIP	13	0	1.44 (1.04, 2.00)	0.03	1.33 (0.47, 3.75)	0.60	1.31 (0.87, 1.98)	0.19	1.24 (0.69, 2.21)	0.48
Smoking initiation	BIP	184	0	1.62 (1.39, 1.88)	2.78E-10	1.16 (0.65, 2.09)	0.61	1.60 (1.34, 1.92)	3.44E-07	2.25 (1.24, 4.07)	8.29E-03
Alcohol consumption per week	BIP	62	0	1.31 (0.81, 2.13)	0.27	1.04 (0.47, 2.29)	0.93	1.17 (0.75, 1.83)	0.49	1.08 (0.67, 1.75)	0.74
Alcohol Use Disorders Identification Test	BIP	3	0	0.61 (0.04, 10.24)	0.73	1.65 (3.83E-03, 711.72)	0.90	1.24 (0.13, 11.72)	0.85	1.59 (0.13, 19.11)	0.75
Insomnia	BIP	146	0	1.18 (1.08, 1.28)	1.30E-04	1.21 (0.88, 1.66)	0.24	1.17 (1.06, 1.28)	2.08E-03	1.20 (0.91, 1.60)	0.20
Long sleep duration	BIP	7	1	0.99 (0.81, 1.20)	0.89	1.12 (0.62, 2.02)	0.72	1.01 (0.79, 1.28)	0.94	1.02 (0.72, 1.42)	0.93
Short sleep duration	BIP	4	0	0.40 (0.23,0.70)	1.23E-03	0.42 (0.02, 9.30)	0.64	0.48 (0.25, 0.93)	0.03	0.58 (0.22, 1.50)	0.34
Sleep duration	BIP	54	1	1.007 (1.001, 1.013)	0.02	0.993 (0.972, 1.013)	0.49	1.007 (0.999, 1.015)	0.06	1.006 (0.995, 1.017)	0.31

Computer use time	BIP	16	0	1.57 (0.91, 2.70)	0.11	480.30 (7.03, 3.28E+04)	0.01	1.13 (0.57, 2.21)	0.73	0.87 (0.21, 3.58)	0.85
Television watching time	BIP	81	0	0.87 (0.67, 1.14)	0.31	0.72 (0.18, 2.87)	0.64	0.98 (0.71, 1.33)	0.88	1.56 (0.62, 3.94)	0.35
Drive time	BIP	3	0	0.50 (0.17, 1.49)	0.21	2.49 (1.23E-04, 5.04E+04)	0.89	0.62 (0.16, 2.40)	0.49	0.72 (0.16, 3.26)	0.71
Adventurousness	BIP	96	0	2.12 (1.58, 2.84)	4.22E-07	2.23 (0.70, 7.10)	0.18	2.13 (1.49, 3.04)	3.05E-05	2.55 (1.30, 4.97)	7.39E-03
Automobile speeding propensity	BIP	24	0	0.78 (0.49, 1.23)	0.29	0.37 (0.04, 3.18)	0.37	0.80 (0.46, 1.39)	0.43	0.77 (0.31, 1.93)	0.58
General risk tolerance	BIP	66	0	3.63 (2.36, 5.58)	4.03E-09	27.61 (3.61, 208.25)	2.14E-03	3.42 (1.97, 5.93)	1.24E-05	10.44 (2.46, 44.35)	2.27E-03
Number of sexual partners	BIP	68	2	1.92 (1.45, 2.53)	4.08E-06	0.89 (0.23, 3.48)	0.87	1.51 (1.07, 2.12)	0.02	1.13 (0.50, 2.57)	0.77
Age at first birth	BIP	9	0	1.03 (0.89, 1.21)	0.67	1.86 (0.39, 8.91)	0.46	1.00 (0.85, 1.16)	0.96	0.99 (0.75, 1.31)	0.94
Number of children ever born	BIP	2	0	0.89 (0.13, 5.61)	0.87	NA	NA	NA	NA	NA	NA
Educational attainment	MDD	369	0	0.72 (0.64, 0.80)	1.43E-09	0.73 (0.4, 1.08)	0.11	0.73 (0.63, 0.84)	8.70E-06	0.61 (0.40, 0.92)	0.02
Total household income before tax	MDD	24	3	0.61 (0.42, 0.87)	7.41E-03	1.19 (0.09, 15.31)	0.90	0.67 (0.42, 1.07)	0.09	0.73 (0.33, 1.60)	0.44
Relative carbohydrate intake	MDD	6	0	0.50 (0.32, 0.80)	4.02E-03	0.48 (9.82E-04, 230.89)	0.83	0.40 (0.23, 0.71)	1.82E-03	0.36 (0.14, 0.92)	0.09
Relative fat intake	MDD	3	0	1.11(0.76,1.62)	0.59	0.92 (0.42, 2.00)	0.86	1.04 (0.70, 1.55)	0.85	1.02 (0.66, 1.60)	0.92
Relative protein intake	MDD	7	0	1.19 (0.80, 1.76)	0.40	0.35 (0.08, 1.50)	0.22	1.04 (0.67, 1.62)	0.87	0.95 (0.54, 1.65)	0.86
Relative sugar intake	MDD	4	0	0.50 (0.31, 0.82)	5.97E-03	0.98 (3.02E-09, 3.21E+08)	0.999	0.53 (0.29, 0.95)	0.03	0.56 (0.24, 1.35)	0.29
Average acceleration	MDD	7	1	0.97 (0.94, 1.00)	0.056	0.93 (0.82, 1.06)	0.31	0.97 (0.94, 1.01)	0.19	1.00 (0.94, 1.06)	0.95
Moderate to vigorous physical activity	MDD	4	0	0.50 (0.25, 1.01)	0.053	1.01E-03 (1.92E-08, 53.78)	0.34	0.50 (0.22, 1.13)	0.10	0.36 (0.12, 1.11)	0.17
Vigorous physical activity	MDD	4	0	0.96 (0.78, 1.19)	0.72	0.33 (0.08, 1.27)	0.25	0.94 (0.74, 1.20)	0.63	0.85 (0.61, 1.20)	0.42
Age of initiation of regular smoke	MDD	7	0	0.50 (0.30, 0.85)	0.01	3.69 (0.44, 30.63)	0.28	0.69 (0.38, 1.26)	0.23	0.80 (0.34, 1.86)	0.62
Number of cigarettes per day	MDD	37	1	1.13 (0.94, 1.36)	0.20	0.83 (0.61, 1.12)	0.23	0.92 (0.77, 1.10)	0.36	0.96 (0.79, 1.15)	0.64
Smoking cessation	MDD	13	0	1.26 (1.03, 1.55)	0.03	1.05 (0.57, 1.93)	0.89	1.19 (0.91, 1.55)	0.20	1.17 (0.83, 1.65)	0.38
Smoking initiation	MDD	183	1	1.52 (1.39,1.66)	3.28E-19	0.92 (0.64, 1.31)	0.63	1.44 (1.28,1.61)	1.39E-10	1.43 (1.06, 1.94)	0.02

Alcohol consumption per week	MDD	63	0	1.12 (0.89,1.43)	0.34	0.93 (0.62, 1.41)	0.73	0.94 (0.69,1.30)	0.72	0.95 (0.70, 1.28)	0.72
Alcohol Use Disorders Identification Test	MDD	3	0	2.40 (0.67, 8.58)	0.18	3.26 (0.39, 27.44)	0.47	2.96 (0.67, 13.05)	0.15	3.23 (0.57, 18.32)	0.32
Insomnia	MDD	147	0	1.26 (1.20, 1.32)	1.01E-22	1.08 (0.91, 1.29)	0.37	1.28 (1.20, 1.36)	3.79E-15	1.29 (1.08, 1.53)	5.27E-03
Long sleep duration	MDD	7	1	0.95 (0.79, 1.14)	0.57	1.20 (0.70, 2.06)	0.54	0.98 (0.82, 1.18)	0.84	1.03 (0.78, 1.35)	0.84
Short sleep duration	MDD	17	1	1.22 (1.00, 1.49)	0.049	0.69 (0.28, 1.68)	0.43	1.25 (1.00, 1.56)	0.051	1.27 (0.87, 1.85)	0.23
Sleep duration	MDD	54	0	0.999 (0.995, 1.004)	0.80	0.999 (0.98, 1.01)	0.95	1.001 (0.996, 1.005)	0.78	1.002 (0.994, 1.009)	0.61
Computer use time	MDD	19	0	1.23 (0.82, 1.85)	0.31	0.82 (0.03, 26.67)	0.94	1.22 (0.79, 1.86)	0.37	1.34 (0.69, 2.61)	0.39
Television watching time	MDD	85	2	1.04 (0.89, 1.23)	0.61	0.70 (0.30, 1.63)	0.41	1.02 (0.84, 1.25)	0.83	1.07 (0.61, 1.88)	0.81
Drive time	MDD	4	0	0.75 (0.40, 1.41)	0.37	7.81 (0.03, 1961.79)	0.54	0.83 (0.39, 1.77)	0.63	1.16 (0.42, 3.16)	0.79
Adventurousness	MDD	97	0	1.04 (0.88, 1.23)	0.62	0.66 (0.35, 1.25)	0.21	0.93 (0.74, 1.18)	0.56	0.93 (0.64, 1.33)	0.68
Automobile speeding propensity	MDD	28	0	0.55 (0.40, 0.76)	2.26E-04	0.22 (0.05, 0.92)	0.049	0.61 (0.42, 0.89)	0.01	0.72 (0.37, 1.42)	0.35
General risk tolerance	MDD	67	0	1.25 (0.96, 1.62)	0.09	1.47 (0.42, 5.20)	0.55	1.25 (0.88, 1.77)	0.22	1.12 (0.49, 2.59)	0.79
Number of sexual partners	MDD	69	1	1.40 (1.16, 1.69)	5.04E-04	1.15 (0.44, 3.00)	0.78	1.42 (1.13, 1.78)	2.35E-03	1.36 (0.74, 2.50)	0.33
Age at first birth	MDD	9	0	0.82 (0.75, 0.90)	2.17E-05	0.52 (0.21, 1.30)	0.20	0.79 (0.72, 0.88)	7.40E-06	0.76 (0.65, 0.90)	0.01
Number of children ever born	MDD	2	0	2.43 (0.79, 7.52)	0.12	NA	NA	NA	NA	NA	NA
Educational attainment	SCZ	347	0	1.06 (0.90, 1.26)	0.46	0.79 (0.43, 1.45)	0.45	1.05 (0.86, 1.27)	0.64	1.38 (0.67, 2.86)	0.39
Total household income before tax	SCZ	19	2	0.32 (0.16, 0.67)	2.28E-03	0.42 (8.83E-04, 201.58)	0.79	0.29 (0.15, 0.56)	2.54E-04	0.26 (0.10, 0.66)	0.01
Relative carbohydrate intake	SCZ	6	0	1.48 (0.77, 2.85)	0.24	4.20 (8.19E-04, 2.15E+04)	0.76	1.98 (1.01, 3.89)	0.04	2.61 (0.79, 8.69)	0.18
Relative fat intake	SCZ	3	0	0.63 (0.18, 2.17)	0.46	0.38 (0.03, 4.94)	0.59	0.53 (0.34, 0.82)	5.10E-03	0.51 (0.32, 0.81)	0.10
Relative protein intake	SCZ	5	0	0.75 (0.45, 1.26)	0.28	2.01 (3.88E-03, 1.04E+03)	0.84	0.73 (0.40, 1.34)	0.31	0.74 (0.33, 1.62)	0.49
Relative sugar intake	SCZ	4	0	1.30 (0.72, 2.34)	0.39	9.89 (9.22E-10, 1.06E+11)	0.86	1.38 (0.70, 2.69)	0.35	1.49 (0.59, 3.72)	0.46
Average acceleration	SCZ	5	0	0.99 (0.95, 1.04)	0.76	0.93 (0.78, 1.10)	0.44	0.99 (0.93, 1.05)	0.74	0.97 (0.90, 1.06)	0.57
Moderate to vigorous physical activity	SCZ	4	0	3.01 (1.30, 6.95)	9.83E-03	0.25 (6.86E-08,	0.87	2.72 (1.03, 7.17)	0.04	2.52 (0.70, 9.01)	0.25

						9.04E+05)					
Vigorous physical activity	SCZ	3	0	1.16 (0.88, 1.53)	0.29	0.85 (0.14, 5.16)	0.89	1.21 (0.89, 1.63)	0.22	1.26 (0.85, 1.86)	0.37
Age of initiation of regular smoke	SCZ	6	0	0.89 (0.50, 1.56)	0.68	1.00 (5.10E-03, 196.05)	0.9999	0.75 (0.36, 1.57)	0.44	0.48 (0.16, 1.43)	0.25
Number of cigarettes per day	SCZ	27	0	1.65 (1.28, 2.13)	1.26E-04	1.67 (1.08, 2.58)	0.03	1.71 (1.36, 2.14)	3.06E-06	1.67 (1.33, 2.09)	1.47E-04
Smoking cessation	SCZ	11	0	1.18 (0.94, 1.50)	0.16	0.97 (0.52, 1.79)	0.92	1.18 (0.85, 1.63)	0.33	1.20 (0.76, 1.87)	0.45
Smoking initiation	SCZ	174	1	1.64 (1.43, 1.88)	2.08E-12	1.39 (0.78, 2.48)	0.26	1.53 (1.30, 1.80)	2.01E-07	1.25 (0.71, 2.21)	0.45
Alcohol consumption per week	SCZ	56	0	1.43 (1.06, 1.93)	0.02	1.28 (0.81, 2.02)	0.29	1.34 (0.99, 1.81)	0.06	1.28 (0.95, 1.73)	0.11
Alcohol Use Disorders Identification Test	SCZ	3	0	0.61 (0.14, 2.62)	0.51	0.59 (0.05, 6.27)	0.74	0.60 (0.11, 3.26)	0.56	0.59 (0.09, 3.73)	0.63
Insomnia	SCZ	135	0	1.11 (1.03, 1.20)	4.56E-03	0.77 (0.58, 1.02)	0.07	1.07 (0.99, 1.17)	0.10	0.88 (0.67, 1.17)	0.39
Long sleep duration	SCZ	7	1	1.41 (1.15, 1.73)	9.79E-04	1.34 (0.69, 2.60)	0.42	1.33 (1.04, 1.68)	0.02	1.29 (0.93, 1.78)	0.18
Short sleep duration	SCZ	16	0	0.81 (0.59, 1.10)	0.18	0.42 (0.11, 1.65)	0.24	0.70 (0.53, 0.93)	0.01	0.67 (0.43, 1.06)	0.11
Sleep duration	SCZ	50	1	1.006 (1.000, 1.012)	0.02	1.01 (0.99, 1.03)	0.32	1.008 (1.002, 1.014)	6.68E-03	1.005 (0.996, 1.014)	0.33
Computer use time	SCZ	18	0	0.72 (0.44, 1.18)	0.19	3.19 (0.04, 228.42)	0.60	1.08 (0.62, 1.87)	0.79	1.41 (0.47, 4.27)	0.55
Television watching time	SCZ	79	2	0.88 (0.68, 1.14)	0.34	0.52 (0.14, 1.99)	0.34	0.81 (0.61, 1.07)	0.13	0.83 (0.41, 1.67)	0.60
Drive time	SCZ	3	0	0.18 (0.03, 1.19)	0.08	4.61E+20 (7.43E-10, 2.86E+50)	0.40	0.25 (0.07, 0.97)	0.045	0.32 (0.05, 2.02)	0.35
Adventurousness	SCZ	90	0	1.45 (1.11, 1.89)	6.73E-03	0.85 (0.30, 2.42)	0.76	1.25 (0.93, 1.67)	0.13	0.85 (0.49, 1.46)	0.55
Automobile speeding propensity	SCZ	27	0	0.42 (0.27, 0.65)	9.88E-05	0.14 (0.02, 1.05)	0.07	0.52 (0.33, 0.83)	6.22E-03	0.51 (0.22, 1.16)	0.12
General risk tolerance	SCZ	59	0	1.54 (1.00, 2.37)	0.0502	3.92 (0.52, 29.55)	0.19	1.61 (0.99, 2.61)	0.054	1.67 (0.42, 6.65)	0.47
Number of sexual partners	SCZ	62	1	2.48 (1.92, 3.21)	3.17E-12	3.61 (0.92, 14.24)	0.07	2.17 (1.62, 2.92)	2.72E-07	1.73 (0.84, 3.55)	0.14
Age at first birth	SCZ	7	0	1.06 (0.95, 1.20)	0.30	3.30 (1.10, 9.88)	0.09	1.09 (0.95, 1.26)	0.23	1.06 (0.84, 1.32)	0.65
Number of children ever born	SCZ	2	0	1.64 (0.77, 3.47)	0.20	NA	NA	NA	NA	NA	NA

BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; NA, not applicable.

[1] Proxies details:

Total household income before tax to BIP/MDD: rs12647647 was proxied by rs12649553 [linkage disequilibrium (LD) $r^2 = 1.00$]; rs17652520 was proxied by rs113520245 (LD $r^2 = 0.98$); rs146301099 was proxied by rs957557 (LD $r^2 = 0.83$).

Total household income before tax to SCZ: rs12647647 was proxied by rs12649553 (LD $r^2 = 1.00$); rs146301099 was proxied by rs957557 (LD $r^2 = 0.83$).

Average acceleration to BIP/MDD: rs56194509 was proxied by rs113093579 (LD $r^2 = 1.00$).

Number of cigarettes per day to MDD: rs28813180 was proxied by rs9867617 (LD $r^2 = 1.00$).

Smoking initiation to MDD/SCZ: rs10698713 was proxied by rs10447365 (LD $r^2 = 0.98$).

Long sleep duration to BIP/MDD/SCZ: rs17688916 was proxied by rs62057112 (LD $r^2 = 0.90$).

Sleep duration to BIP/MDD/SCZ: rs1991556 was proxied by rs112310745 (LD $r^2 = 0.98$).

Television watching time to BIP/MDD/SCZ: rs7834121 was proxied by rs7834248 (LD $r^2 = 0.96$); rs111901094 was proxied by rs28720066 (LD $r^2 = 0.98$).

Number of sexual partners to BIP: rs62063281 was proxied by rs112385572 (LD $r^2 = 0.98$); rs6908726 was proxied by rs13208096(LD $r^2 = 0.86$).

Number of sexual partners to MDD/SCZ: rs62063281 was proxied by rs112385572 (LD $r^2 = 0.98$).

Table S8. Statistical power calculation for Mendelian randomization effects derived from random-effects inverse variance weighted method.

Exposures	BIP			MDD			SCZ		
	R^2 (%)	*F*-statistics	Power (%)	R^2 (%)	*F*-statistics	Power (%)	R^2 (%)	*F*-statistics	Power (%)
Educational attainment	1.87	28.44-373.78	100	1.90	28.44-373.78	100	1.77	28.44-373.78	19
Total household income before tax	0.26	30.10-52.35	6	0.33	30.10-72.87	100	0.25	30.19-72.17	100
Relative carbohydrate intake	0.07	30.47-48.73	12	0.08	30.47-48.73	87	0.08	30.47-48.73	36
Relative fat intake	0.10	31.70-121.73	23	0.10	31.70-121.73	9	0.10	31.70-121.73	51
Relative protein intake	0.08	32.06-59.47	50	0.14	32.06-111.53	22	0.08	32.06-59.47	20
Relative sugar intake	0.06	25.00-44.44	15	0.06	25.00-44.44	76	0.06	25.00-44.44	15
Average acceleration	0.26	30.12-47.42	6	0.26	30.12-47.42	6	0.18	30.12-36.00	5
Moderate to vigorous physical activity	0.03	25.70-31.76	92	0.03	25.70-36.44	47	0.03	25.70-36.44	87
Vigorous physical activity	0.92	793.52-814.67	10	1.48	793.52-1461.92	14	1.17	798.17-1461.92	62
Age of initiation of regular smoking	0.08	31.80-63.50	27	0.08	31.80-63.50	87	0.07	31.80-63.50	7
Number of cigarettes per day	0.84	29.80-1309.99	59	0.89	29.80-1309.99	55	0.77	29.80-1309.99	100
Smoking cessation	0.13	30.90-155.00	34	0.13	30.90-155.00	34	0.11	30.90-155.00	12
Smoking initiation	0.74	29.80-211.00	100	0.72	29.80-211.00	100	0.67	29.80-211.00	100
Alcohol consumption per week	0.43	29.80-1520.00	54	0.44	29.80-1520.00	27	0.41	29.80-1520.00	91
Alcohol Use Disorder Identification Test	0.13	49.00-64.00	48	0.13	49.00-64.00	100	0.13	49.00-64.00	68
Insomnia	0.48	25.53-216.93	26	0.48	25.53-216.93	84	0.44	25.53-216.93	16
Long sleep duration	0.06	15.74-47.84	5	0.06	15.74-47.84	6	0.06	15.74-47.84	23
Short sleep duration	0.02	18.09-26.12	27	0.10	16.89-55.73	21	0.10	16.89-55.73	15
Sleep duration	0.50	29.63-220.78	5	0.50	29.63-220.78	5	0.46	29.63-220.78	5
Computer use time	0.16	34.45-52.06	58	0.19	33.00-79.56	38	0.18	33.00-79.56	48
Television watching time	0.89	33.63-144.19	31	0.94	33.63-144.19	10	0.87	33.63-144.19	38
Drive time	0.03	34.13-45.01	24	0.04	34.13-45.01	16	0.03	34.13-40.90	98
Adventurousness	0.77	29.72-375.97	100	0.79	29.72-375.97	9	0.73	29.72-375.97	100
Automobile speeding propensity	0.23	30.82-59.14	26	0.27	29.91-87.18	100	0.27	30.59-87.18	100
General risk tolerance	0.30	30.04-177.05	100	0.31	30.04-177.05	63	0.27	30.04-177.05	90

Number of sexual partners	0.74	29.80-79.58	100	0.75	29.80-79.58	100	0.67	29.80-79.58	100
Age at first birth	3.21	689.24-1409.50	9	3.21	689.24-1409.50	100	2.30	689.24-935.80	24
Number of children ever born	0.04	62.81-64.78	6	0.04	62.81-64.78	97	0.04	62.81-64.78	31

BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.

R^2 presented the proportion of variance in exposure phenotypes explained by single nucleotide polymorphisms (SNPs) using the formula $R^2 = [2 \times BETA^2 \times EAF \times (1 - EAF)]/[2 \times BETA^2 \times EAF \times (1 - EAF) + 2 \times SE(BETA)^2 \times N \times EAF \times (1 - EAF)]$. Here, BETA is the genetic effects on exposures; EAF is effect allele frequency; SE(BETA) is standard error of the genetic effects; N is the sample size. *F*-statistic quantified the strength of each selected SNP using the formula $R^2 \times (N - 2)/(1 - R^2)$.

Table S9. Heterogeneity and pleiotropy assessment for significant results ($p < 0.05$).

Exposures	Outcomes	Directional pleiotropy		Cochran's Q test			Rucker's Q' test		$Q - Q'$	p
		MR-Egger intercept	p	I^2	Q statistic	p	Q' statistic	p		
Educational attainment	BIP	0.0047	0.25	46%	675.0	4.76e-21	672.5	6.23e-21	2.5	0.11
Smoking cessation	BIP	0.0031	0.87	34%	18.2	0.11	18.2	0.08	0	0.83
Smoking initiation	BIP	0.0069	0.26	46%	342.5	8.80e-12	340.0	1.14e-11	2.5	0.19
Insomnia	BIP	-0.0013	0.86	55%	319.4	3.77e-15	319.3	2.57e-15	0.1	0.79
Short sleep duration	BIP	-0.0017	0.98	23%	3.89	0.27	3.89	0.14	0	0.97
Sleep duration	BIP	0.0156	0.16	50%	106.5	1.84e-05	102.5	3.68e-05	4.0	**0.046**
Adventurousness	BIP	-0.0007	0.93	49%	186.5	6.39e-08	186.5	4.49e-08	0	0.90
General risk tolerance	BIP	-0.0221	**0.05**	39%	107.4	7.42e-04	101.1	2.16e-03	6.3	**0.01**
Number of sexual partners	BIP	0.0134	0.27	40%	112.0	4.74e-04	109.9	5.74e-04	2.1	0.15
Educational attainment	MDD	-0.0002	0.94	38%	588.9	1.92e-12	588.9	1.51e-12	0	0.92
Total household income before tax	MDD	-0.0088	0.61	28%	32.1	0.10	31.7	0.08	0.4	0.53
Relative carbohydrate intake	MDD	0.0009	0.99	16.5%	5.99	0.31	5.99	0.20	0	0.98
Relative sugar intake	MDD	-0.0132	0.95	0%	2.09	0.55	2.08	0.35	0.1	0.95
Age of initiation of regular smoke	MDD	-0.0381	0.12	32%	8.87	0.18	5.18	0.39	3.69	0.055
Smoking cessation	MDD	0.0070	0.54	23%	15.5	0.21	15.0	0.18	0.5	0.46
Smoking initiation	MDD	0.0104	**0.004**	35%	281.1	3.33e-06	268.7	2.49e-05	12.4	**4.27E-04**
Insomnia	MDD	0.0069	0.08	34%	221.8	5.24e-05	217.1	9.87e-05	4.7	**0.03**
Short sleep duration	MDD	0.0200	0.22	49%	31.1	0.01	28.0	0.02	3.1	0.08
Automobile speeding propensity	MDD	0.0146	0.21	43%	47.2	0.01	44.5	0.01	2.7	0.09
Number of sexual partners	MDD	0.0034	0.68	45%	122.7	5.40e-05	122.4	4.2e-05	0.3	0.58
Age at first birth	MDD	0.0411	0.36	43%	14.1	0.08	12.4	0.09	1.7	0.19
Total household income before tax	SCZ	-0.0034	0.93	65%	51.1	5.11e-05	51.1	2.85e-05	0	0.88
Moderate to vigorous physical activity	SCZ	0.0325	0.78	0%	0.5	0.92	0.4	0.82	0.1	0.75
Number of cigarettes per day	SCZ	-0.0003	0.96	57%	60.2	1.60e-04	60.1	9.99e-05	0.1	0.94

Smoking initiation	SCZ	0.0033	0.57	57%	401.0	3.82e-20	400.2	3.10e-20	0.8	0.38
Alcohol consumption per week	SCZ	0.0022	0.52	46%	101.2	1.50e-04	100.4	1.30e-04	0.8	0.38
Insomnia	SCZ	0.0167	**0.01**	61%	346.9	8.55e-21	329.4	1.15e-18	17.5	**2.89E-05**
Long sleep duration	SCZ	0.0034	0.88	40%	10.0	0.12	10.0	0.08	0	0.83
Sleep duration	SCZ	-0.0038	0.71	61%	126.2	9.77e-09	125.8	6.68e-09	0.4	0.54
Adventurousness	SCZ	0.0080	0.31	60%	220.3	4.00e-13	217.7	5.61e-13	2.6	0.10
Automobile speeding propensity	SCZ	0.0179	0.28	57%	59.9	1.71e-04	57.2	2.52e-04	2.7	0.10
Number of sexual partners	SCZ	-0.0064	0.59	52%	126.6	1.69e-06	126.0	1.35e-06	0.6	0.43

BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.

Table S10. Confirmed confounders for mental disorders (BIP, MDD and SCZ) from previous Mendelian randomization studies.

Outcomes	Confounders
BIP	Except for adventurousness, insomnia, smoking initiation and educational attainment identified in the present study, following factors have been confirmed: C-Reactive Protein (PMID: 27327646) Magnesium, copper (PMID: 27327646)
MDD	Except for age at first birth, automobile speeding propensity, number of sexual partners and educational attainment identified in the present study, following factors have been confirmed: Trunk fat percentage, Arm fat percentage (right), Arm fat percentage (left), Leg fat percentage (right), Leg fat percentage (left), Trunk fat mass, Arm fat mass (right), Arm fat mass (left), Leg fat mass (right), Leg fat mass (left), body mass index (BMI), weight, Body fat percentage, Body fat mass (PMID: 31383844) statin and PCSK9 inhibitor therapy (PMID: 29986042) neuroticism (PMID: 30697695) Bacilli (PMID: 33008395) intra-cellular volume fraction (PMID: 32385265) serum morning plasma cortisol level (PMID: 31474942) triglycerides, interleukin-6 (IL-6), and C-reactive protein (CRP) (PMID: 30886334) ADHD (PMID: 32249726) confiding in others, daytime napping (PMID: 32791893) testosterone (PMID: 32610558) Aminoacyl-tRNA biosynthesis (PMID: 31919502)
SCZ	Except for automobile speeding propensity, number of sexual partners, cigarettes per day and smoking initiation identified in the present study, following factor have been confirmed: Cannabis use (PMID: 28115737) C-reactive protein, sIL-6R (PMID: 29094161) fasting insulin levels (PMID: 30100396) neuroticism (PMID: 32578352) plasma total homocysteine (PMID: 26208850)

	plays computer games (PMID: 31766499) 2-methoxyacetaminophen sulfate, glycine, serine, threonine metabolism (PMID: 31919502) Enterobacteriaceae family, Enterobacteriales order, Gammaproteobacteria class (PMID: 33008395)

BIP, bipolar disorders; MDD, major depressive disorders; SCZ, schizophrenia; PMID: PubMed identifier.

Table S11. SNPs associated with confirmed confounders at genome-wide significance ($p < 5 \times 10^{-8}$).

Phenotype in the present study	Outcome	SNP	Confounders
Adventurousness	BIP	rs10789436	Years of educational attainment
Adventurousness	BIP	rs12023775	Years of educational attainment
Adventurousness	BIP	rs12534625	Years of educational attainment
Adventurousness	BIP	rs734073	Serum magnesium
insomnia	BIP	rs11090039	Neuroticism
insomnia	BIP	rs13010288	Years of educational attainment
insomnia	BIP	rs13135092	Adventurousness
insomnia	BIP	rs1620977	Years of educational attainment
insomnia	BIP	rs28582096	Years of educational attainment
insomnia	BIP	rs34967082	Years of educational attainment
insomnia	BIP	rs3774751	Years of educational attainment
insomnia	BIP	rs6119267	Years of educational attainment
Smoking initiation	BIP	rs2526390	Years of educational attainment
Smoking initiation	BIP	rs2710634	Years of educational attainment
Smoking initiation	BIP	rs329124	Years of educational attainment
Smoking initiation	BIP	rs76608582	Years of educational attainment
Smoking initiation	BIP	rs951740	Years of educational attainment
Number of sexual partners	MDD	rs10786721	Weight
Number of sexual partners	MDD	rs12042107	Years of educational attainment
Number of sexual partners	MDD	rs13093086	Drive faster than motorway speed limit
Number of sexual partners	MDD	rs17149632	Neuroticism
Number of sexual partners	MDD	rs2163971	Drive faster than motorway speed limit; Weight
Number of sexual partners	MDD	rs2422136	Body Mass Index, Leg fat mass left, Leg fat mass right, Leg fat percentage right, Leg fat percentage left, Weight, Arm fat mass left, Whole body fat mass, Arm fat mass right
Number of sexual partners	MDD	rs273512	Body fat percentage, Trunk fat percentage, Leg fat percentage right,

			Trunk fat mass, Leg fat mass right, Arm fat percentage left, Whole body fat mass, Leg fat percentage left, Leg fat mass left, Arm fat percentage right, Arm fat mass left, Arm fat mass right, Body mass index, Weight
Number of sexual partners	MDD	rs539096	Years of educational attainment
Number of sexual partners	MDD	rs62063281	Neuroticism
Number of sexual partners	MDD	rs6504568	Trunk fat mass; Trunk fat percentage; Body fat percentage; Whole body fat mass; Arm fat percentage left; Leg fat mass left; Leg fat mass right; Arm fat mass left; Weight; Arm fat percentage right; Arm fat mass right; Leg fat percentage right; Leg fat percentage left; Body mass index
Number of sexual partners	MDD	rs7942078	Body mass index
Number of sexual partners	MDD	rs9922596	Weight; Arm fat mass left; Arm predicted mass left; Whole body fat mass; Arm fat mass right; Trunk fat mass
Educational attainment	MDD	rs10761251	Leg fat percentage right; Leg fat percentage left; Leg fat mass right; Leg fat mass left
Educational attainment	MDD	rs10773208	Weight; Trunk fat mass; Whole body fat mass; Arm fat mass right; Arm fat mass left; Leg fat mass left; Leg fat mass right; Trunk fat percentage; Body fat percentage; Arm fat percentage left; Arm fat percentage right; Body mass index
Educational attainment	MDD	rs10798888	Leg fat mass right; Leg fat mass left; Whole body fat mass; Leg fat percentage right; Body fat percentage; Trunk fat mass; Leg fat percentage left; Arm fat mass right; Arm fat mass left; Trunk fat percentage; Arm fat percentage left; Weight; Arm fat percentage right; Body mass index
Educational attainment	MDD	rs10805383	Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Body mass index; Arm fat mass right; Leg fat mass right; Leg fat mass left; Leg fat percentage left; Leg fat percentage right; Body fat

			percentage; Trunk fat mass; Whole body fat mass; Trunk fat percentage
Educational attainment	MDD	rs10875121	Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Body mass index; Arm fat mass right; Leg fat mass right; Leg fat mass left; Leg fat percentage left; Leg fat percentage right; Body fat percentage; Trunk fat mass; Whole body fat mass; Trunk fat percentage
Educational attainment	MDD	rs11030102	Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Body mass index; Arm fat mass right; Leg fat mass right; Leg fat mass left; Leg fat percentage left; Leg fat percentage right; Body fat percentage; Trunk fat mass; Whole body fat mass; Trunk fat percentage
Educational attainment	MDD	rs11082011	Neuroticism
Educational attainment	MDD	rs1167827	Body mass index; Arm fat mass right; Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Leg fat mass right; Leg fat mass left; Weight; Body fat percentage; Leg fat percentage left; Leg fat percentage right Trunk fat mass; Trunk fat percentage
Educational attainment	MDD	rs12375949	Leg fat percentage right; Leg fat percentage left; Leg fat mass right; Body fat percentage; Leg fat mass left
Educational attainment	MDD	rs12981405	Leg fat percentage left; Leg fat percentage right
Educational attainment	MDD	rs13018640	Body mass index; Arm fat mass right; Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Leg fat mass right; Leg fat mass left; Weight; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Trunk fat mass; Trunk fat percentage
Educational attainment	MDD	rs1334297	Body mass index; Arm fat mass right; Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Leg fat mass right; Leg fat mass left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Whole body fat mass
Educational attainment	MDD	rs1564347	Leg fat percentage right; Leg fat percentage left
Educational attainment	MDD	rs1689510	Weight; Body mass index; Arm fat mass right

Educational attainment	MDD	rs17411339	Neuroticism
Educational attainment	MDD	rs2034631	Trunk fat mass
Educational attainment	MDD	rs2183271	Body mass index; Arm fat mass right; Arm fat percentage left; Arm fat mass left; Arm fat percentage right; Leg fat mass right; Leg fat mass left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Whole body fat mass
Educational attainment	MDD	rs2725370	Leg fat percentage left; Leg fat mass left; Leg fat percentage right; Body mass index; Leg fat mass right; Whole body fat mass; Body fat percentage; Trunk fat mass; Arm fat mass right; Weight; Trunk fat percentage; Arm fat percentage left; Arm fat percentage right
Educational attainment	MDD	rs2838006	Body mass index
Educational attainment	MDD	rs303752	Weight; Trunk fat mass; Whole body fat mass; Leg fat mass left; Leg fat mass right; Arm fat mass right; Body fat percentage; Trunk fat percentage; Arm fat mass left
Educational attainment	MDD	rs34720381	Body Mass Index
Educational attainment	MDD	rs3809634	Weight
Educational attainment	MDD	rs3948495	Leg fat mass left; Leg fat mass right; Leg fat percentage left; Leg fat percentage right
Educational attainment	MDD	rs42302	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Arm fat percentage left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Arm fat percentage right; Trunk fat percentage
Educational attainment	MDD	rs4500930	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Arm fat percentage left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Arm fat percentage right; Trunk fat percentage

Educational attainment	MDD	rs4787457	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Arm fat percentage left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Arm fat percentage right; Trunk fat percentage
Educational attainment	MDD	rs4899012	Weight; Trunk fat mass
Educational attainment	MDD	rs56319902	Neuroticism
Educational attainment	MDD	rs56391344	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Arm fat percentage right
Educational attainment	MDD	rs62155873	Body mass index
Educational attainment	MDD	rs66568921	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Arm fat percentage left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Arm fat percentage right
Educational attainment	MDD	rs72828517	Drive faster than motorway speed limit
Educational attainment	MDD	rs746839	Leg fat mass left; Leg fat mass right; Weight; Whole body fat mass; Trunk fat mass; Arm fat mass left; Body mass index
Educational attainment	BIP	rs75177132	Smoking initiation
Educational attainment	MDD	rs7650602	Weight; Trunk fat mass; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Trunk fat percentage
Educational attainment	MDD	rs7692359	Trunk fat percentage; Body fat percentage
Educational attainment	MDD	rs78648104	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Arm fat percentage left; Arm fat percentage right
Educational attainment	MDD	rs7924036	Body mass index
Educational attainment	MDD	rs7974852	Leg fat percentage right

Educational attainment	MDD	rs8024	Weight; Body mass index; Leg fat mass right; Leg fat mass left; Arm fat mass right; Arm fat mass left; Whole body fat mass; Trunk fat mass; Arm fat percentage left; Body fat percentage; Leg fat percentage left; Leg fat percentage right; Arm fat percentage right
Educational attainment	MDD	rs9375188	Leg fat percentage right; Body fat percentage; Trunk fat percentage; Leg fat percentage left; Arm fat percentage left; Leg fat mass right; Leg fat mass left; Whole body fat mass; Arm fat percentage right; Trunk fat mass; Arm fat mass left; Arm fat mass right; Body mass index
Educational attainment	MDD	rs9859556	Leg fat percentage right; Body fat percentage; Trunk fat percentage; Leg fat percentage left; Arm fat percentage left; Leg fat mass right; Leg fat mass left; Whole body fat mass; Arm fat percentage right; Trunk fat mass; Arm fat mass left; Arm fat mass right; Body mass index
Educational attainment	MDD	rs9927137	Leg fat percentage right; Body fat percentage; Trunk fat percentage; Leg fat percentage left; Arm fat percentage left; Leg fat mass right; Leg fat mass left; Whole body fat mass; Arm fat percentage right; Trunk fat mass; Arm fat mass left; Arm fat mass right; Body mass index
Age at first birth	MDD	rs10056247	Body mass index
Age at first birth	MDD	rs1160544	Years of educational attainment
Age at first birth	MDD	rs2777888	Years of educational attainment; Leg fat percentage right; Body fat percentage; Trunk fat percentage; Leg fat percentage left; Arm fat percentage left; Leg fat mass right; Leg fat mass left; Whole body fat mass; Arm fat percentage right; Trunk fat mass; Arm fat mass left; Arm fat mass right; Body mass index; Weight
Automobile speeding propensity	MDD	rs10465231	Arm fat percentage right; Body fat percentage; Arm fat percentage left; Body mass index; Leg fat percentage right; Leg fat percentage left;

			Trunk fat percentage; Whole body fat mass; Arm fat mass left; Arm fat mass right; Leg fat mass right; Leg fat mass left; Trunk fat mass
Automobile speeding propensity	MDD	rs10858922	Body fat percentage; Body mass index; Leg fat percentage right; Leg fat percentage left; Trunk fat percentage; Whole body fat mass; Arm fat mass left; Arm fat mass right; Leg fat mass right; Leg fat mass left; Trunk fat mass
Automobile speeding propensity	MDD	rs12325727	Years of educational attainment
Automobile speeding propensity	MDD	rs13083798	Body mass index
Automobile speeding propensity	MDD	rs17516256	Weight; Body mass index; Leg fat mass left; Leg fat mass right; Arm fat mass left; Arm fat mass right
Automobile speeding propensity	MDD	rs185819	Weight; Neuroticism
Automobile speeding propensity	MDD	rs362307	Years of educational attainment; Arm fat percentage right; Arm fat percentage left; Body mass index; Leg fat percentage right; Leg fat percentage left; Arm fat mass left; Arm fat mass right; Leg fat mass right; Leg fat mass left
Automobile speeding propensity	MDD	rs619466	Neuroticism
Automobile speeding propensity	MDD	rs2409691	Neuroticism; Body mass index; Leg fat mass right; Arm fat mass right; Leg fat mass left; Arm fat mass left
Number of sexual partners	SCZ	rs13093086	Drive faster than motorway speed limit
Number of sexual partners	SCZ	rs17149632	Neuroticism
Number of sexual partners	SCZ	rs17785382	Schizophrenia
Number of sexual partners	SCZ	rs2163971	Drive faster than motorway speed limit
Number of sexual partners	SCZ	rs35219418	Smoking initiation
Number of sexual partners	SCZ	rs62063281	Neuroticism
Smoking initiation	SCZ	rs1549979	Drive faster than motorway speed limit
Smoking initiation	SCZ	rs2155646	Neuroticism
Smoking initiation	SCZ	rs62007780	Neuroticism
Automobile speeding propensity	SCZ	rs185819	Neuroticism

Automobile speeding propensity	SCZ	rs2409691	Neuroticism
Automobile speeding propensity	SCZ	rs619466	Neuroticism

SNP, single nucleotide polymorphisms; BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia

Table S12. Inverse variance weighted (IVW) analysis after exclusion of SNPs associated with potential confounders.

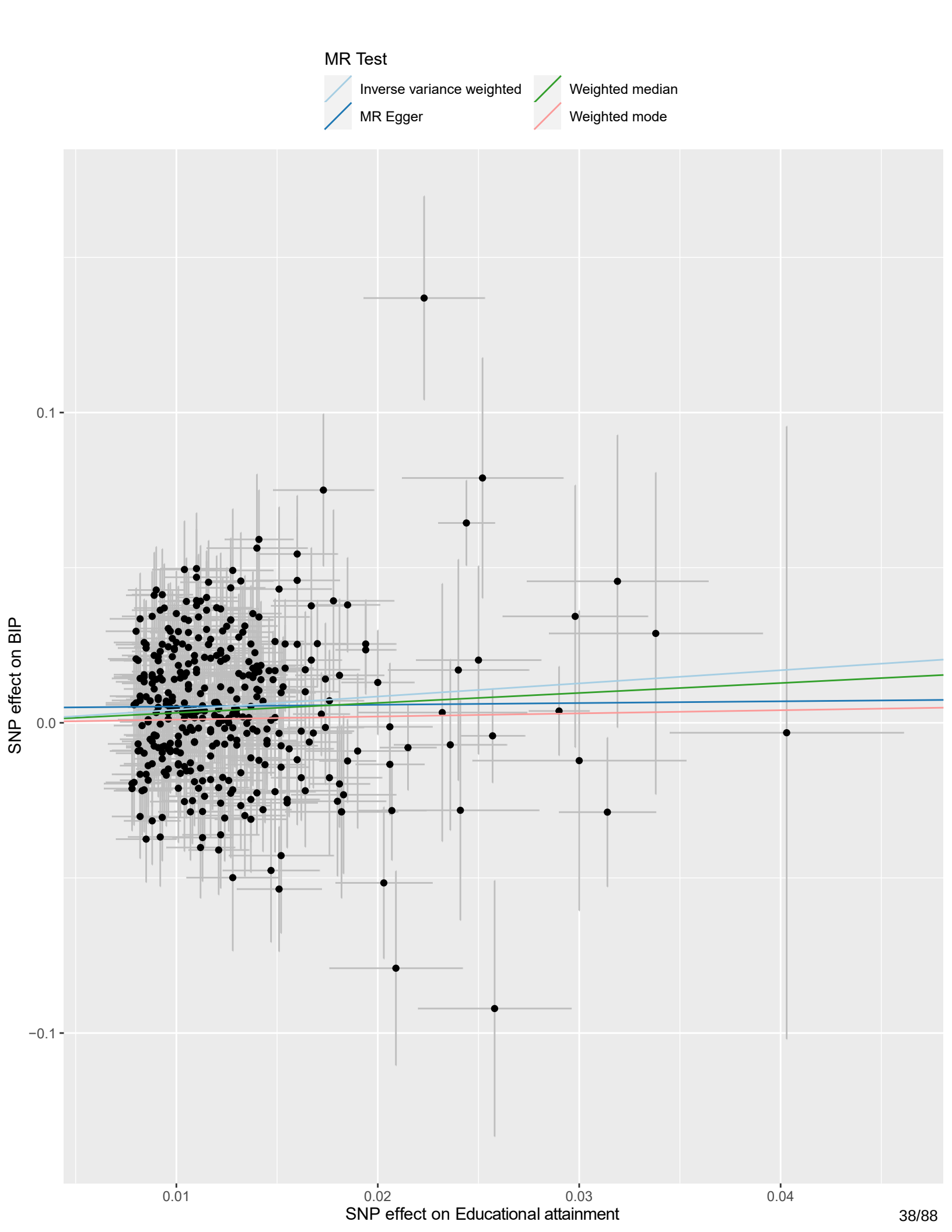
Exposures	Outcomes	IVW analysis		
		OR	95% CI	*p* values
Smoking initiation	BIP	1.59	1.37-1.86	2.34E-09
Insomnia	BIP	1.17	1.08-1.28	2.53E-04
Adventurousness	BIP	1.93	1.44-2.59	1.01E-05
Educational attainment	MDD	0.73	0.65-0.82	1.80E-07
Automobile speeding propensity	MDD	0.56	0.38-0.82	2.78E-03
Number of sexual partners	MDD	1.39	1.13-1.71	1.49E-03
Age at first birth	MDD	0.83	0.72-0.96	1.02E-02
Smoking initiation	SCZ	1.64	1.42-1.88	8.20E-12
Automobile speeding propensity	SCZ	0.42	0.28-0.65	1.04E-04
Number of sexual partners	SCZ	2.33	1.79-3.04	4.28E-10

SNP, single nucleotide polymorphisms; BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia; OR, odds ratio; CI, confidence interval.

Figure S1. Scatter plots showing robust genetic associations of socioeconomic status/individual behaviors with mental disorders.

Each of the SNPs associated with exposures is represented by a black dot with the error bar depicting the standard error of its association with a specific exposure (horizontal) and the target mental disorder (vertical). The slopes of each line represent the causal association for each Mendelian randomization method.

BIP, bipolar disorder; MDD, major depression; SCZ, schizophrenia.


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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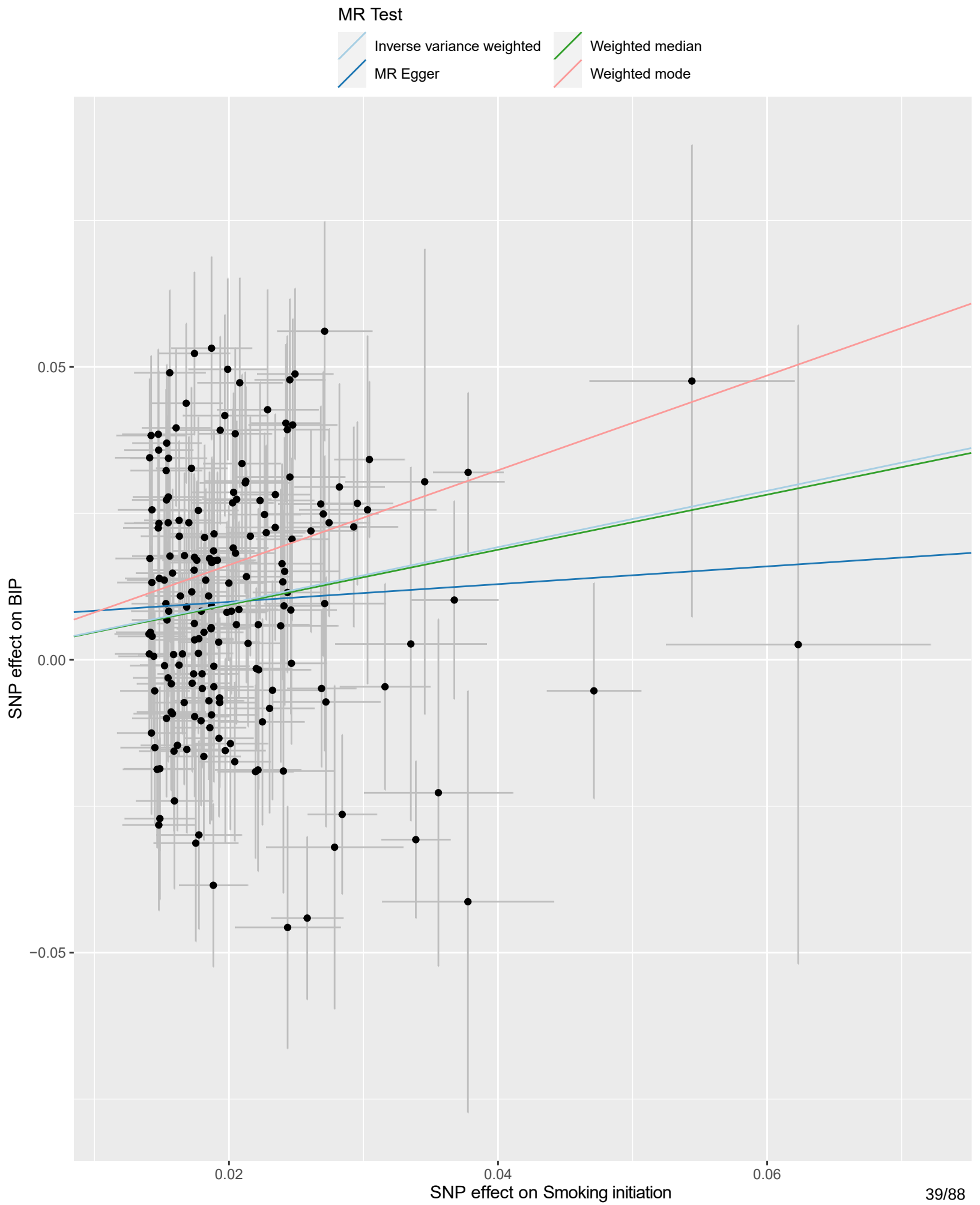
0.0
−0.1
SNP effect on BIP
0.01
0.02
0.03
0.04
SNP effect on Educational attainment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Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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0.00
−0.05
SNP effect on BIP
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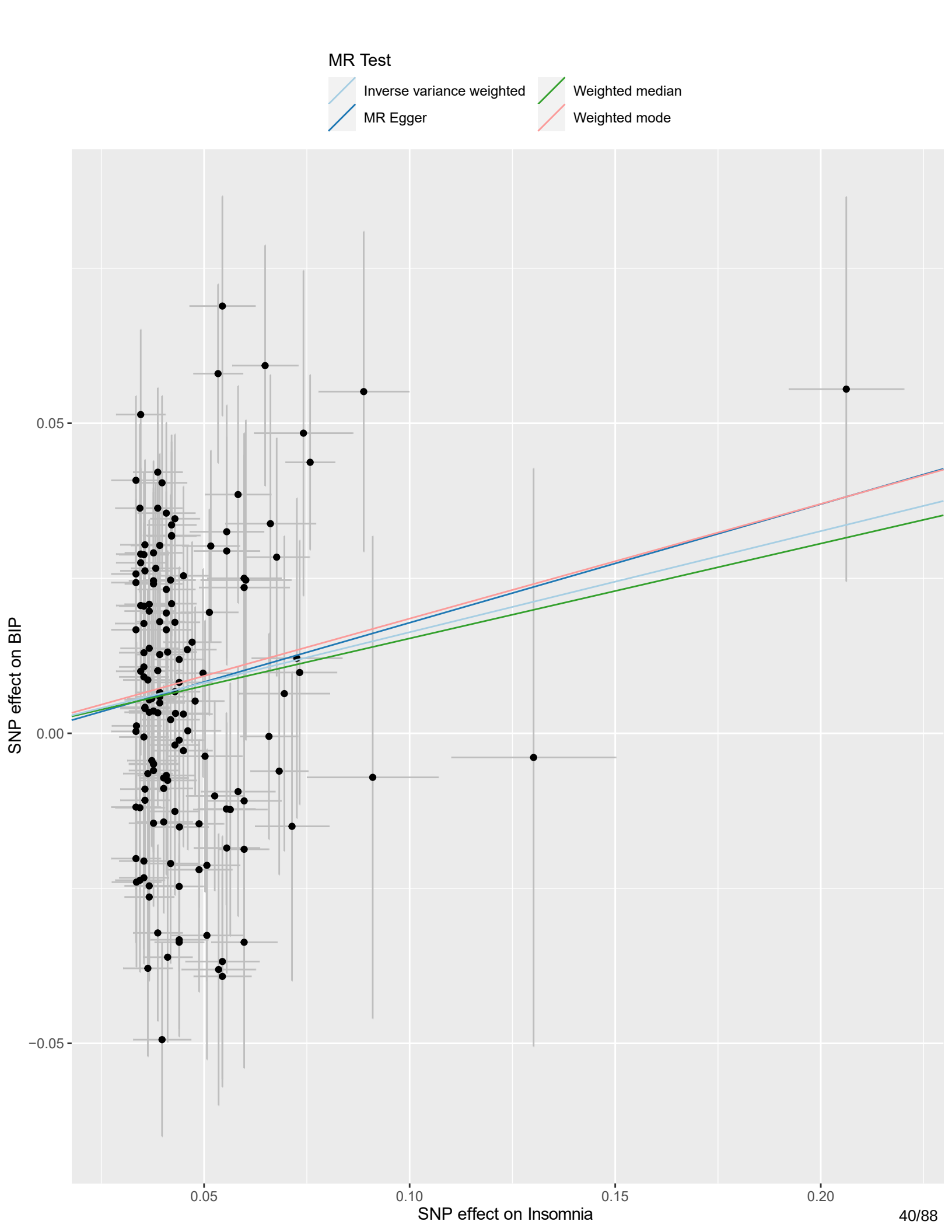
0.04
0.06
SNP effect on Smoking initiation


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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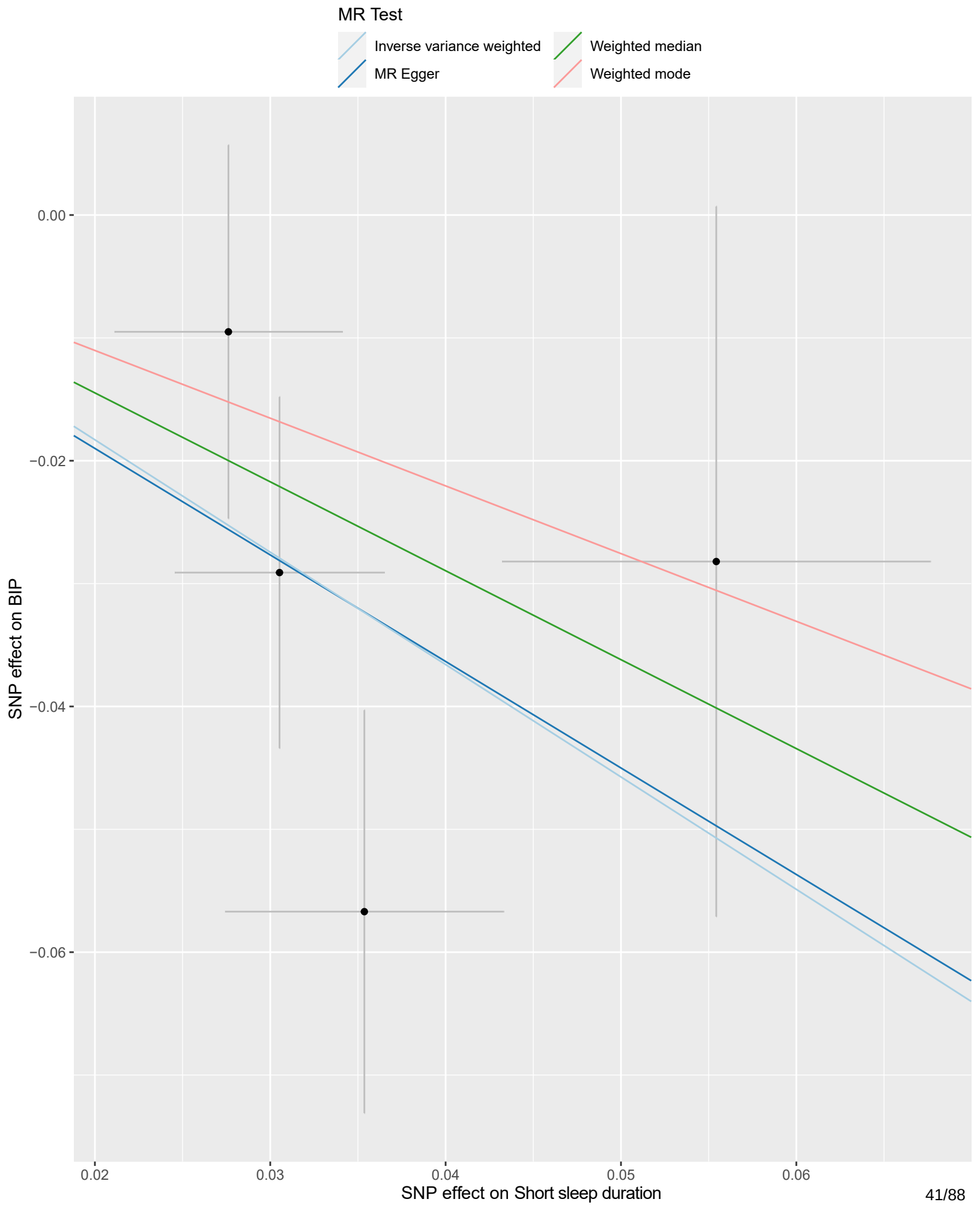
0.00
−0.05
SNP effect on BIP
0.05
0.10
0.15
0.20
SNP effect on Insomnia


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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−0.04
−0.06
SNP effect on BIP
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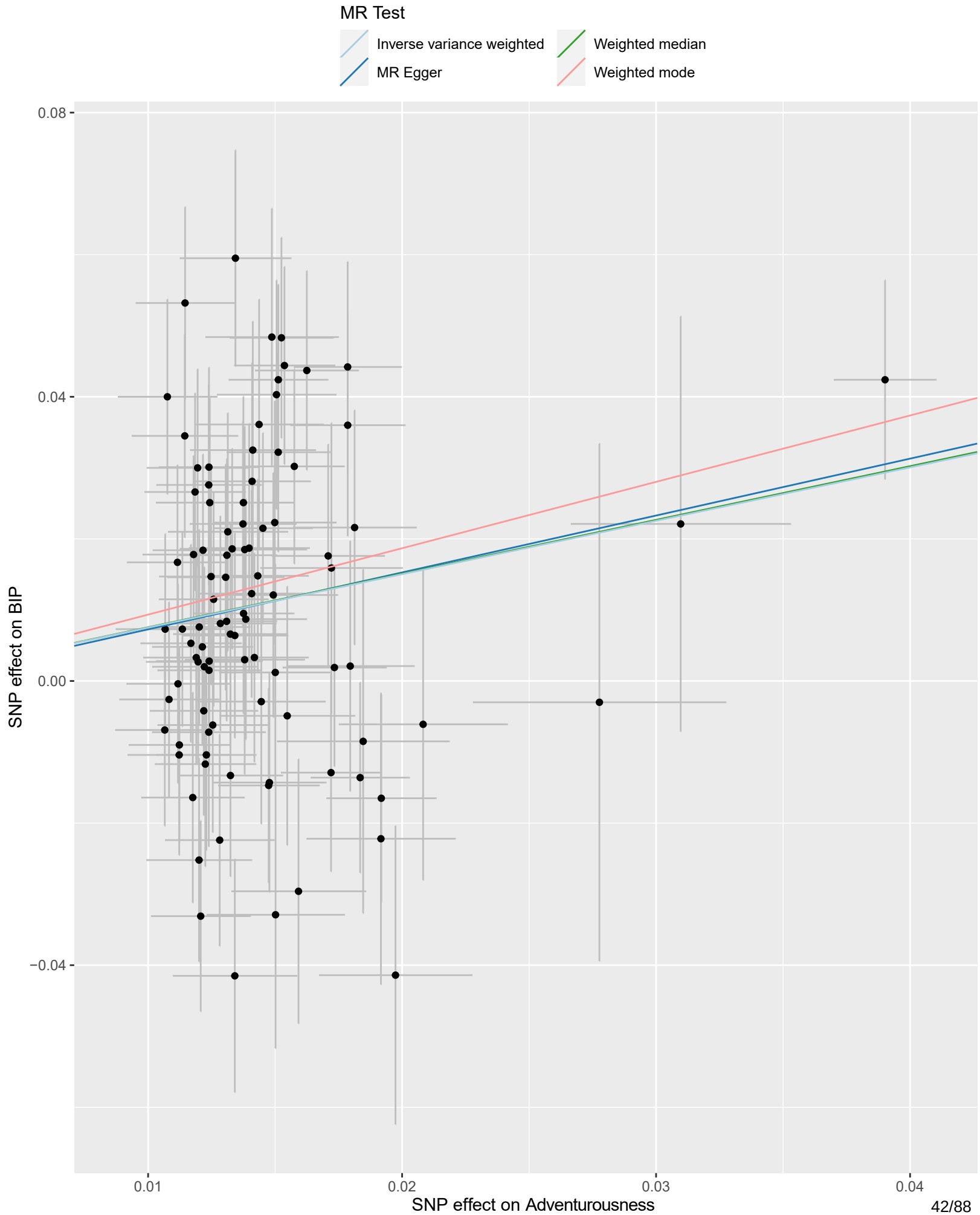
0.03
0.04
0.05
0.06
SNP effect on Short sleep duration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MR Egger
Weighted median
Weighted mode
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0.00
−0.04
SNP effect on BIP
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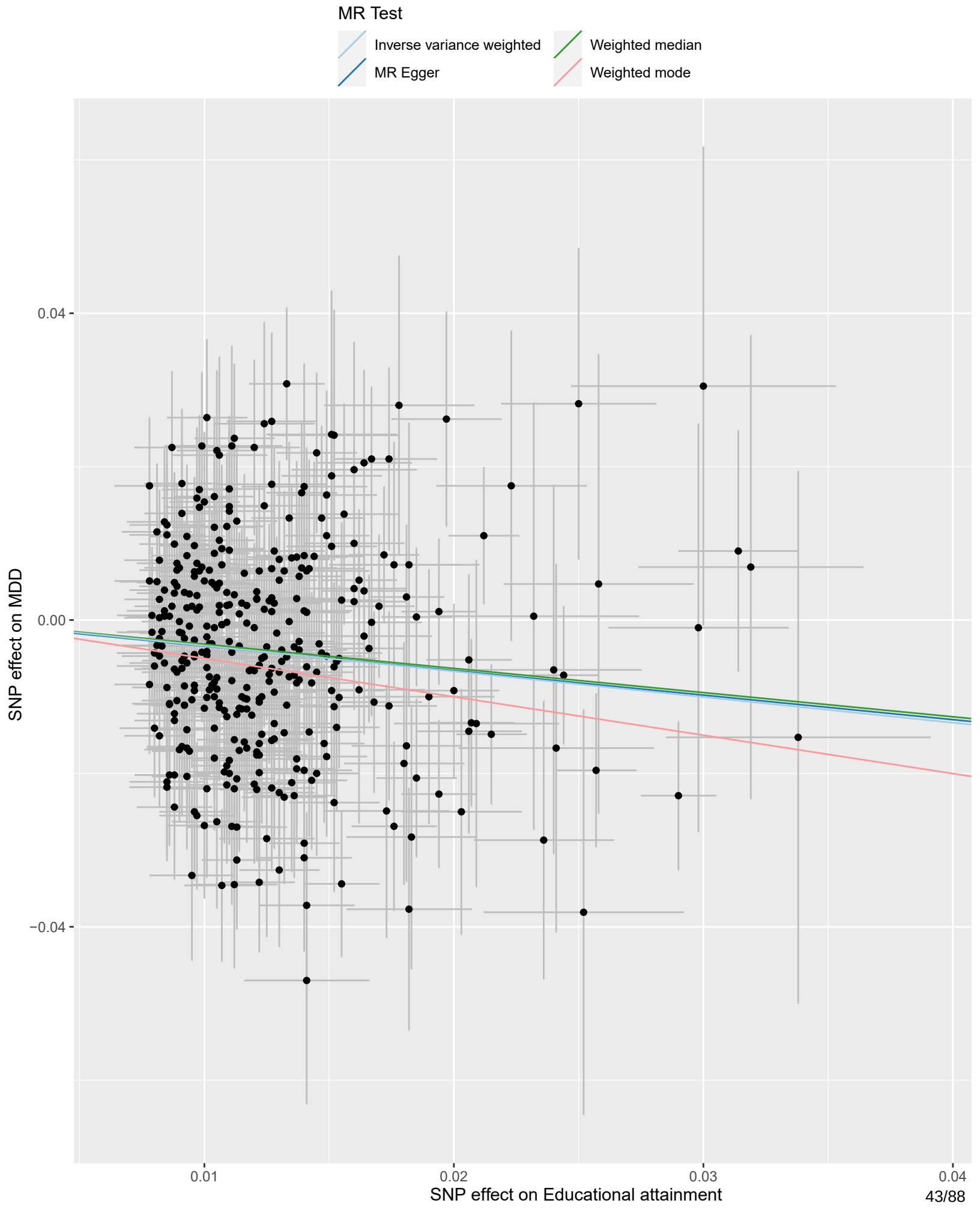
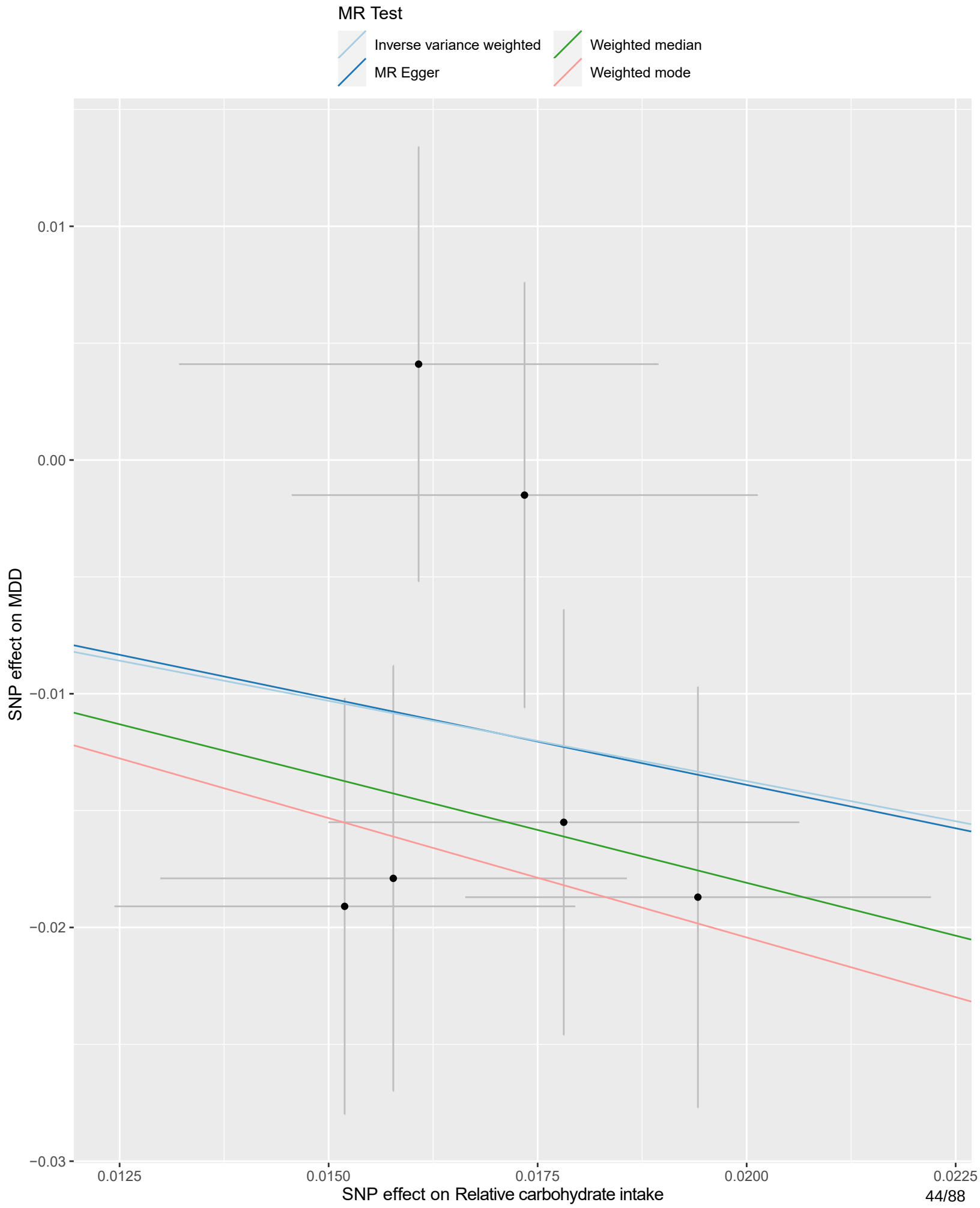
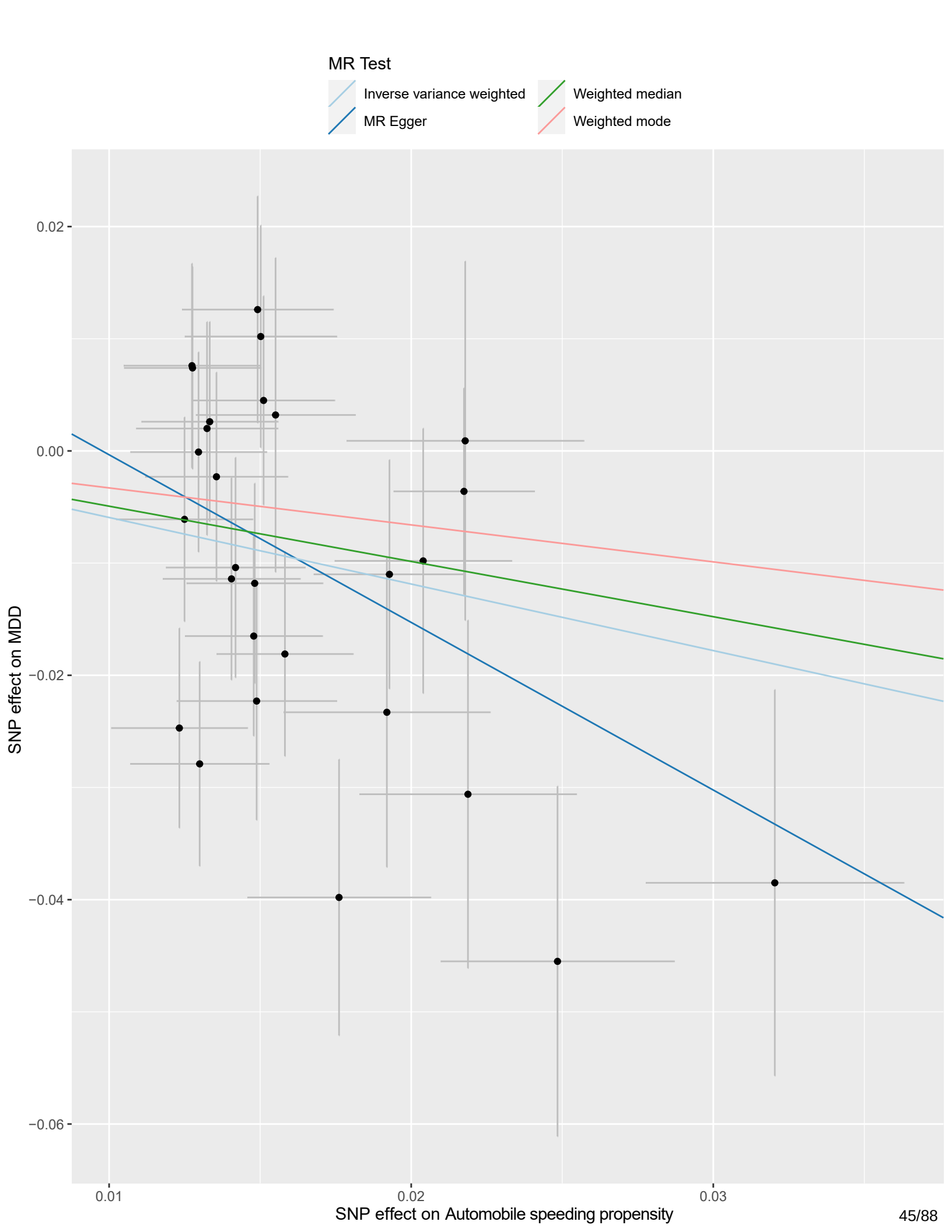
0.02
0.03
0.04
SNP effect on Adventurousness


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.04
0.00
−0.04
SNP effect on MDD
0.01
0.02
0.03
0.04
SNP effect on Educational attainment


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.01
0.00
−0.01
−0.02
−0.03
SNP effect on MDD
0.0125
0.0150
0.0175
0.0200
0.0225
SNP effect on Relative carbohydrate intake


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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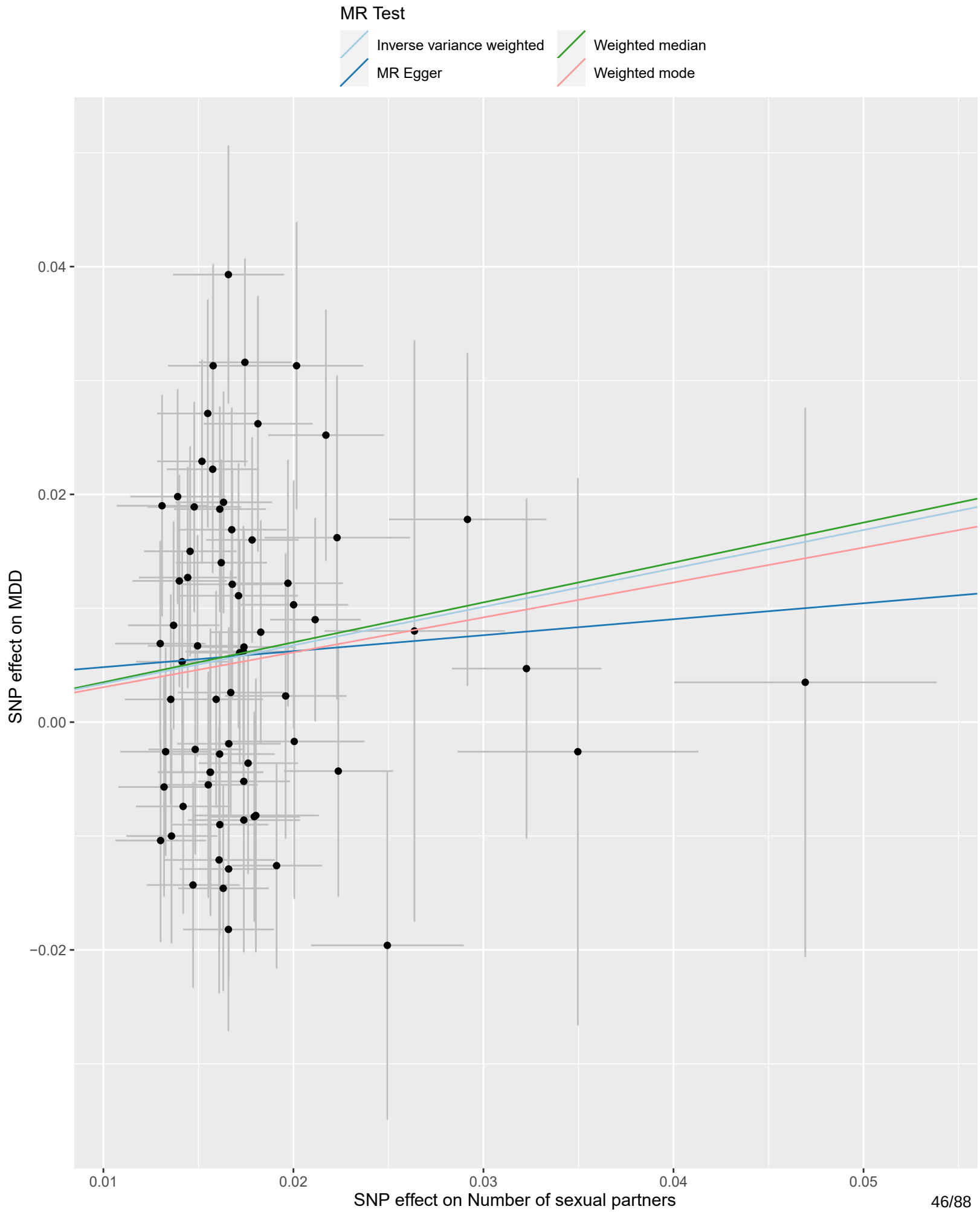
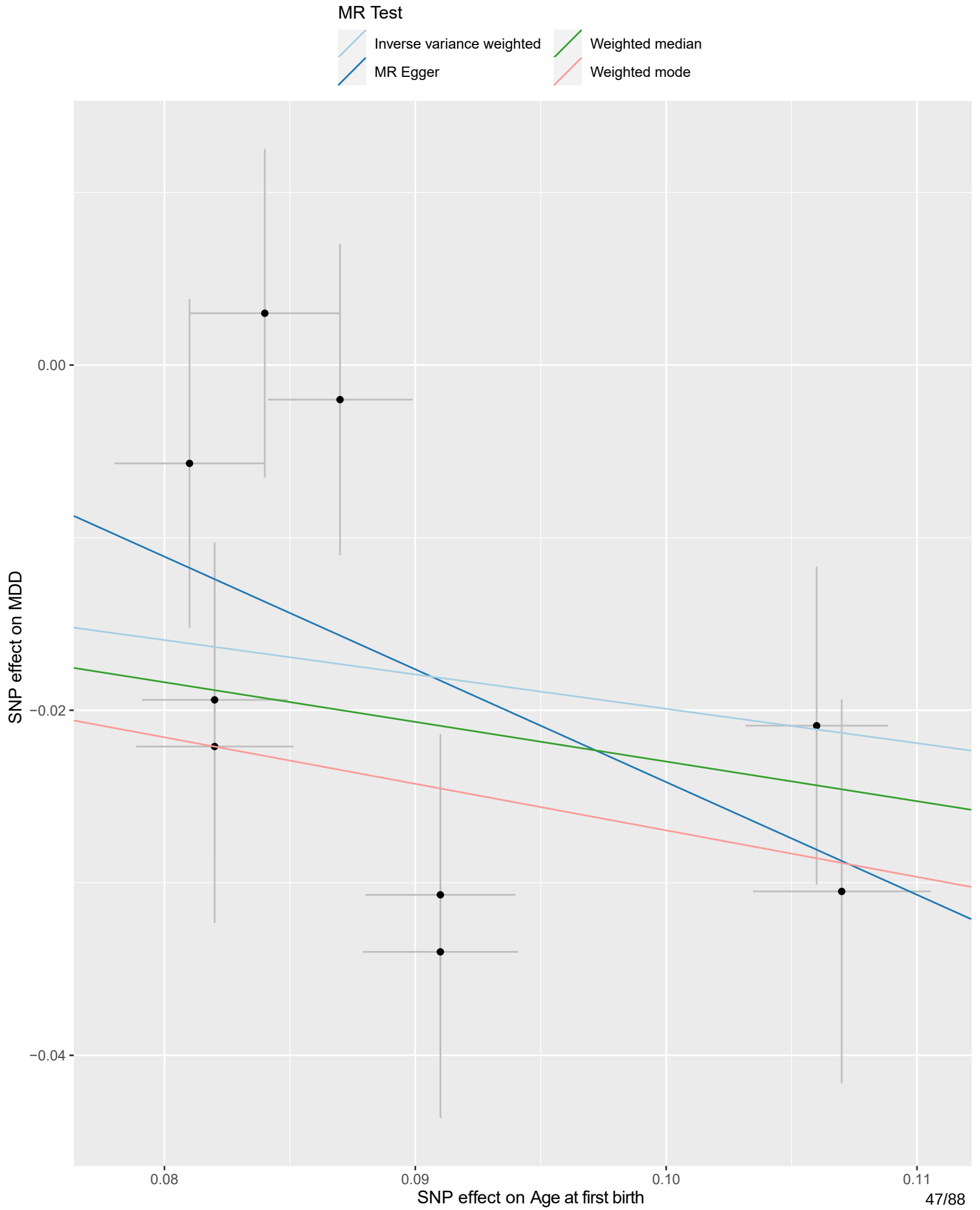
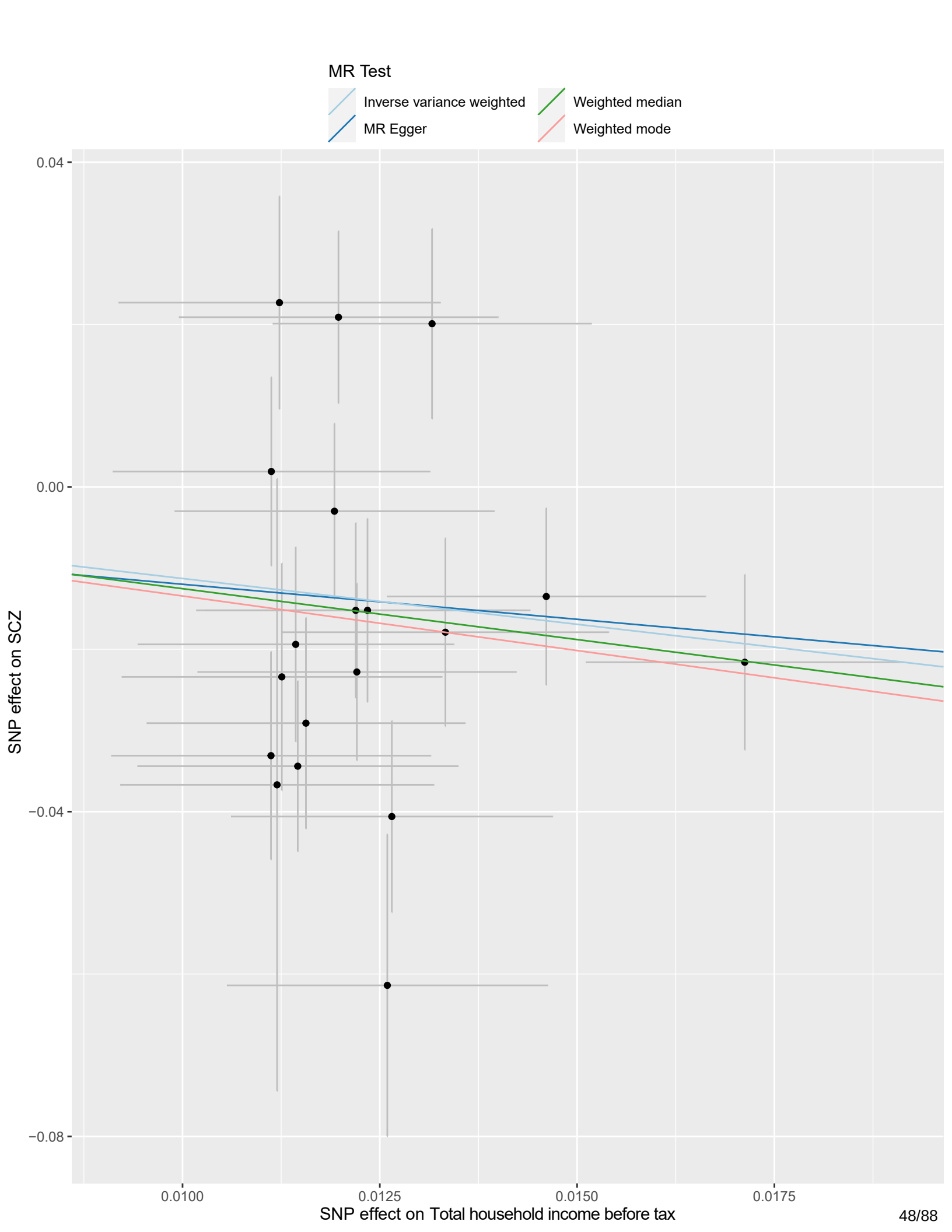
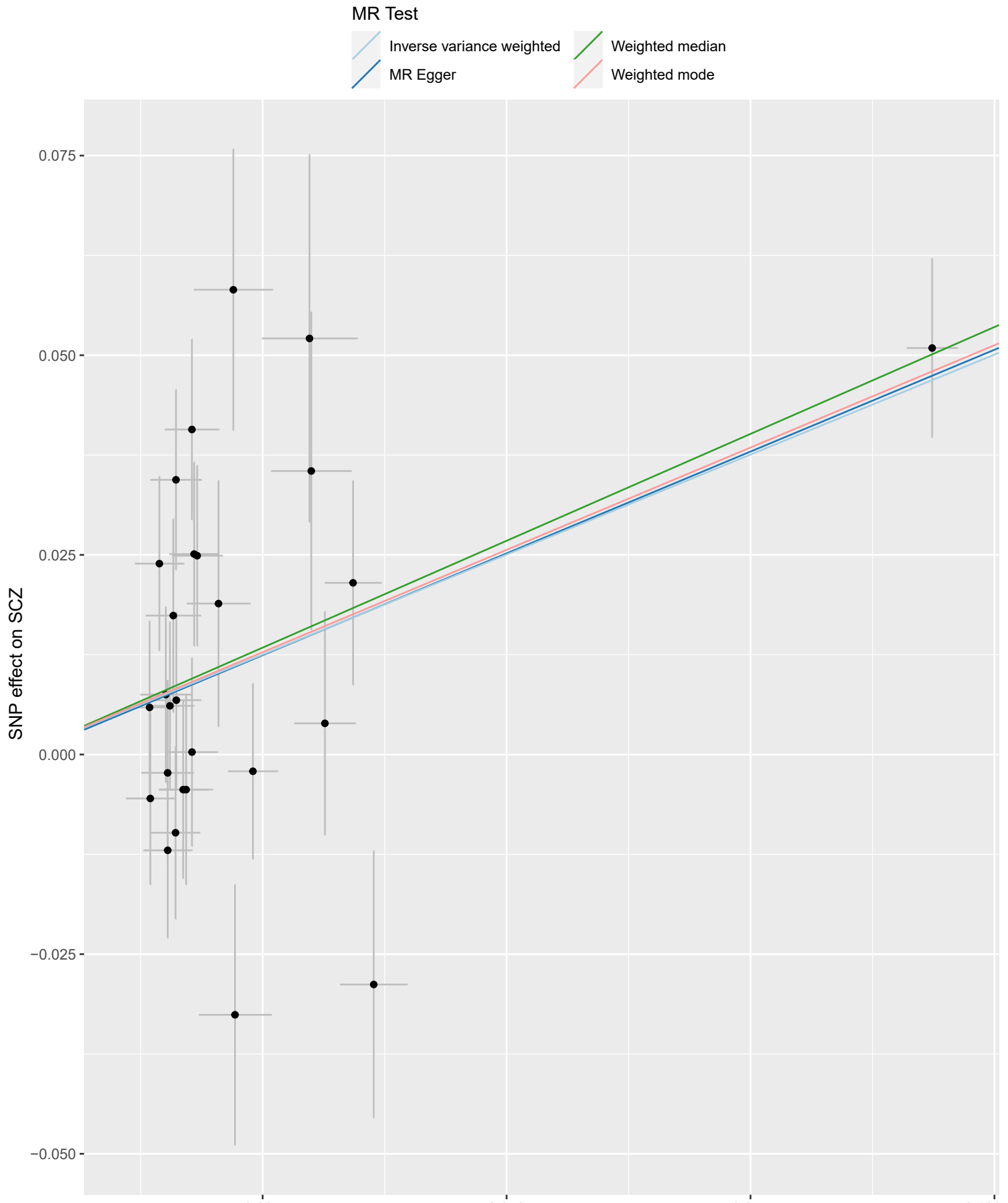
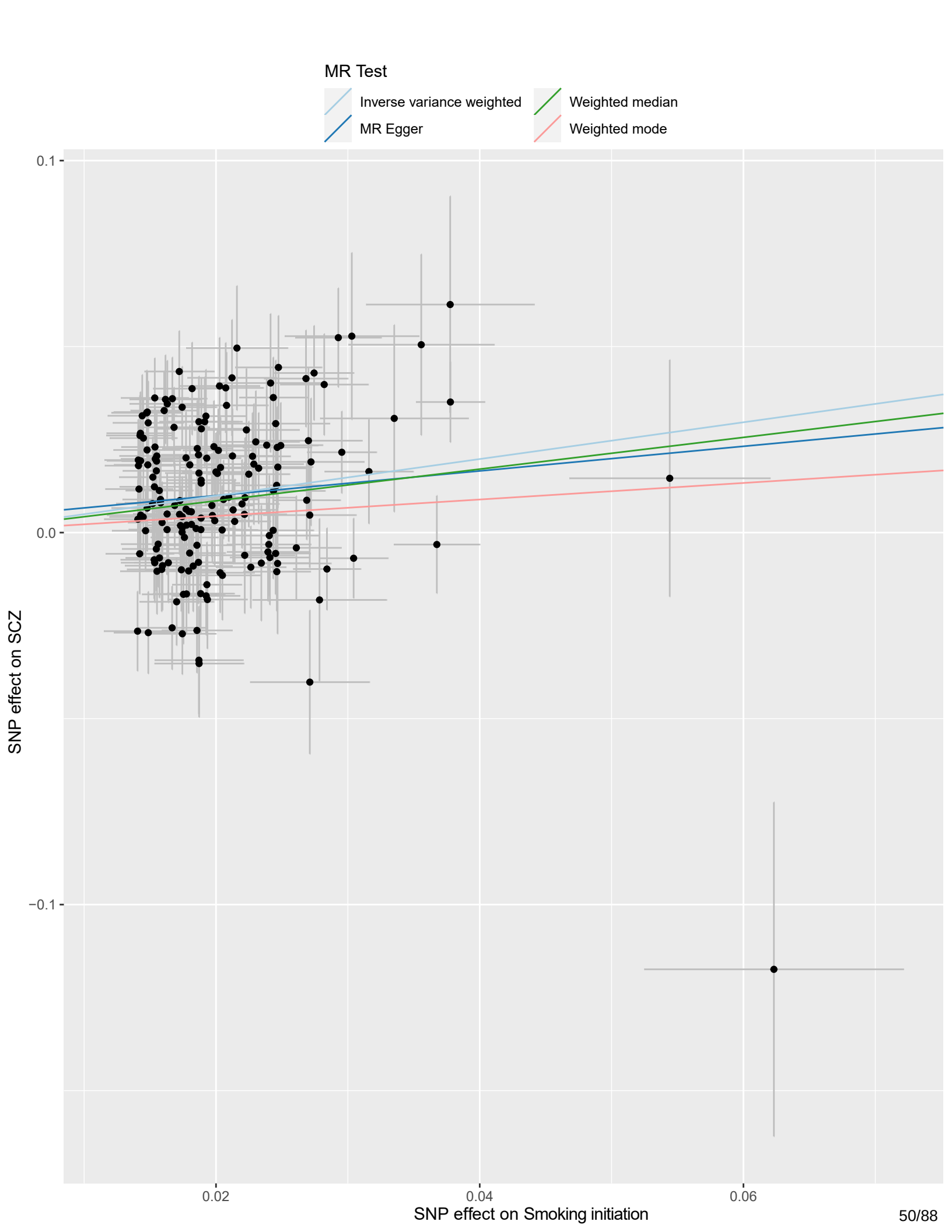
0.00
−0.02
−0.04
−0.06
SNP effect on MDD
0.01
0.02
0.03
SNP effect on Automobile speeding propensity

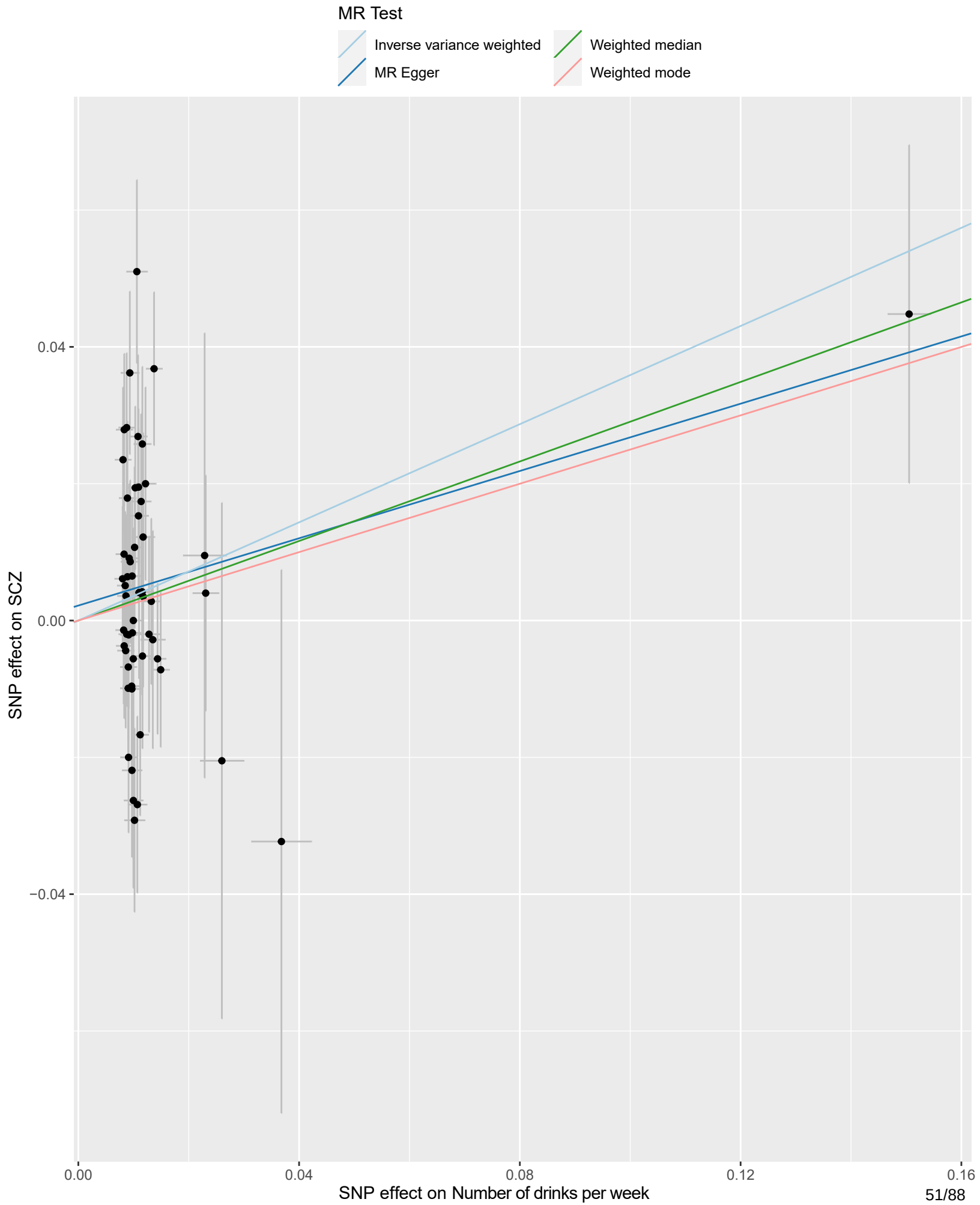

MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.04
0.02
0.00
−0.02
SNP effect on MDD
0.01
0.02
0.03
0.04
0.05
SNP effect on Number of sexual partners


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.00
−0.02
−0.04
SNP effect on MDD
0.08
0.09
0.10
0.11
SNP effect on Age at first birth


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.04
0.00
−0.04
−0.08
SNP effect on SCZ
0.0100
0.0125
0.0150
0.0175
SNP effect on Total household income before tax


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.075
0.050
0.025
0.000
−0.025
−0.050
SNP effect on SCZ
0.025
0.050
0.075
0.100
SNP effect on Number of cigarettes per day


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.1
0.0
−0.1
SNP effect on SCZ
0.02
0.04
0.06
SNP effect on Smoking initiation


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
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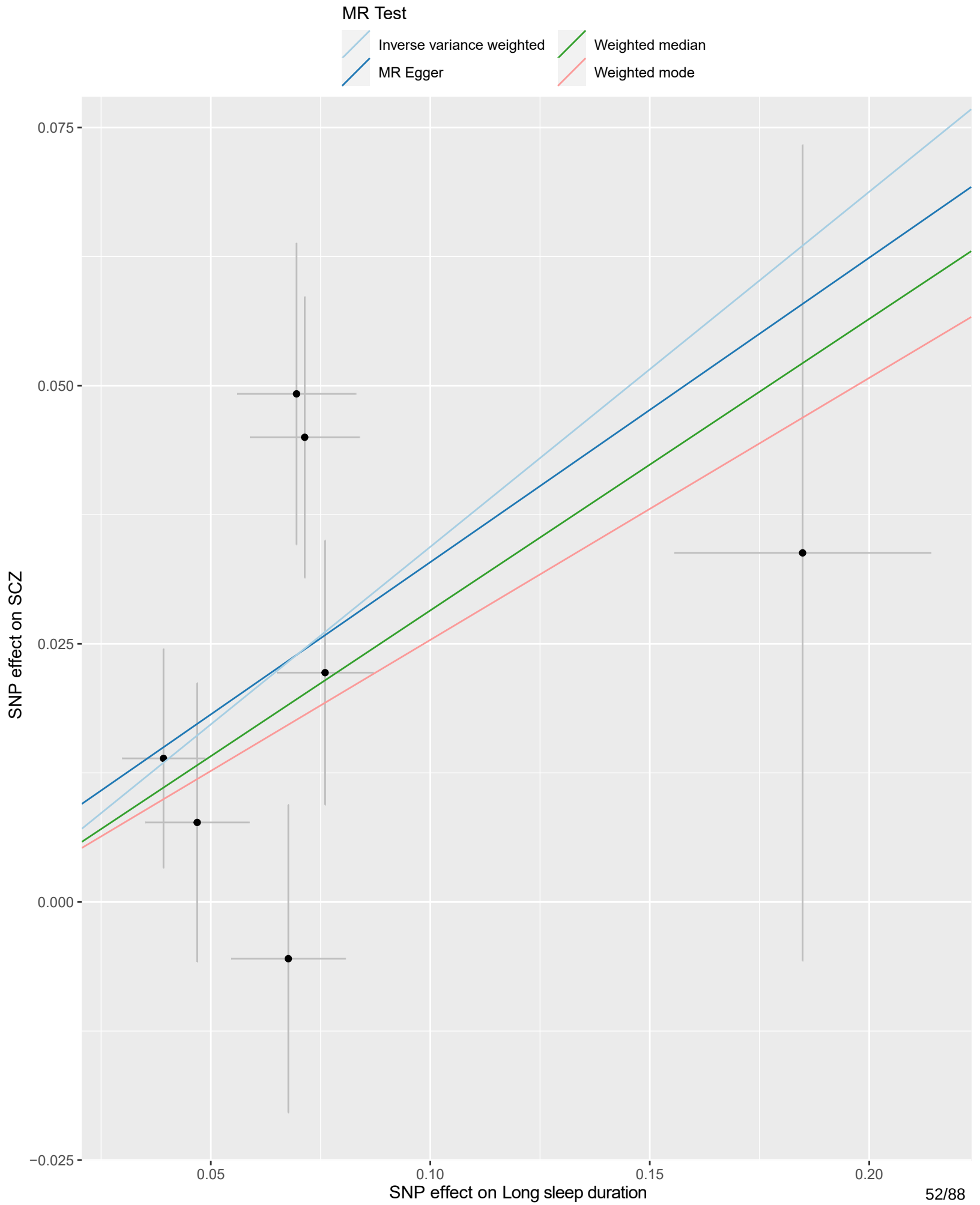
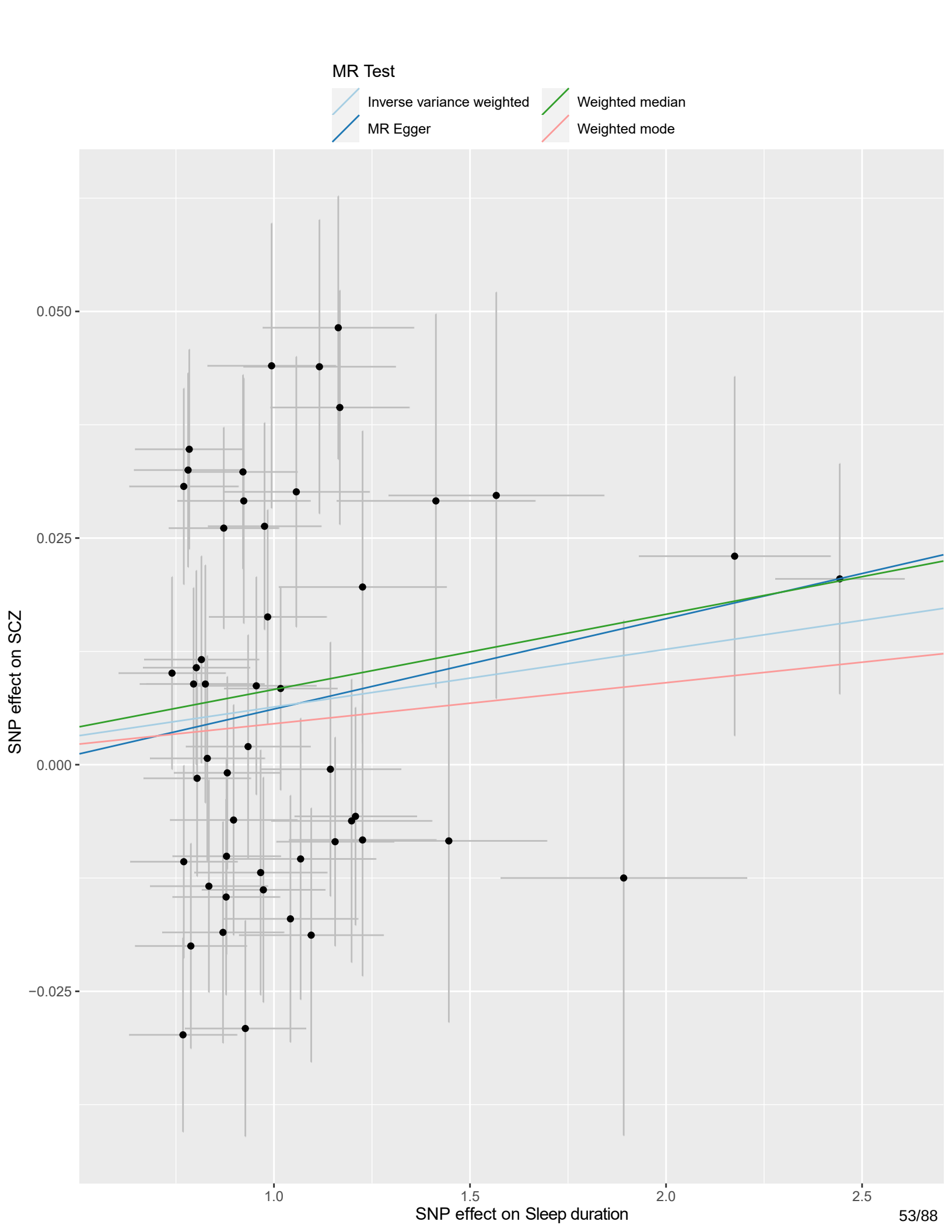
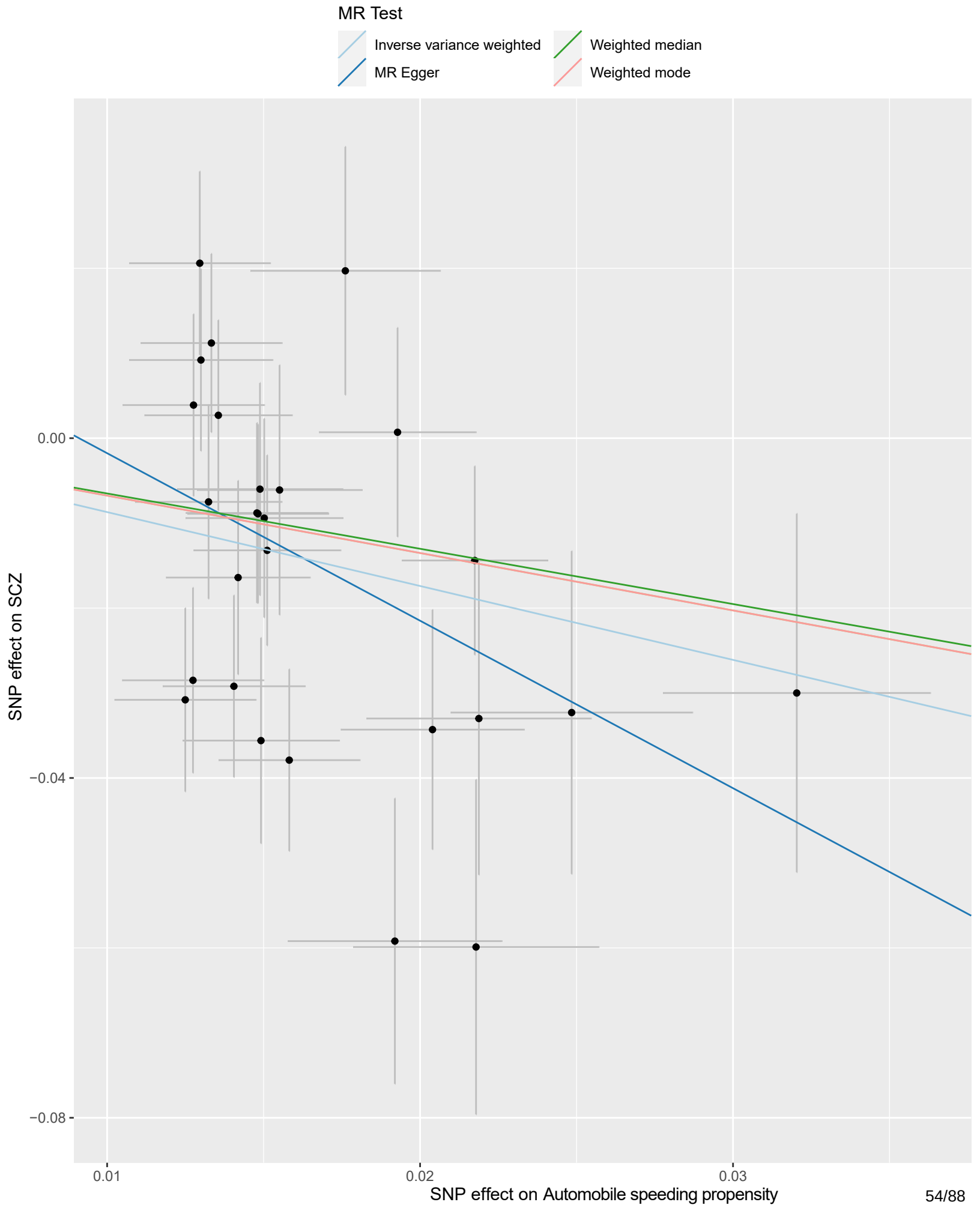
−0.04
SNP effect on SCZ
0.00
0.04
0.08
0.12
0.16
SNP effect on Number of drinks per week


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.075
0.050
0.025
0.000
−0.025
SNP effect on SCZ
0.05
0.10
0.15
0.20
SNP effect on Long sleep duration


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.050
0.025
0.000
−0.025
SNP effect on SCZ
1.0
1.5
2.0
2.5
SNP effect on Sleep duration


MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.00
−0.04
−0.08
SNP effect on SCZ
0.01
0.02
0.03
SNP effect on Automobile speeding propensity

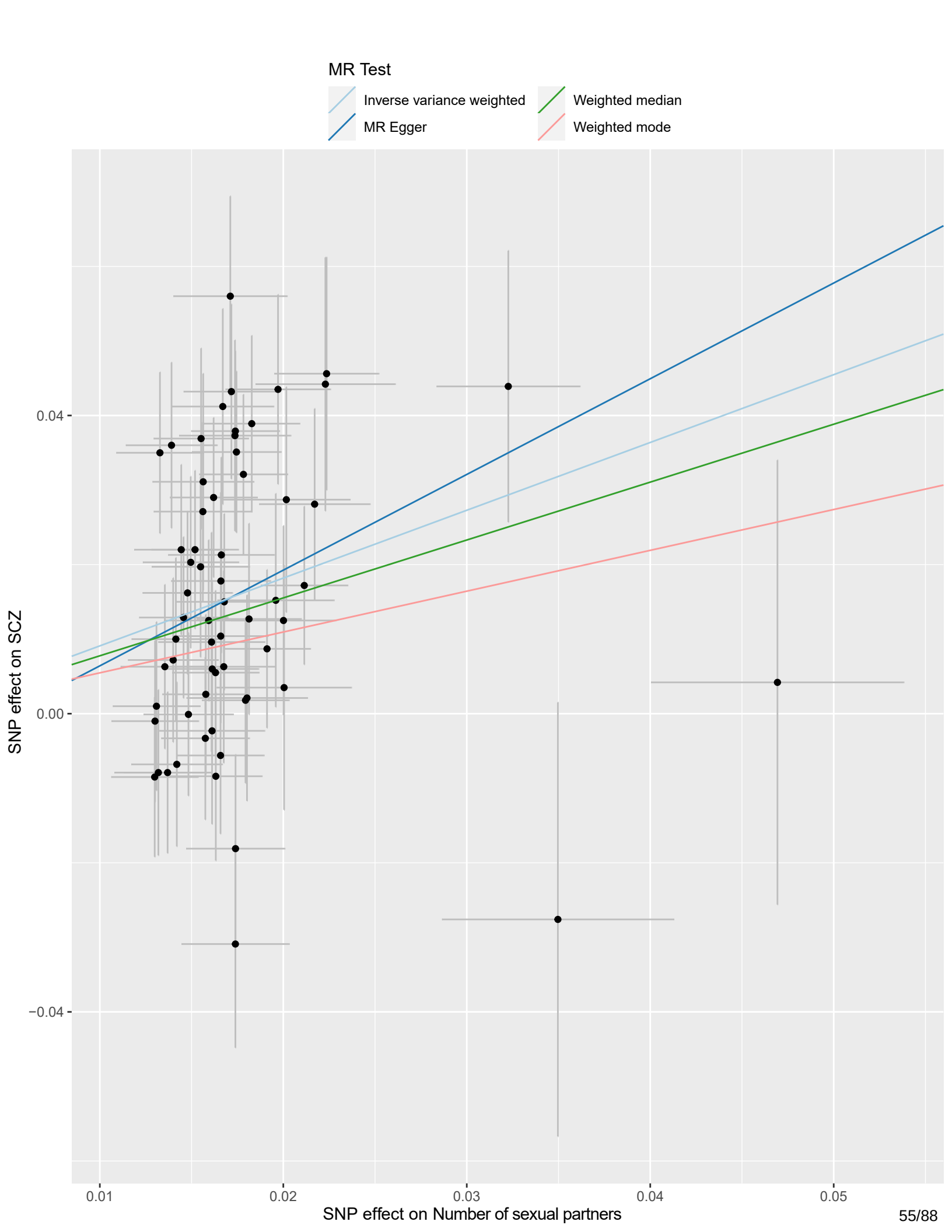
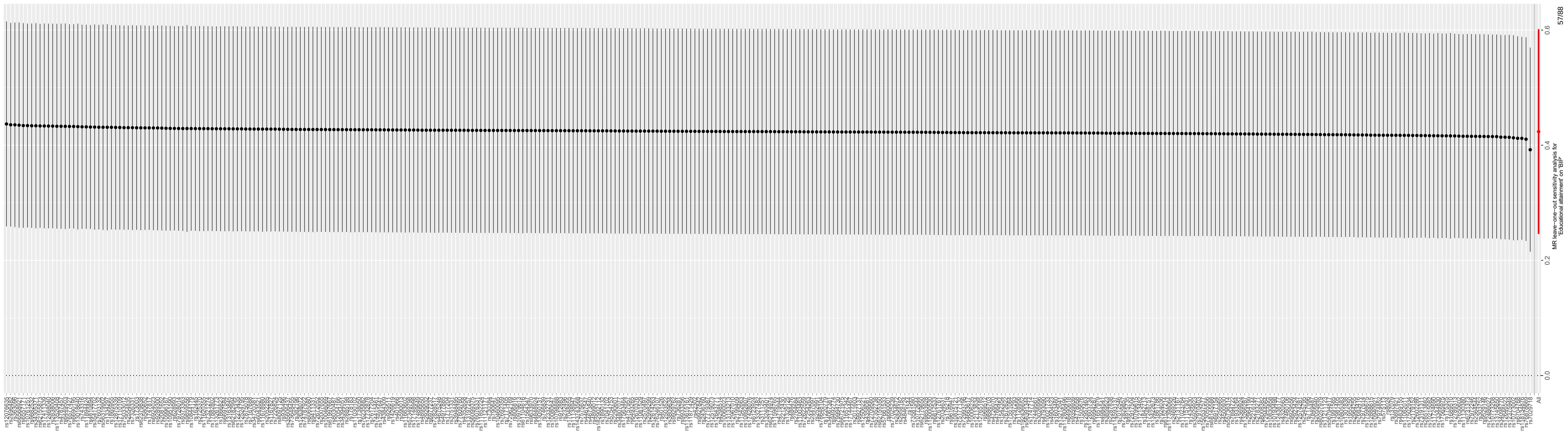
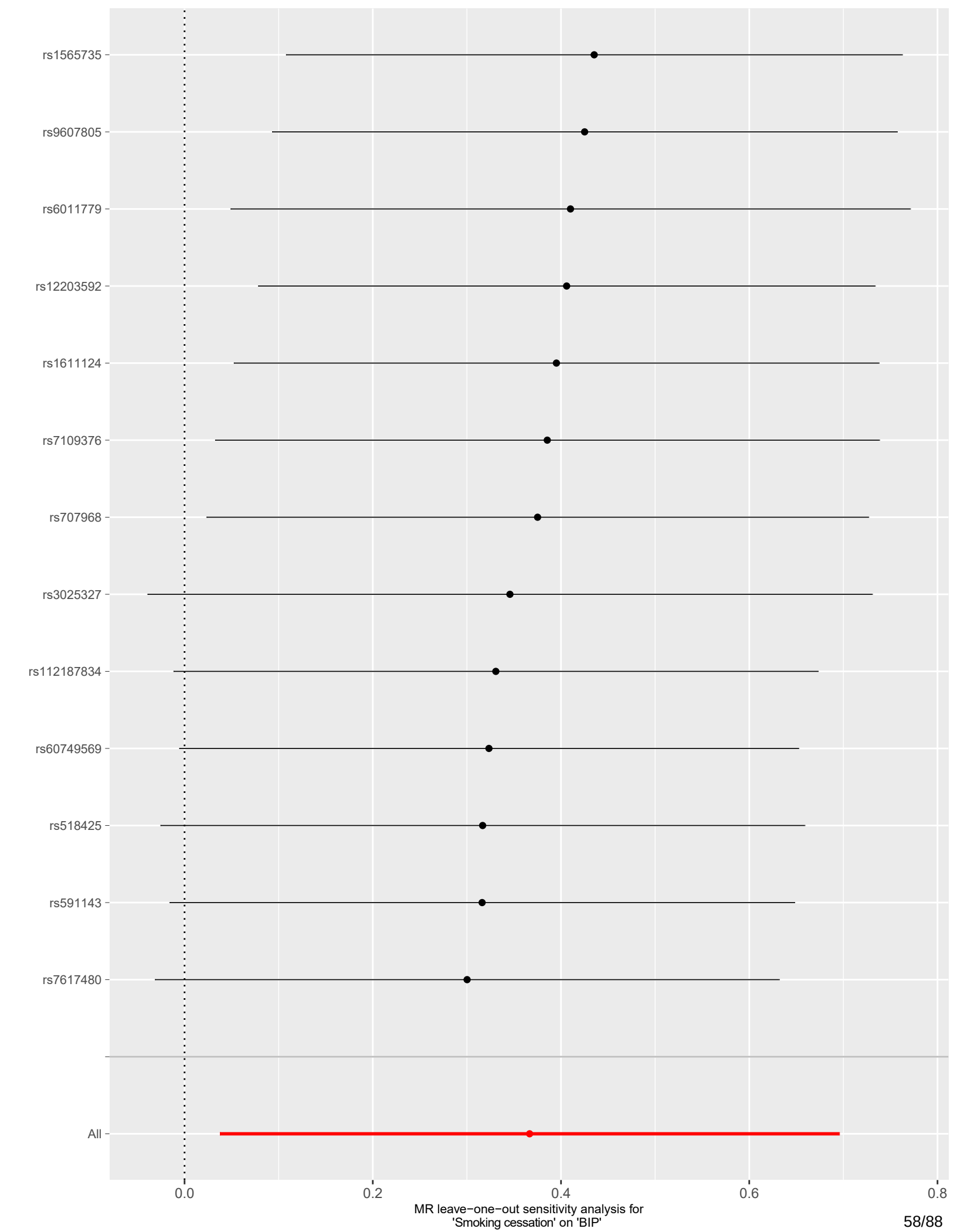

MR Test
Inverse variance weighted
MR Egger
Weighted median
Weighted mode
0.04
0.00
−0.04
SNP effect on SCZ
0.01
0.02
0.03
0.04
0.05
SNP effect on Number of sexual partners

Figure S2. Leave-one-out analysis for all significant causal relationships detected in primary analysis. Within each panel, the black points represent the causal estimate of association between a specific exposure and target mental disorder after discarding each SNP in turn. Red points represent the overall causal estimate using the random-effects inverse variance weighted. Horizontal lines denote 95% confidence intervals.

BIP, bipolar disorder; MDD, major depressive disorder; SCZ, schizophrenia.


57/80
MR leave−one−out sensitivity analysis for
'Educational attainment on 'BIP'
0.0
0.2
0.4
0.6
All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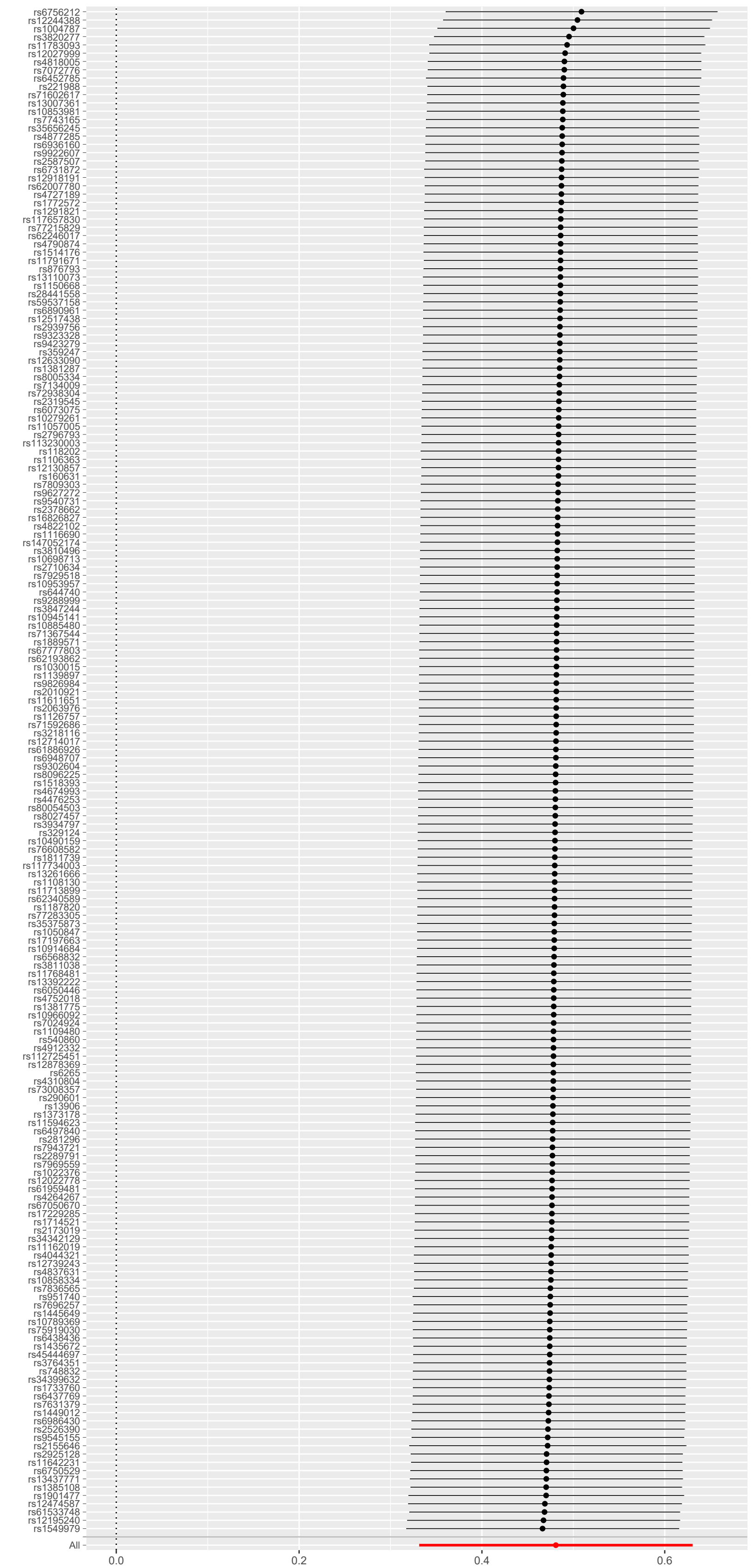
rs12203592
rs1611124
rs7109376
rs707968
rs3025327
rs112187834
rs60749569
rs518425
rs591143
rs7617480
All
0.0
0.2
0.4
0.6
0.8
MR leave−one−out sensitivity analysis for
'Smoking cessation' on 'BIP'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rs62246017
rs4790874
rs1514176
rs11791671
rs876793
rs13110073
rs1150668
rs28441558
rs59537158
rs6890961
rs12517438
rs2939756
rs9323328
rs9423279
rs359247
rs12633090
rs1381287
rs8005334
rs7134009
rs72938304
rs2319545
rs6073075
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rs11057005
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rs1106363
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rs160631
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rs4822102
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rs9288999
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rs10885480
rs71367544
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rs2063976
rs1126757
rs71592686
rs3218116
rs12714017
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rs6948707
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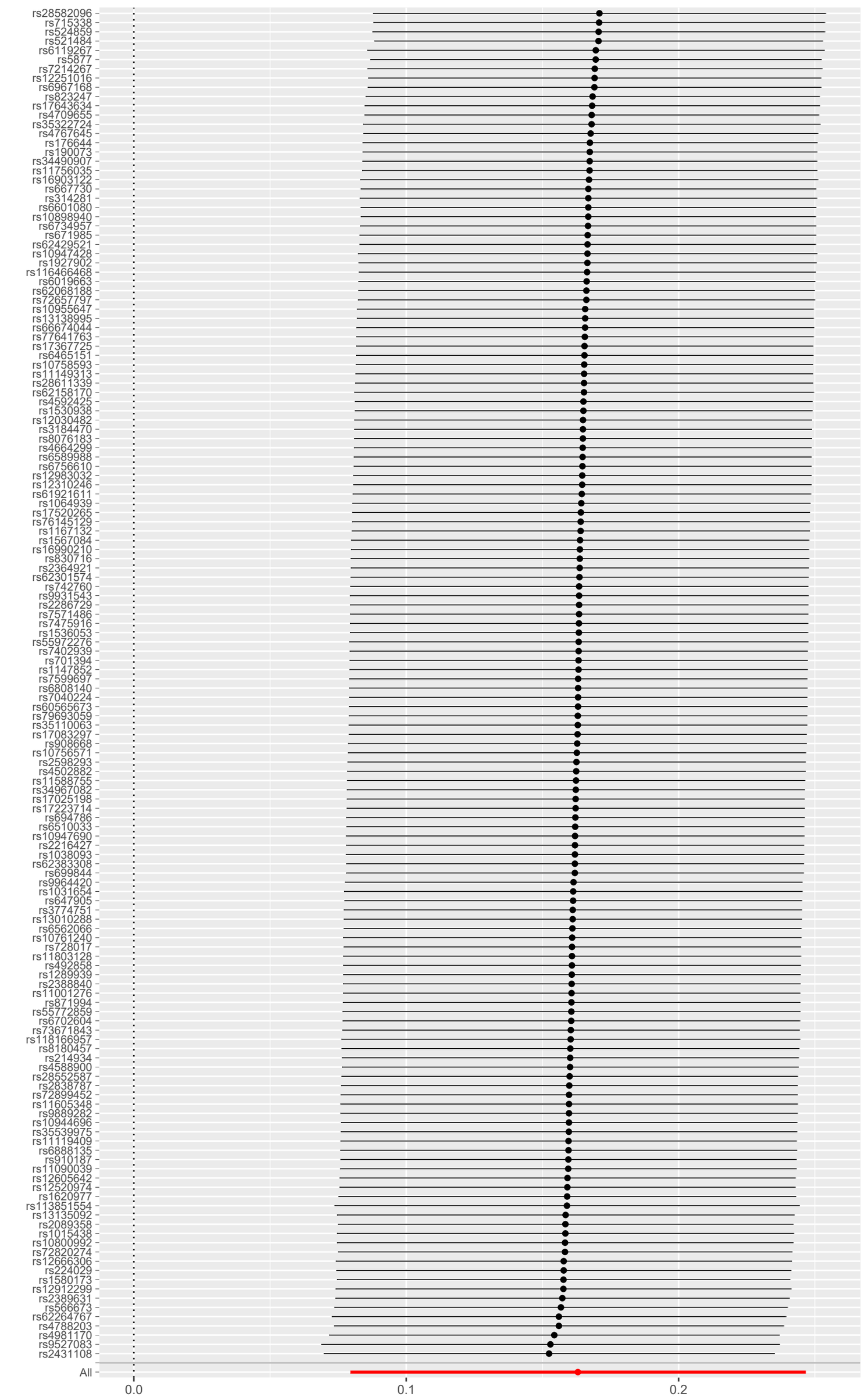
All
0.0
0.2
0.4
0.6
MR leave−one−out sensitivity analysis for
'smoking initiation' on 'BIP'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rs566673
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rs4788203
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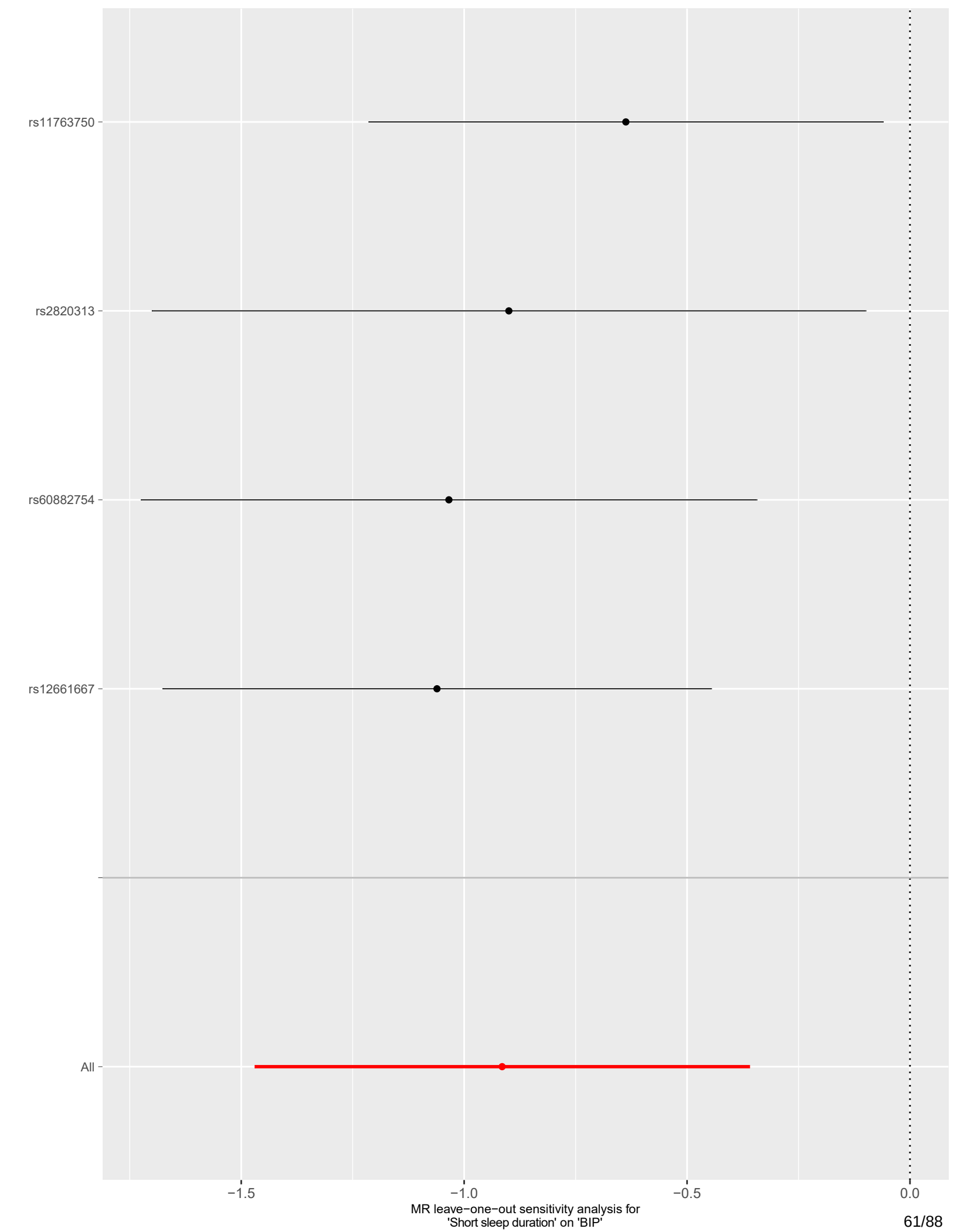
All
0.0
0.1
0.2
MR leave−one−out sensitivity analysis for
'Insomnia' on 'BIP'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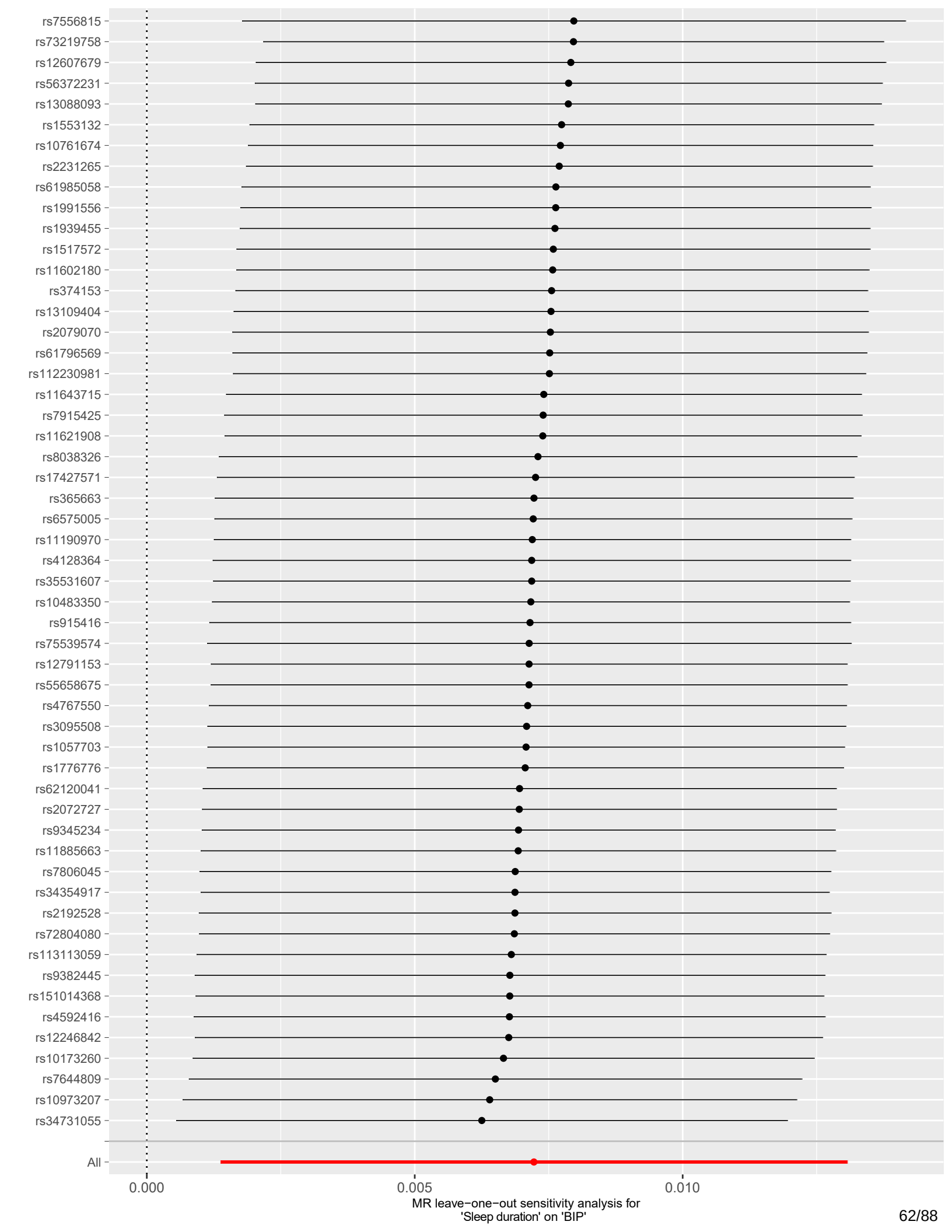
−1.0
−0.5
0.0
MR leave−one−out sensitivity analysis for
'Short sleep duration' on 'BIP'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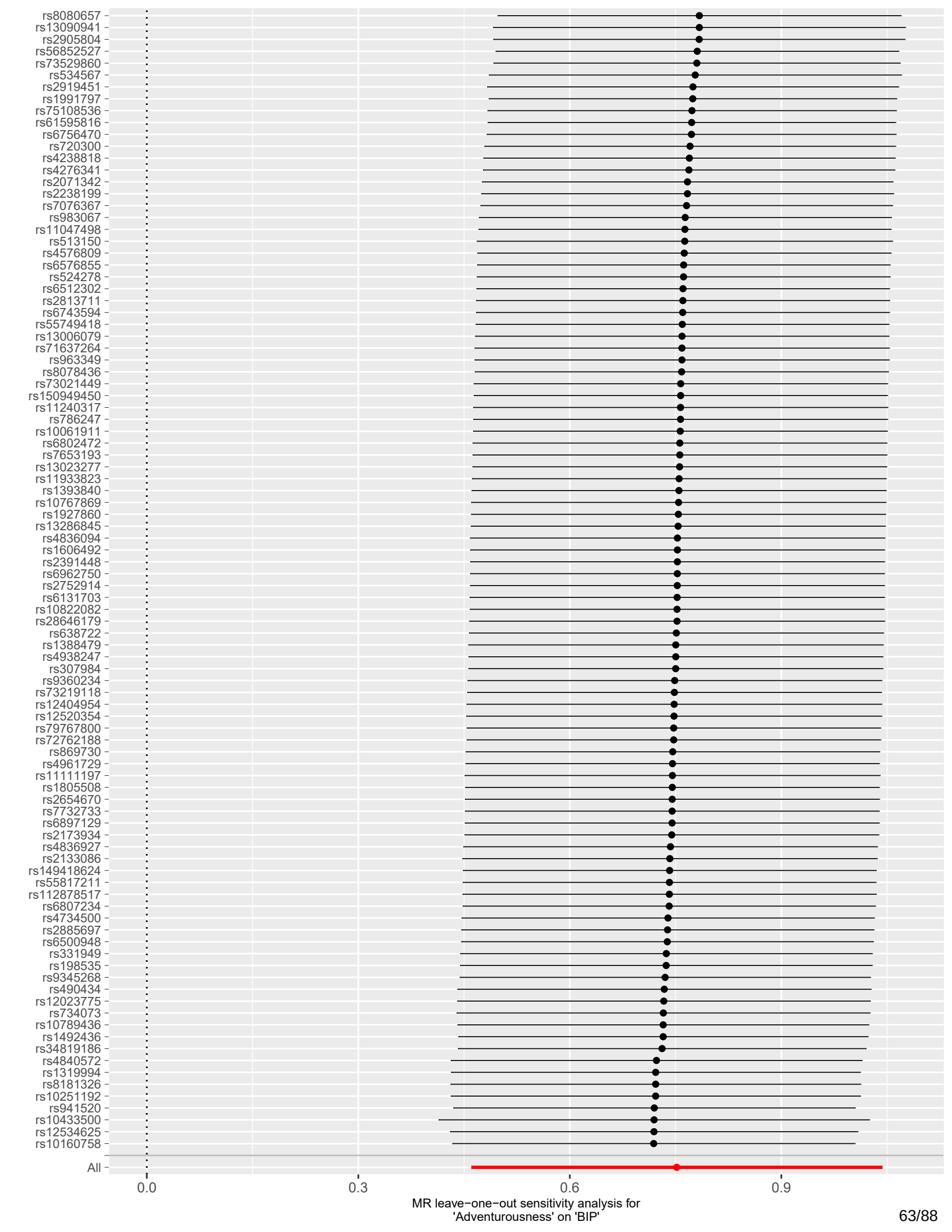
All
0.000
0.005
0.010
MR leave−one−out sensitivity analysis for
'Sleep duration' on 'BIP'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rs941520
rs10433500
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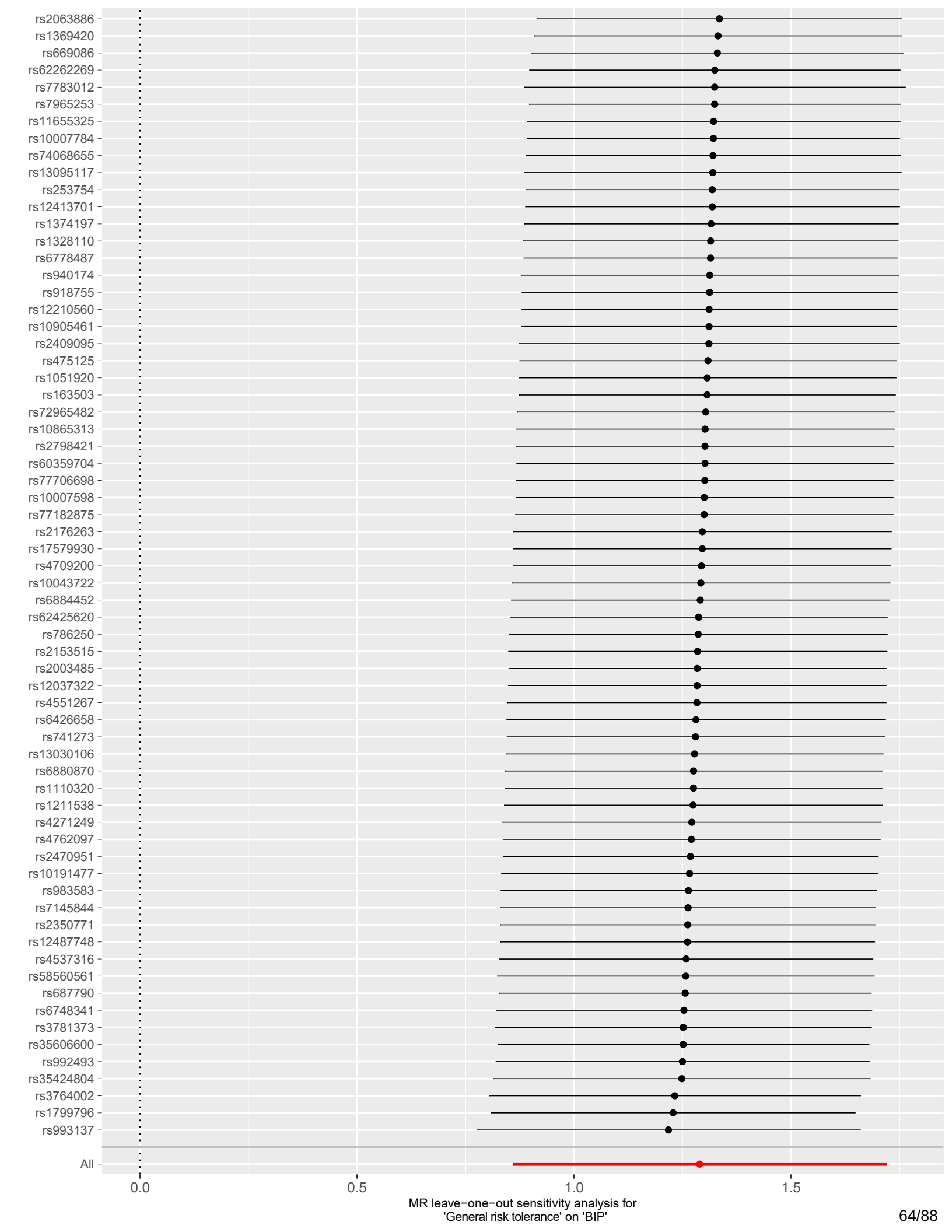
0.6
0.9
MR leave−one−out sensitivity analysis for
'Adventurousness' on 'BIP'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rs35424804
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All
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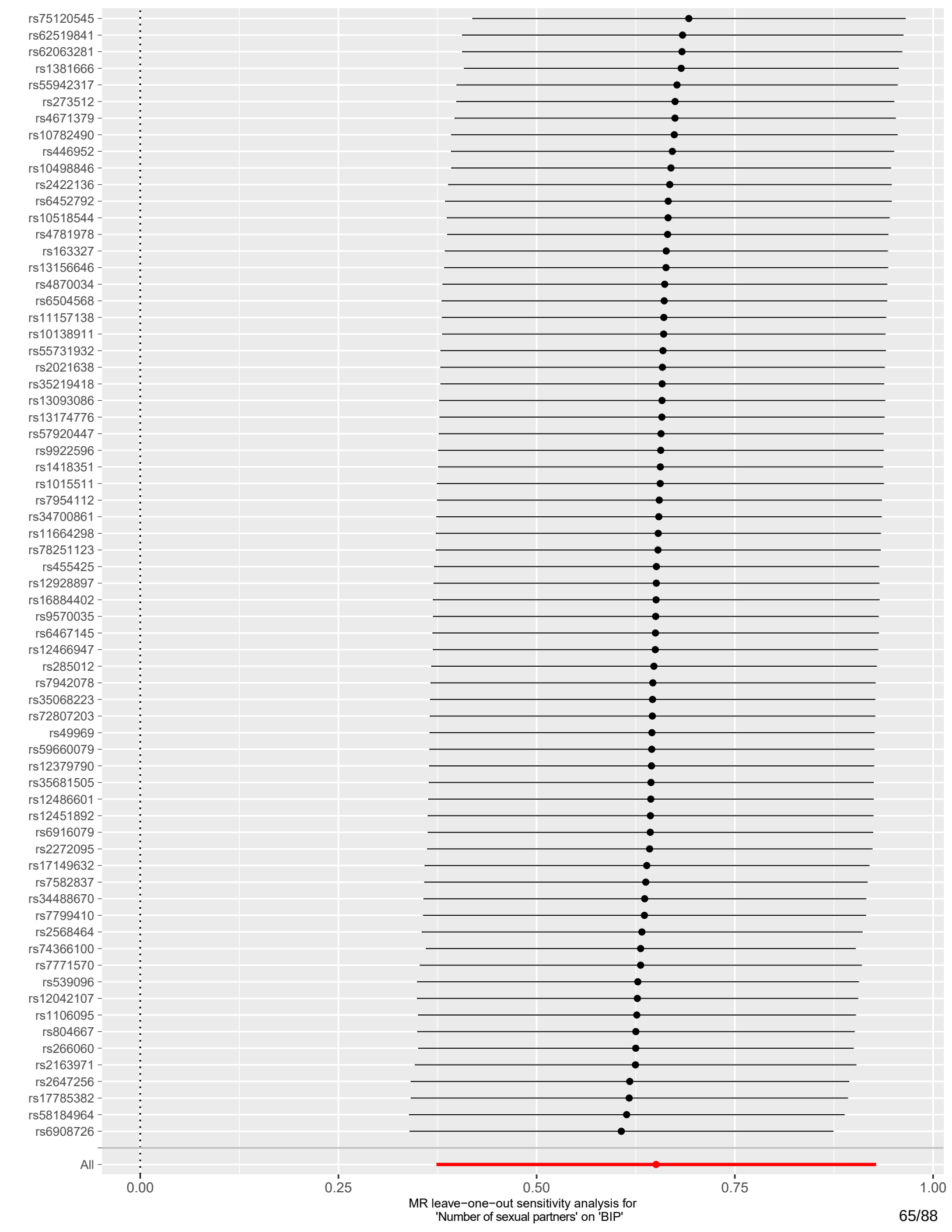
0.5
1.0
1.5
MR leave−one−out sensitivity analysis for
'General risk tolerance' on 'BIP'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rs6908726
All
0.00
0.25
0.50
0.75
1.00
MR leave−one−out sensitivity analysis for
'Number of sexual partners' on 'BIP'

All
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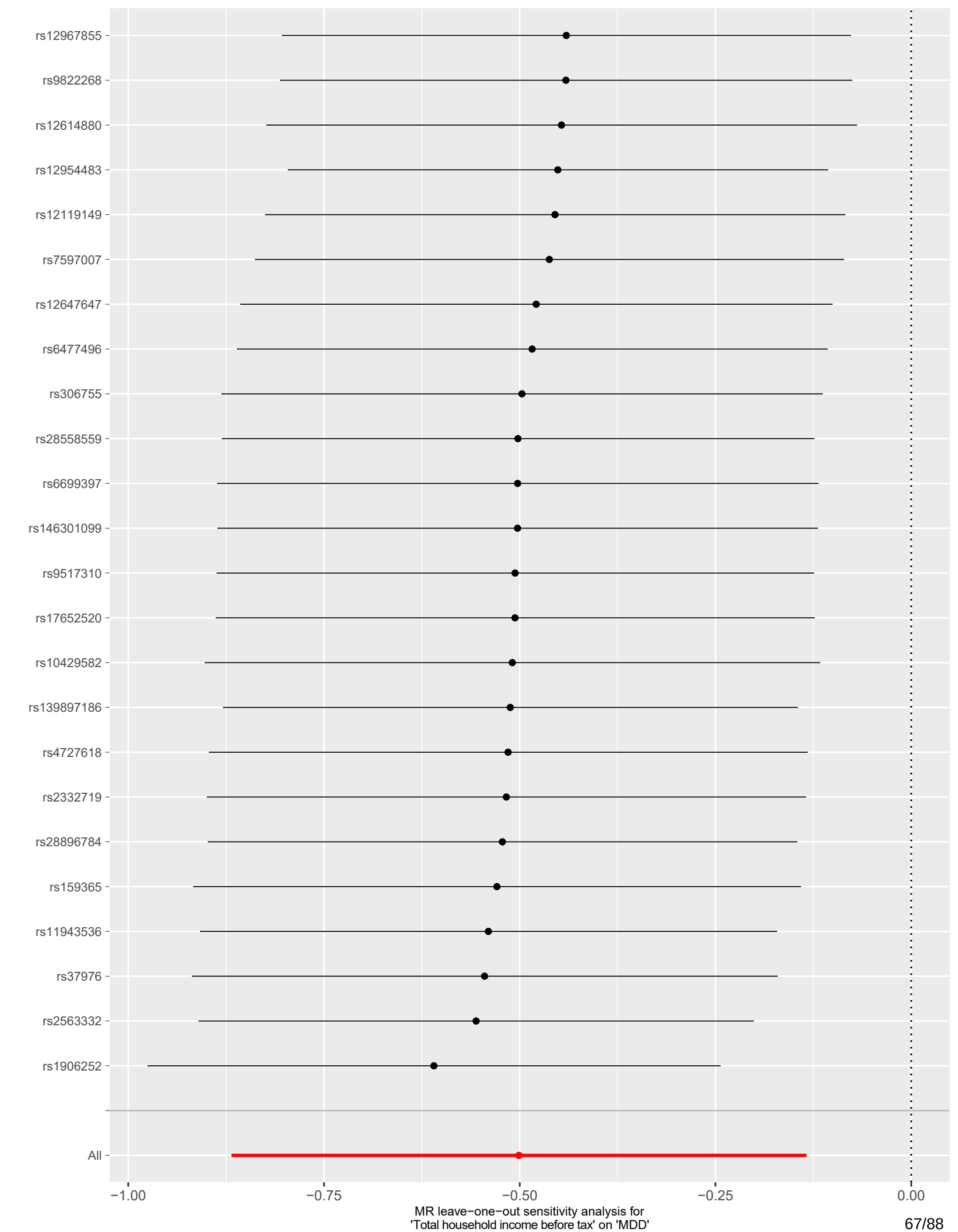
−0.3
−0.2
−0.1
0.0
MR leave−one−out sensitivity analysis for
'Educational attainment' on 'MDD'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rs10429582
rs139897186
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rs2332719
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rs159365
rs11943536
rs37976
rs2563332
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All
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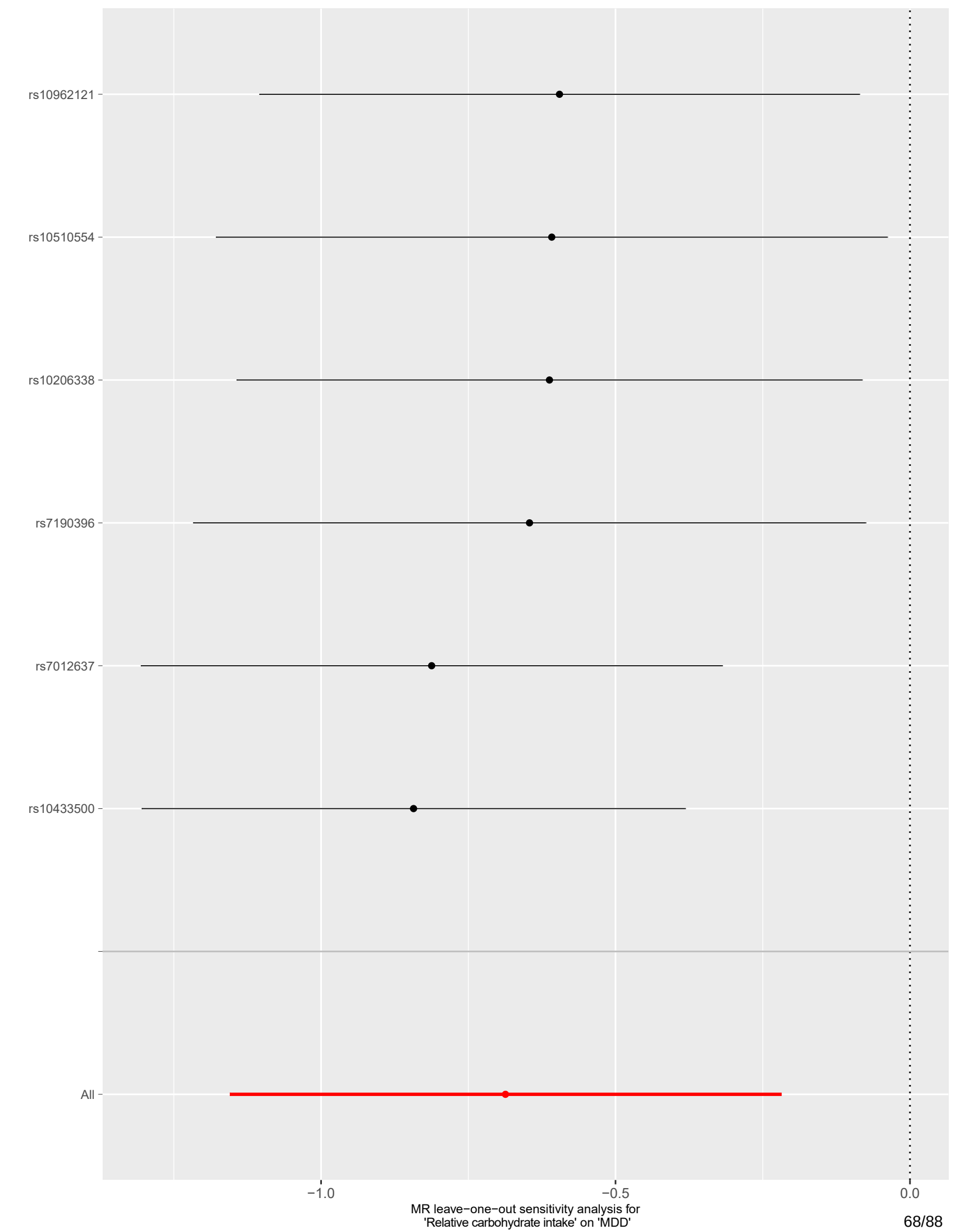
−0.75
−0.50
−0.25
0.00
MR leave−one−out sensitivity analysis for
'Total household income before tax' on 'MDD'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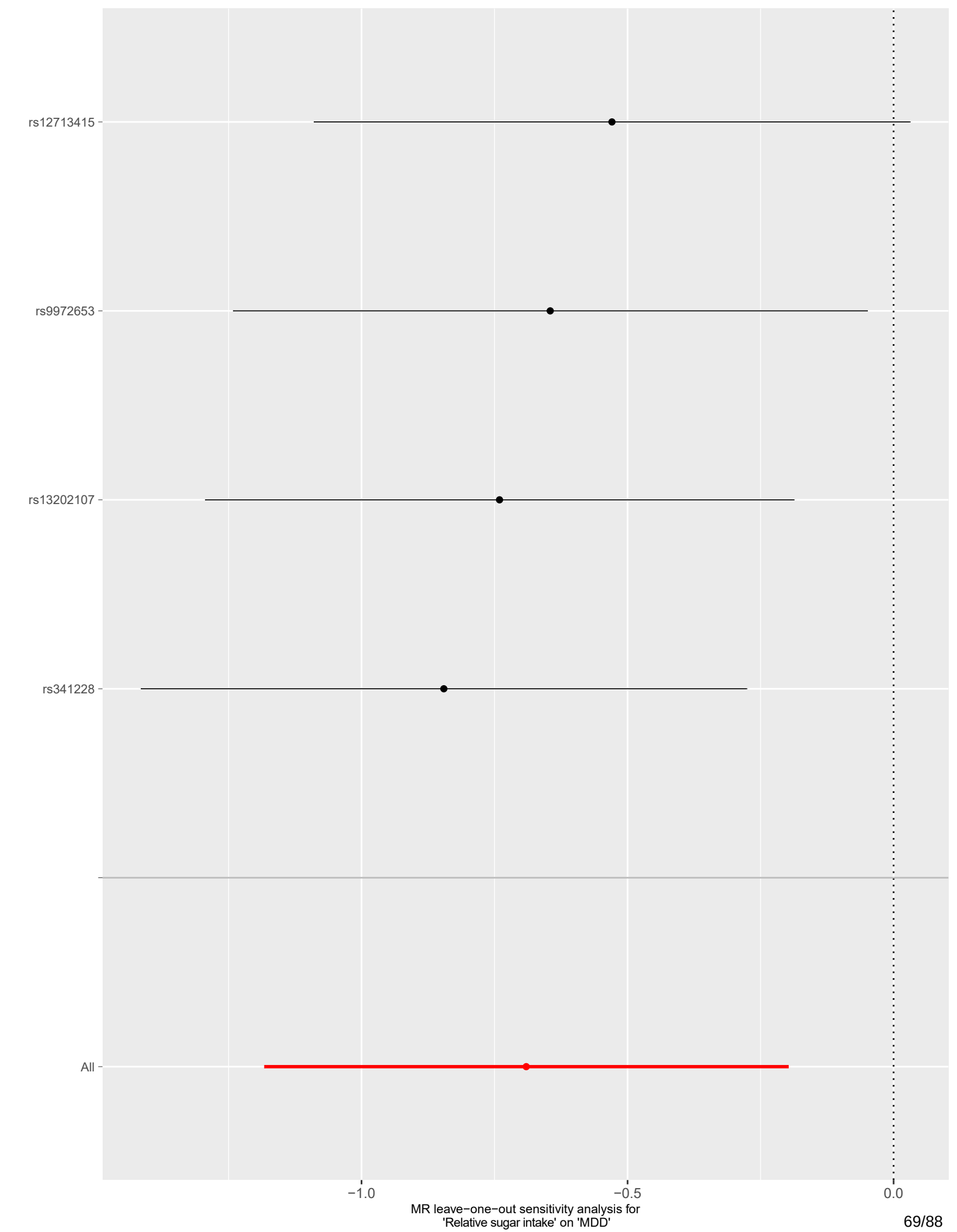
All
−1.0
−0.5
0.0
MR leave−one−out sensitivity analysis for
'Relative carbohydrate intake' on 'MDD'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rs13202107
rs341228
All
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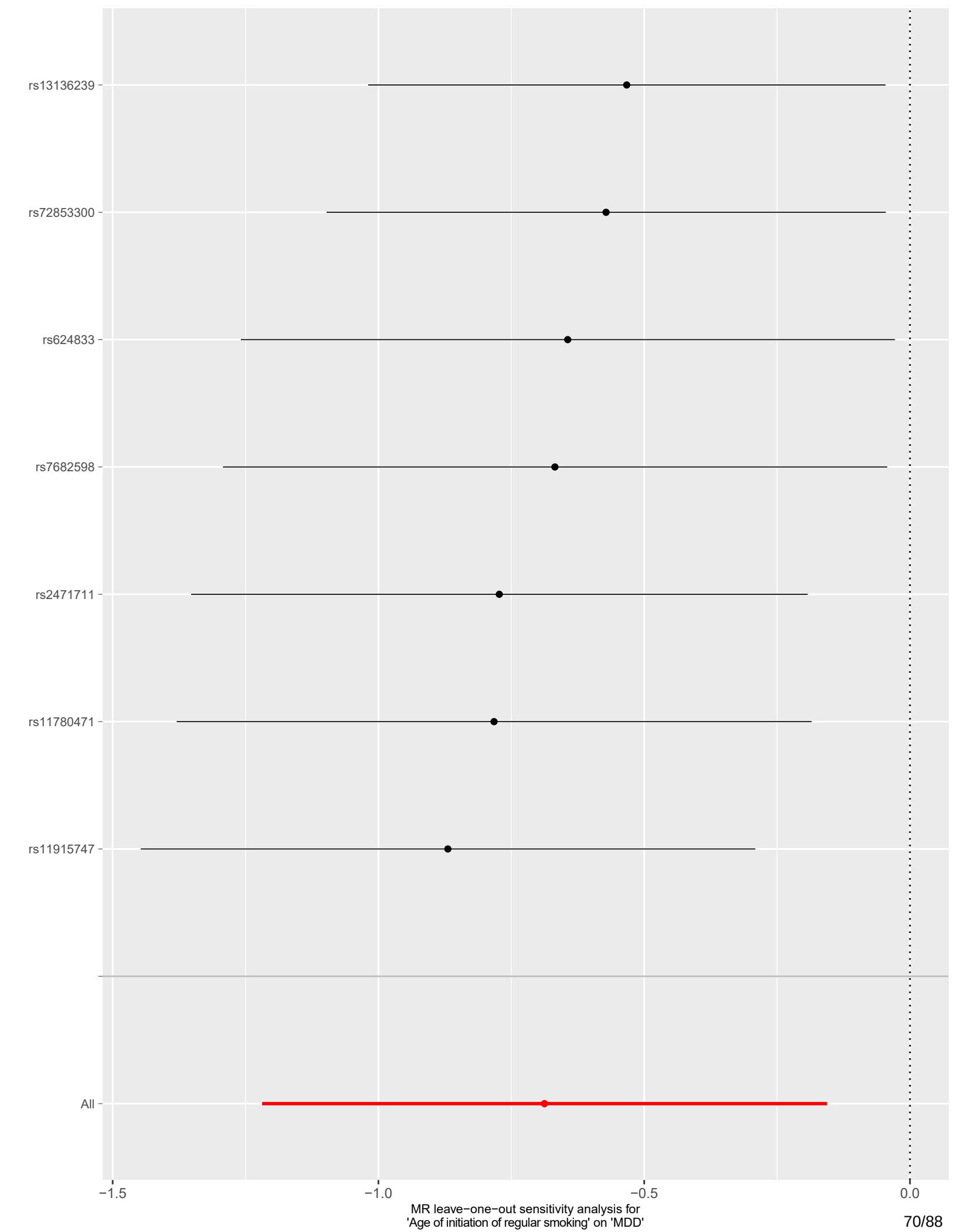
−0.5
0.0
MR leave−one−out sensitivity analysis for
'Relative sugar intake' on 'MDD'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rs72853300
rs624833
rs7682598
rs2471711
rs11780471
rs11915747
All
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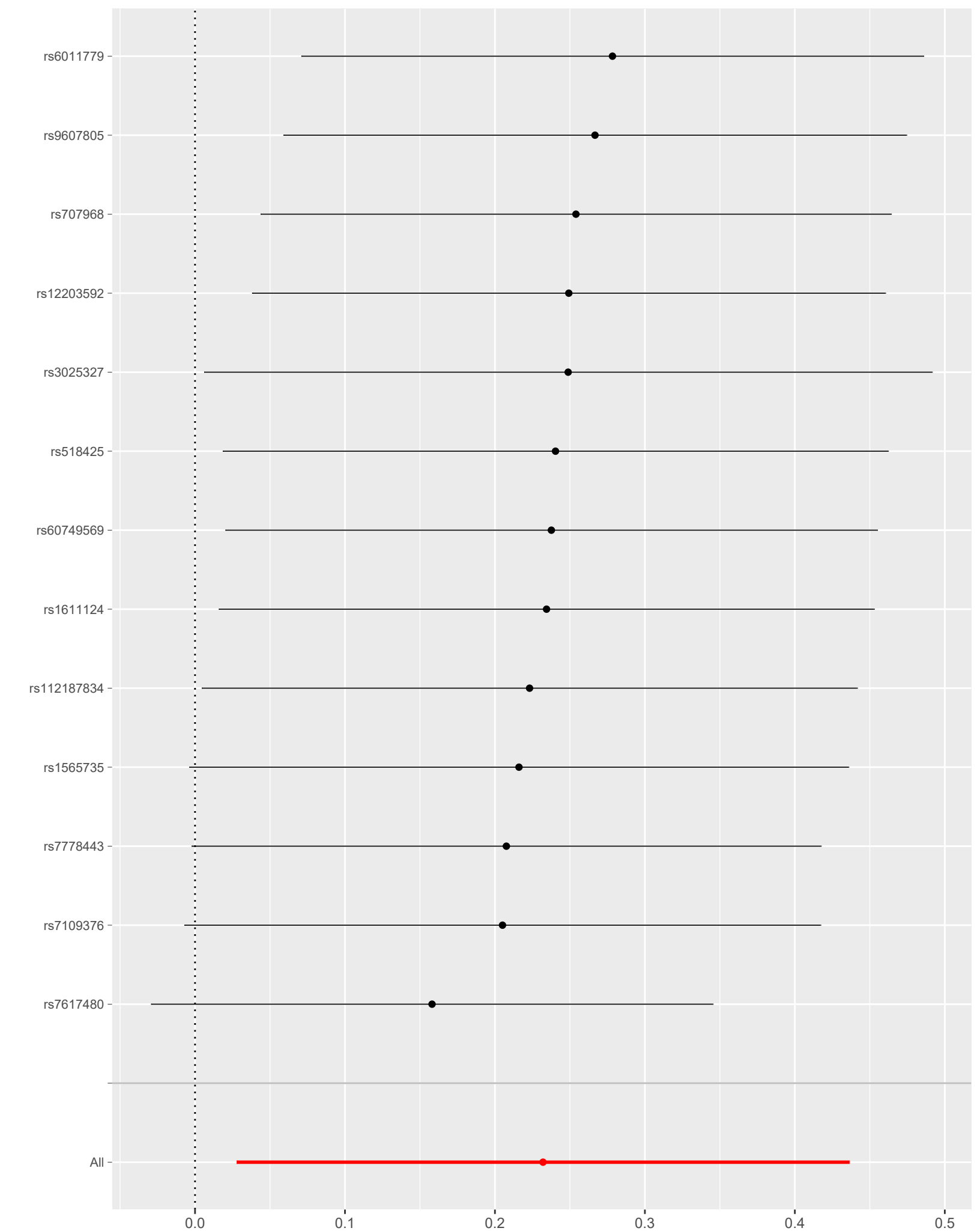
−1.0
−0.5
0.0
MR leave−one−out sensitivity analysis for
'Age of initiation of regular smoking' on 'MDD'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rs518425
rs60749569
rs1611124
rs112187834
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rs7778443
rs7109376
rs7617480
All
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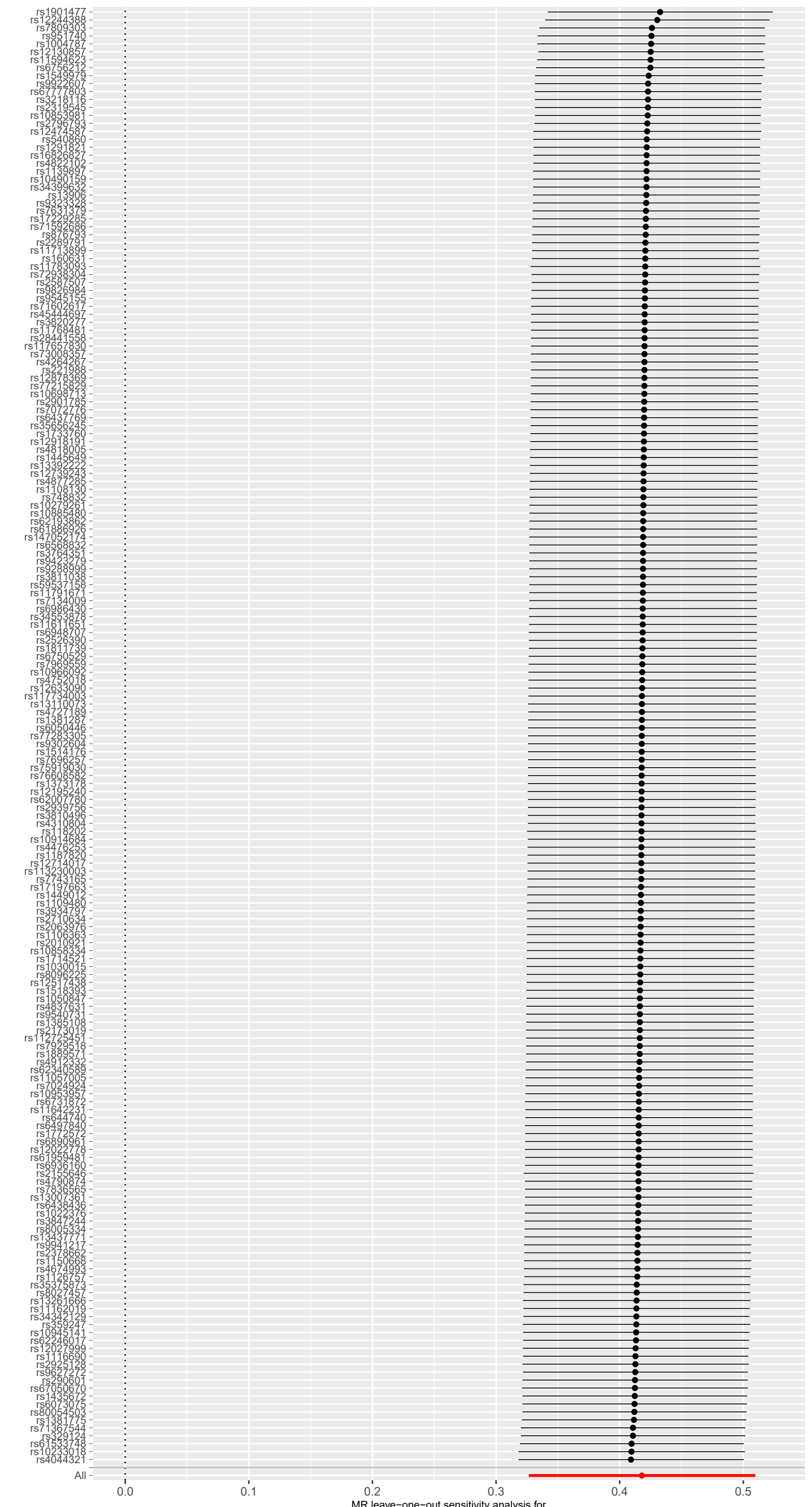
0.1
0.2
0.3
0.4
0.5
MR leave−one−out sensitivity analysis for
'Smoking cessation' on 'MDD'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rs10853981
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rs11783093
rs72938304
rs2587507
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rs71602617
rs45444697
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rs10945141
rs62246017
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rs67050670
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rs6073075
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rs1381775
rs71367544
rs329124
rs61533748
rs10233018
rs4044321
All
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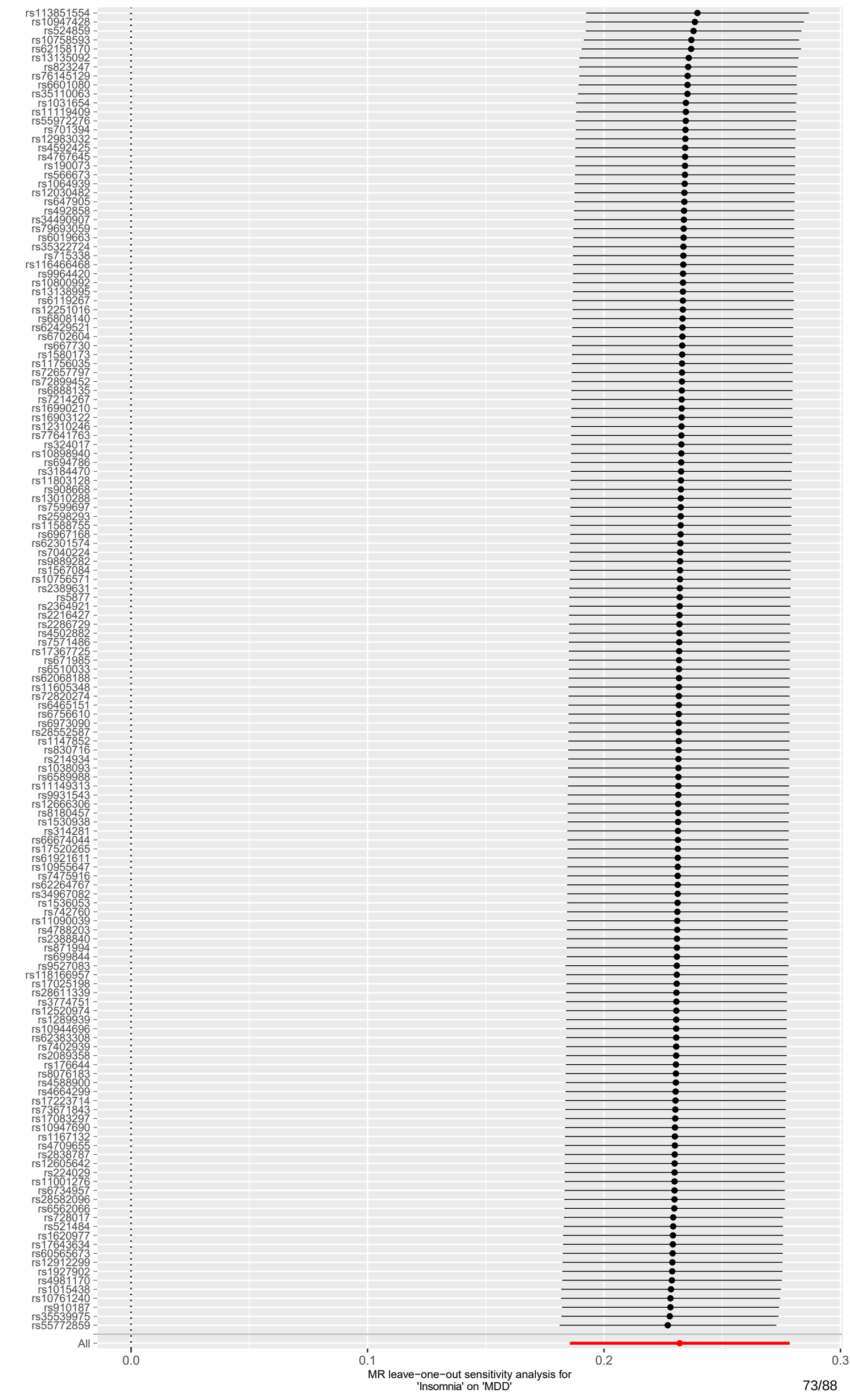
0.1
0.2
0.3
0.4
0.5
MR leave−one−out sensitivity analysis for
'Smoking initiation' on 'MDD'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rs6601080
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rs1031654
rs11119409
rs55972276
rs701394
rs12983032
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rs647905
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rs34490907
rs79693059
rs6019663
rs35322724
rs715338
rs116466468
rs9964420
rs10800992
rs13138995
rs6119267
rs12251016
rs6808140
rs62429521
rs6702604
rs667730
rs1580173
rs11756035
rs72657797
rs72899452
rs6888135
rs7214267
rs16990210
rs16903122
rs12310246
rs77641763
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rs694786
rs3184470
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rs13010288
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rs4502882
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rs17367725
rs671985
rs6510033
rs62068188
rs11605348
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rs6465151
rs6756610
rs6973090
rs28552587
rs1147852
rs830716
rs214934
rs1038093
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rs9931543
rs12666306
rs8180457
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rs314281
rs66674044
rs17520265
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rs1536053
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rs1289939
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rs62383308
rs7402939
rs2089358
rs176644
rs8076183
rs4588900
rs4664299
rs17223714
rs73671843
rs17083297
rs10947690
rs1167132
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rs2838787
rs12605642
rs224029
rs11001276
rs6734957
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rs6562066
rs728017
rs521484
rs1620977
rs17643634
rs60565673
rs12912299
rs1927902
rs4981170
rs1015438
rs10761240
rs910187
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All
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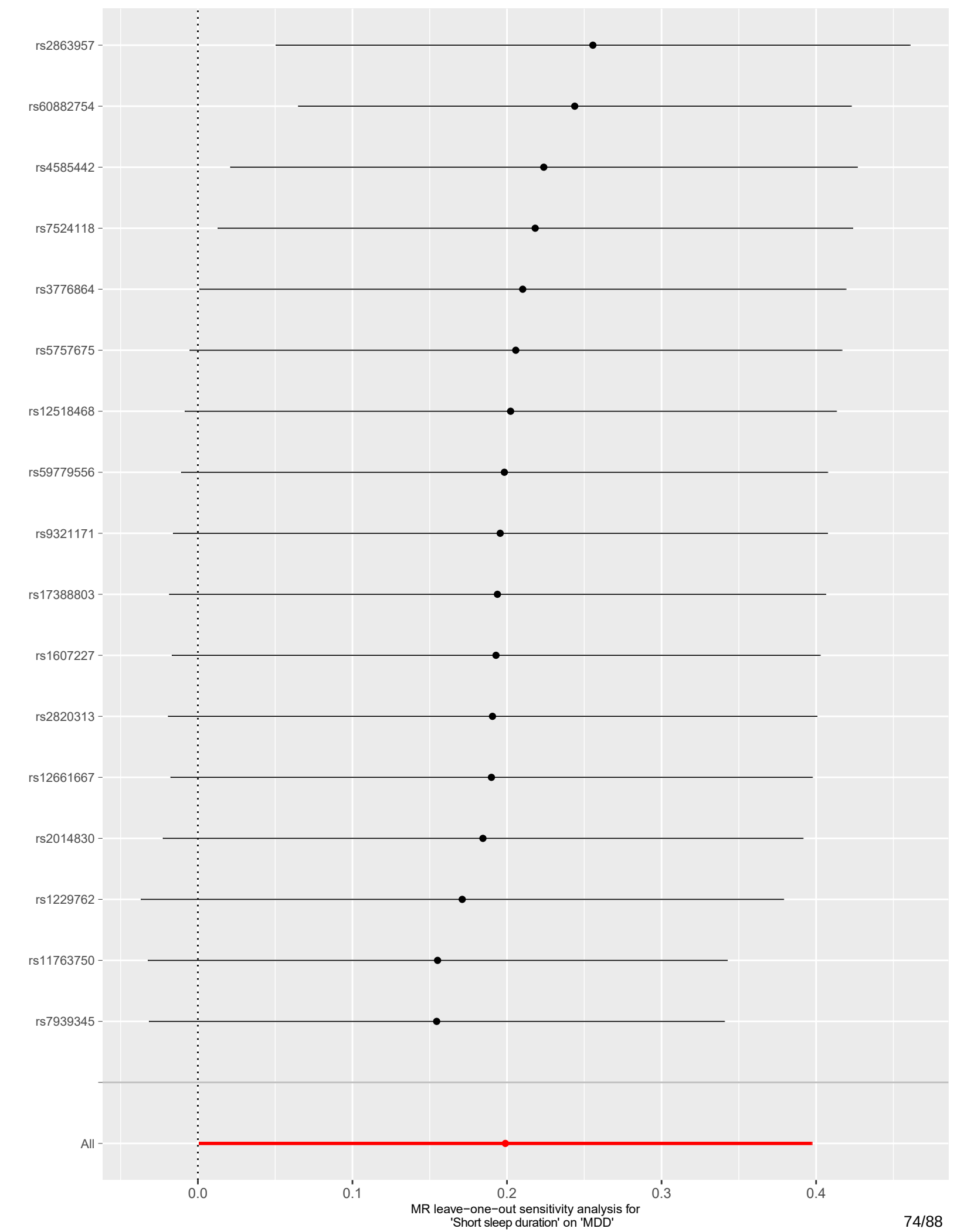
0.1
0.2
0.3
MR leave−one−out sensitivity analysis for
'Insomnia' on 'MDD'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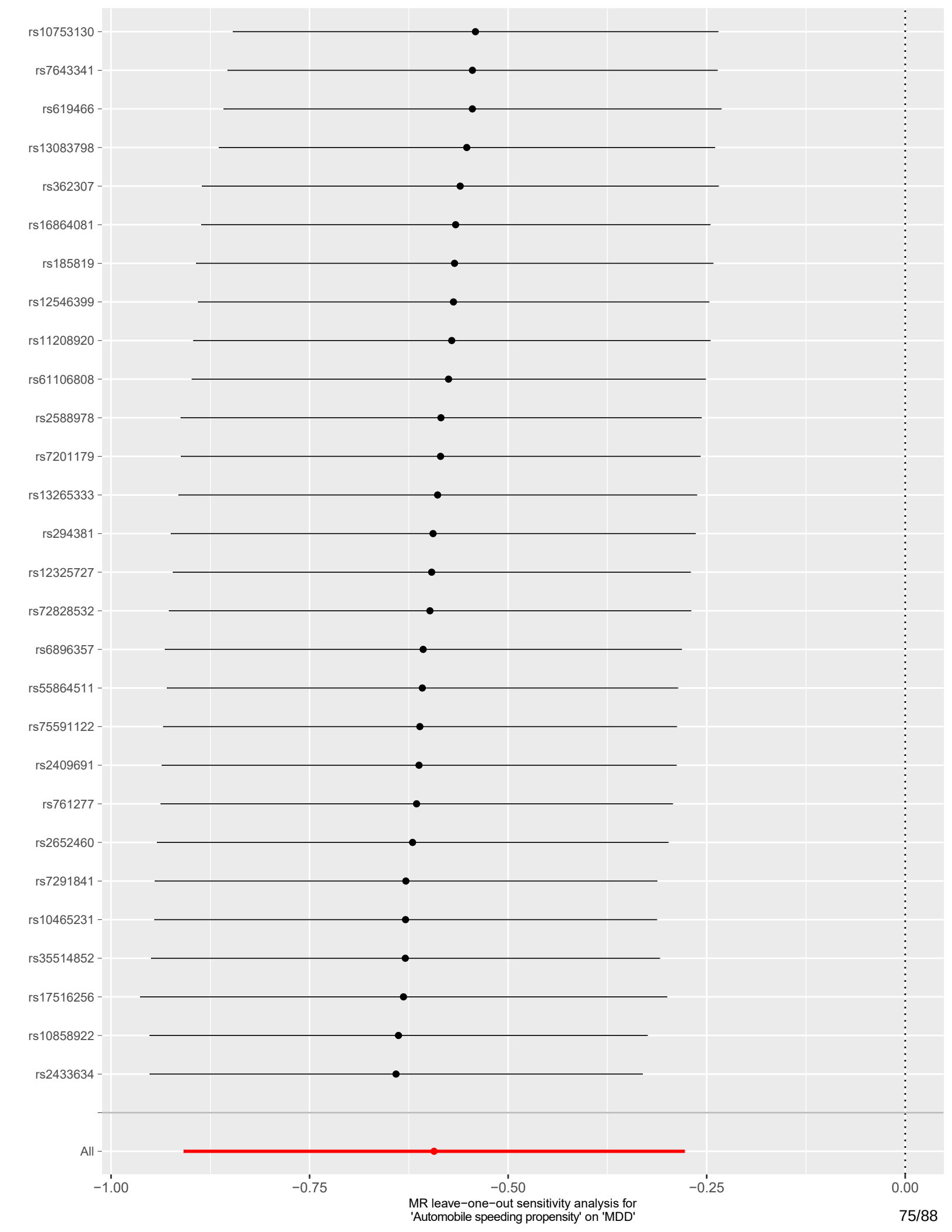
rs59779556
rs9321171
rs17388803
rs1607227
rs2820313
rs12661667
rs2014830
rs1229762
rs11763750
rs7939345
All
0.0
0.1
0.2
0.3
0.4
MR leave−one−out sensitivity analysis for
'Short sleep duration' on 'MDD'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rs13083798
rs362307
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rs12546399
rs11208920
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rs7201179
rs13265333
rs294381
rs12325727
rs72828532
rs6896357
rs55864511
rs75591122
rs2409691
rs761277
rs2652460
rs7291841
rs10465231
rs35514852
rs17516256
rs10858922
rs2433634
All
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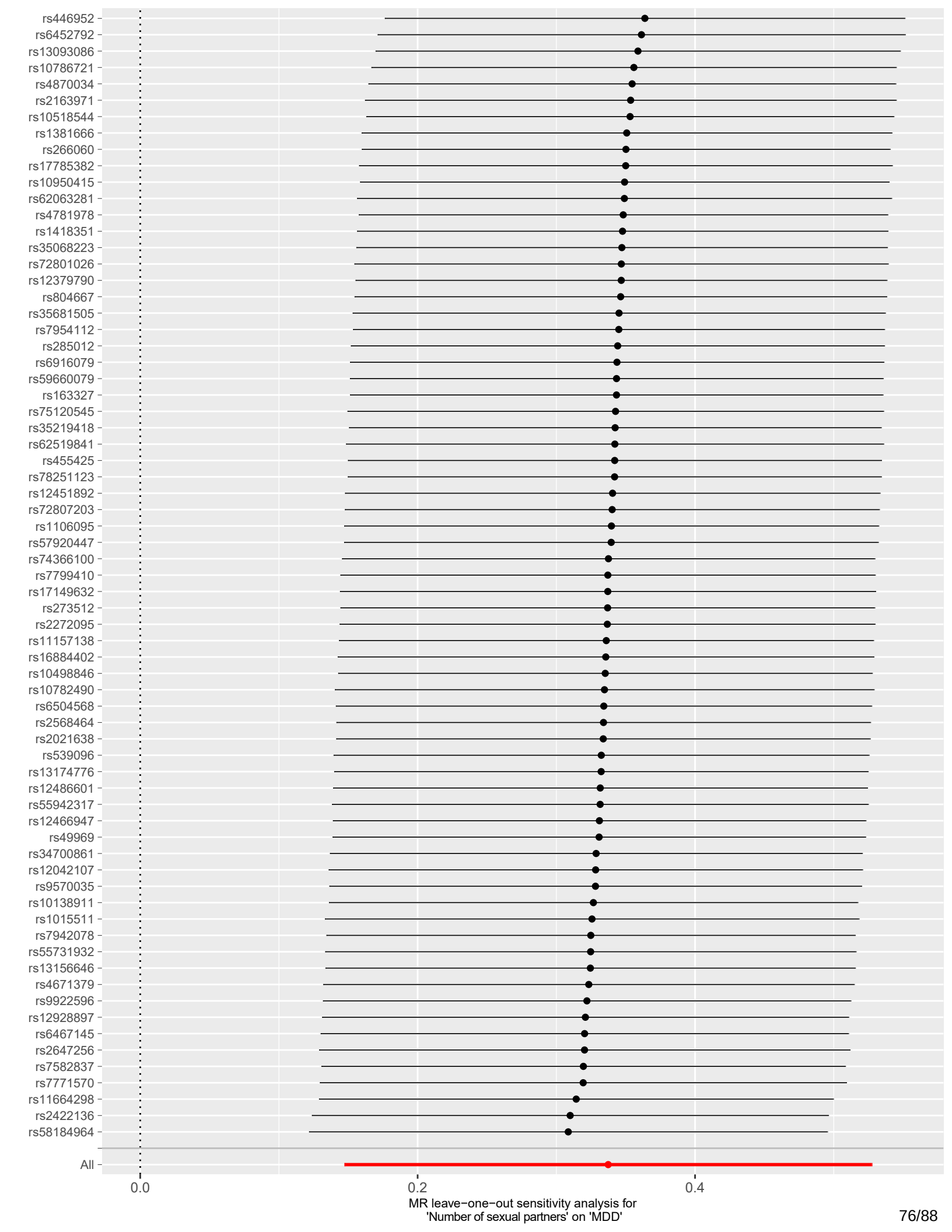
−0.75
−0.50
−0.25
0.00
MR leave−one−out sensitivity analysis for
'Automobile speeding propensity' on 'MDD'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rs13156646
rs4671379
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rs12928897
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rs2647256
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rs7771570
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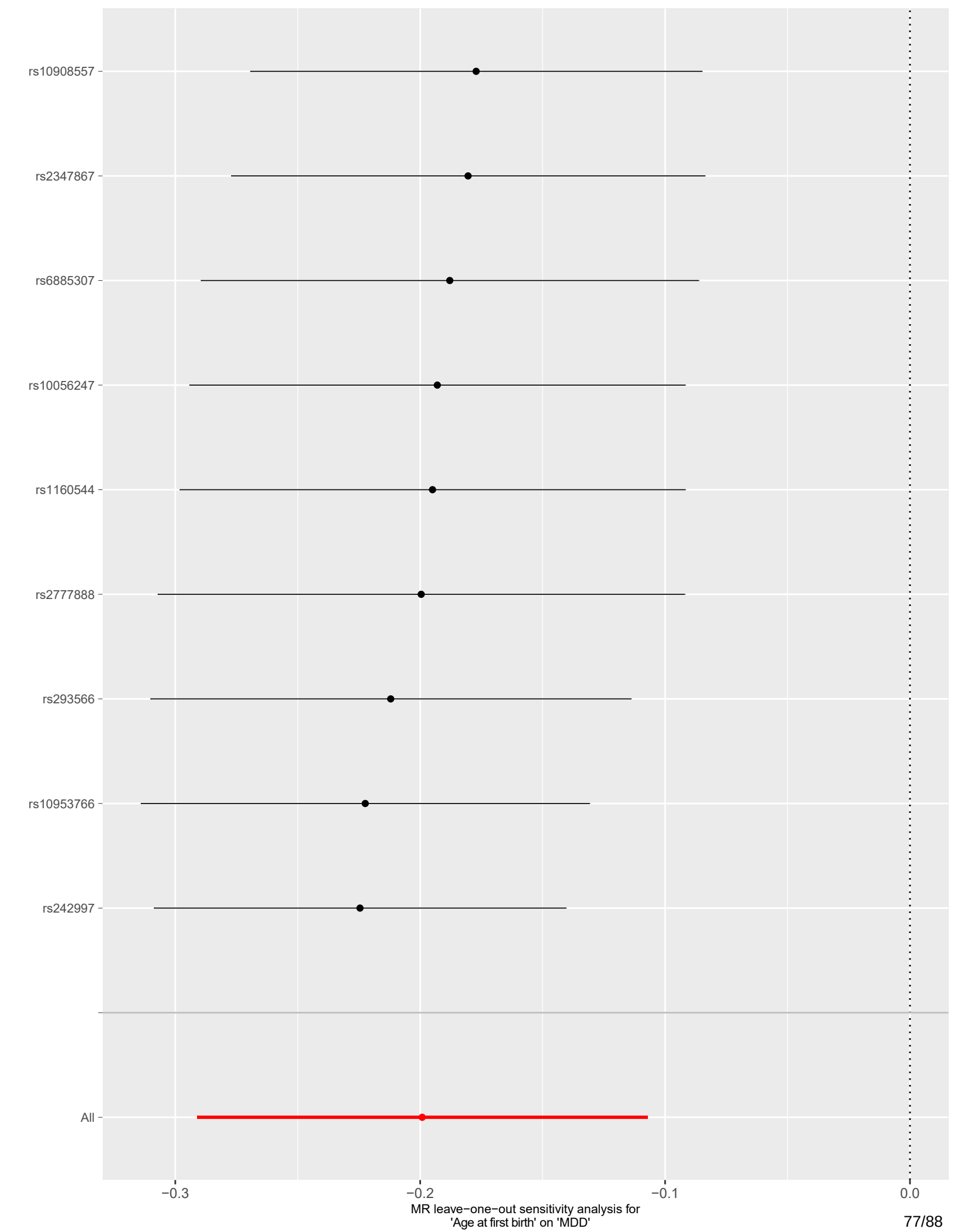
rs58184964
All
0.0
0.2
0.4
MR leave−one−out sensitivity analysis for
'Number of sexual partners' on 'MDD'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rs1160544
rs2777888
rs293566
rs10953766
rs242997
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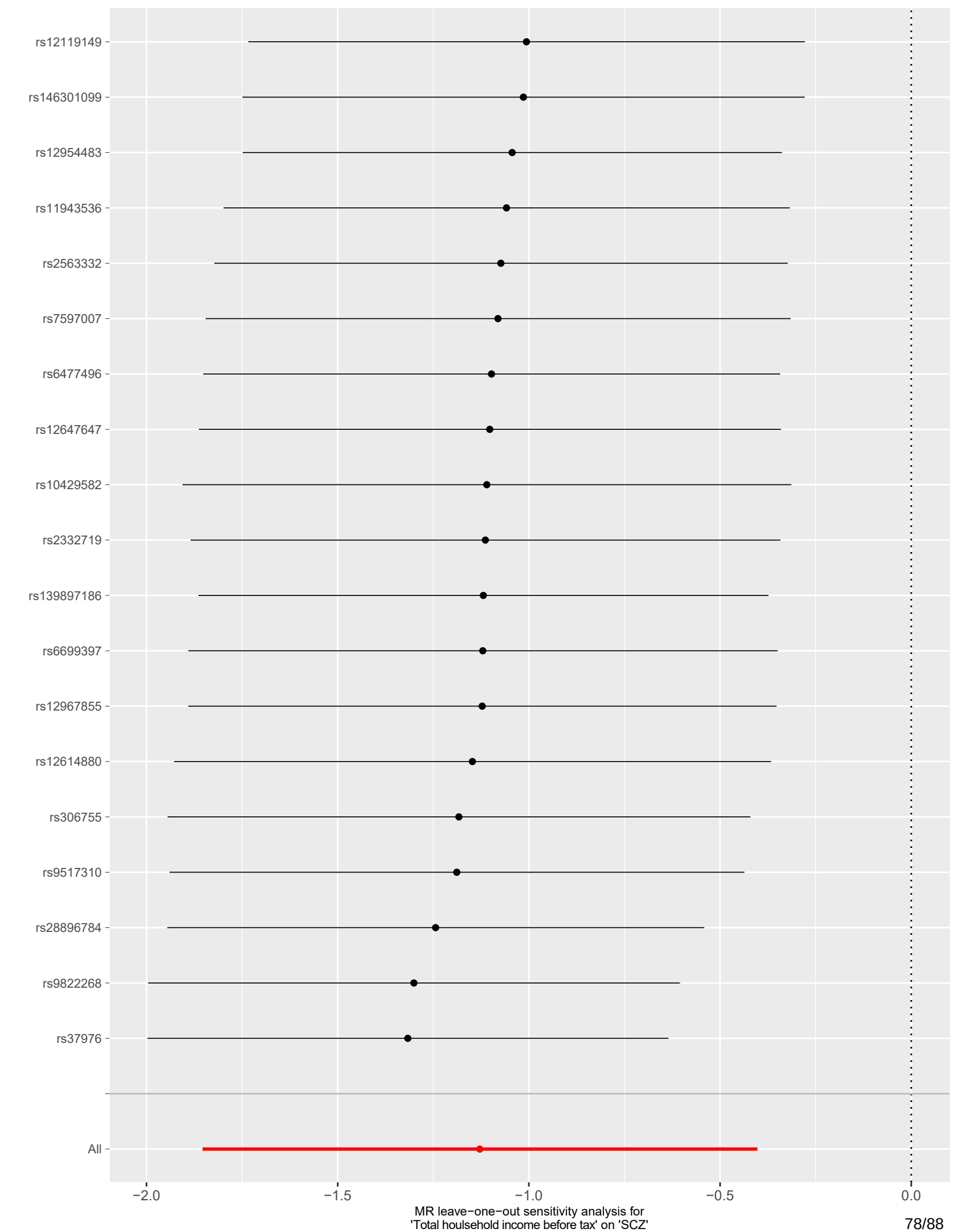
−0.1
0.0
MR leave−one−out sensitivity analysis for
'Age at first birth' on 'MDD'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rs2563332
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rs6477496
rs12647647
rs10429582
rs2332719
rs139897186
rs6699397
rs12967855
rs12614880
rs306755
rs9517310
rs28896784
rs9822268
rs37976
All
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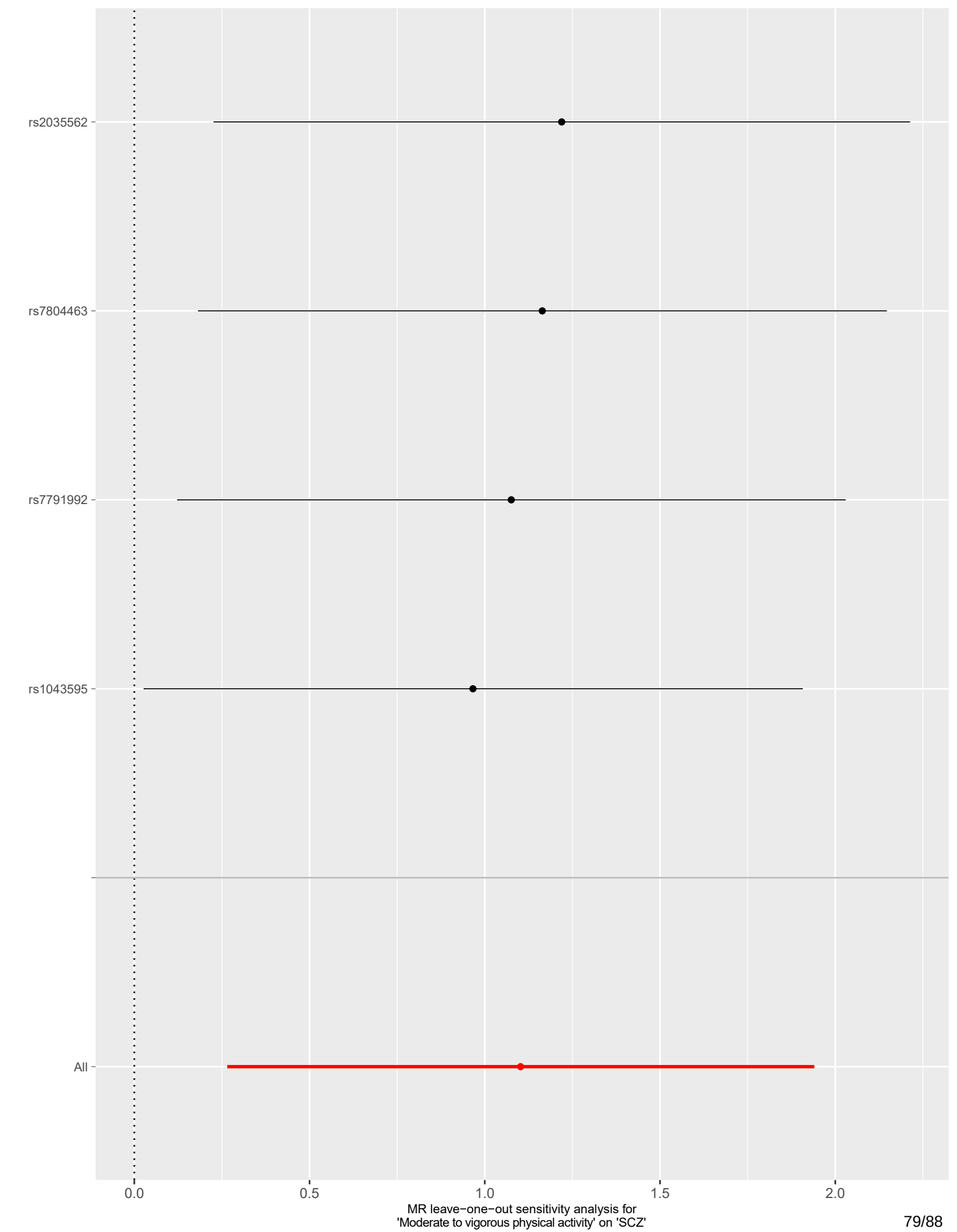
−1.5
−1.0
−0.5
0.0
MR leave−one−out sensitivity analysis for
'Total houlsehold income before tax' on 'SCZ'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rs7804463
rs7791992
rs1043595
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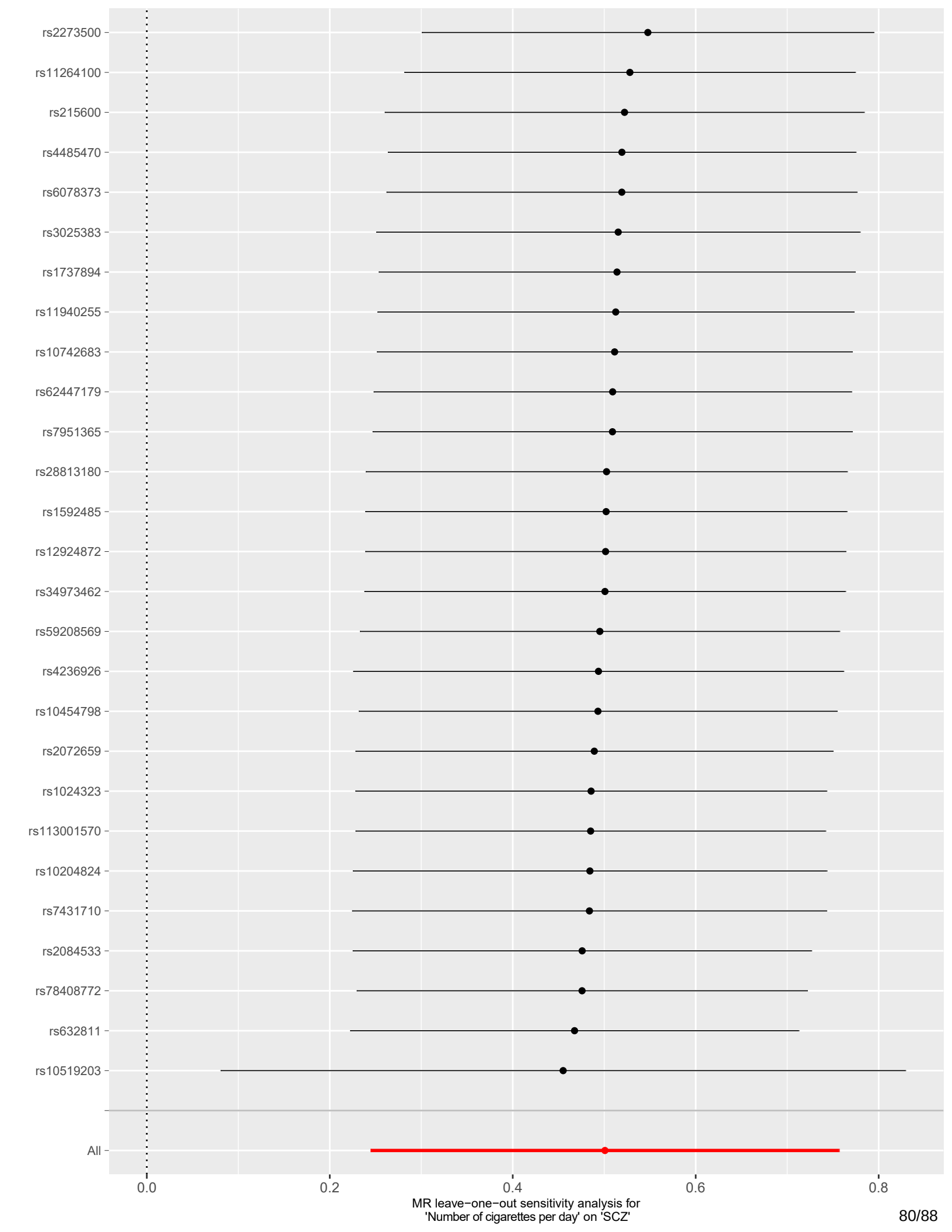
1.0
1.5
2.0
MR leave−one−out sensitivity analysis for
'Moderate to vigorous physical activity' on 'SCZ'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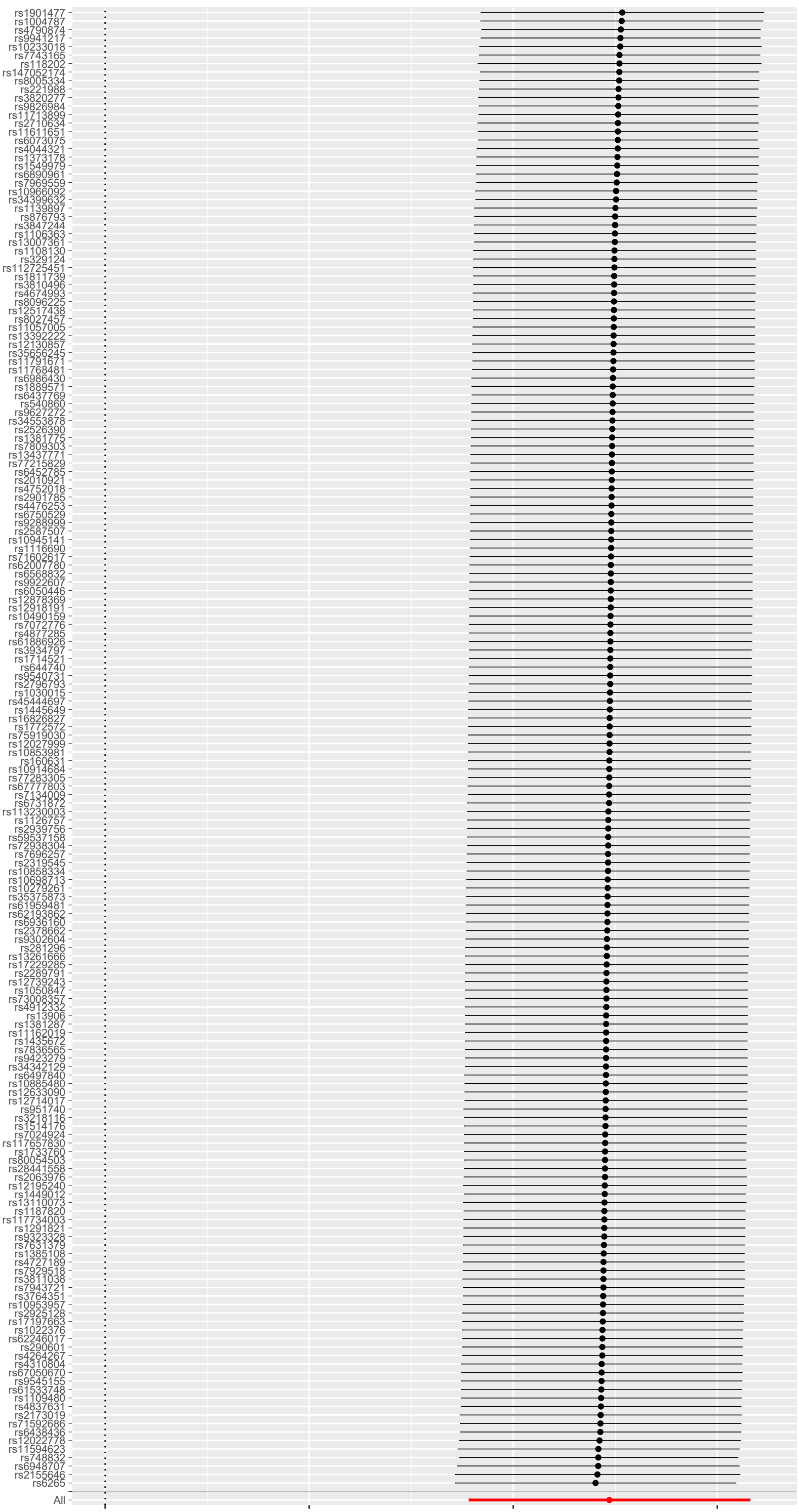
rs10204824
rs7431710
rs2084533
rs78408772
rs632811
rs10519203
All
0.0
0.2
0.4
0.6
0.8
MR leave−one−out sensitivity analysis for
'Number of cigarettes per day' on 'SCZ'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rs1549979
rs6890961
rs7969559
rs10966092
rs34399632
rs1139897
rs876793
rs3847244
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rs13007361
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rs112725451
rs1811739
rs3810496
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rs11057005
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rs540860
rs9627272
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rs1381775
rs7809303
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rs71602617
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rs9540731
rs2796793
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rs45444697
rs1445649
rs16826827
rs1772572
rs75919030
rs12027999
rs10853981
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rs10914684
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rs7134009
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rs2939756
rs59537158
rs72938304
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rs290601
rs4264267
rs4310804
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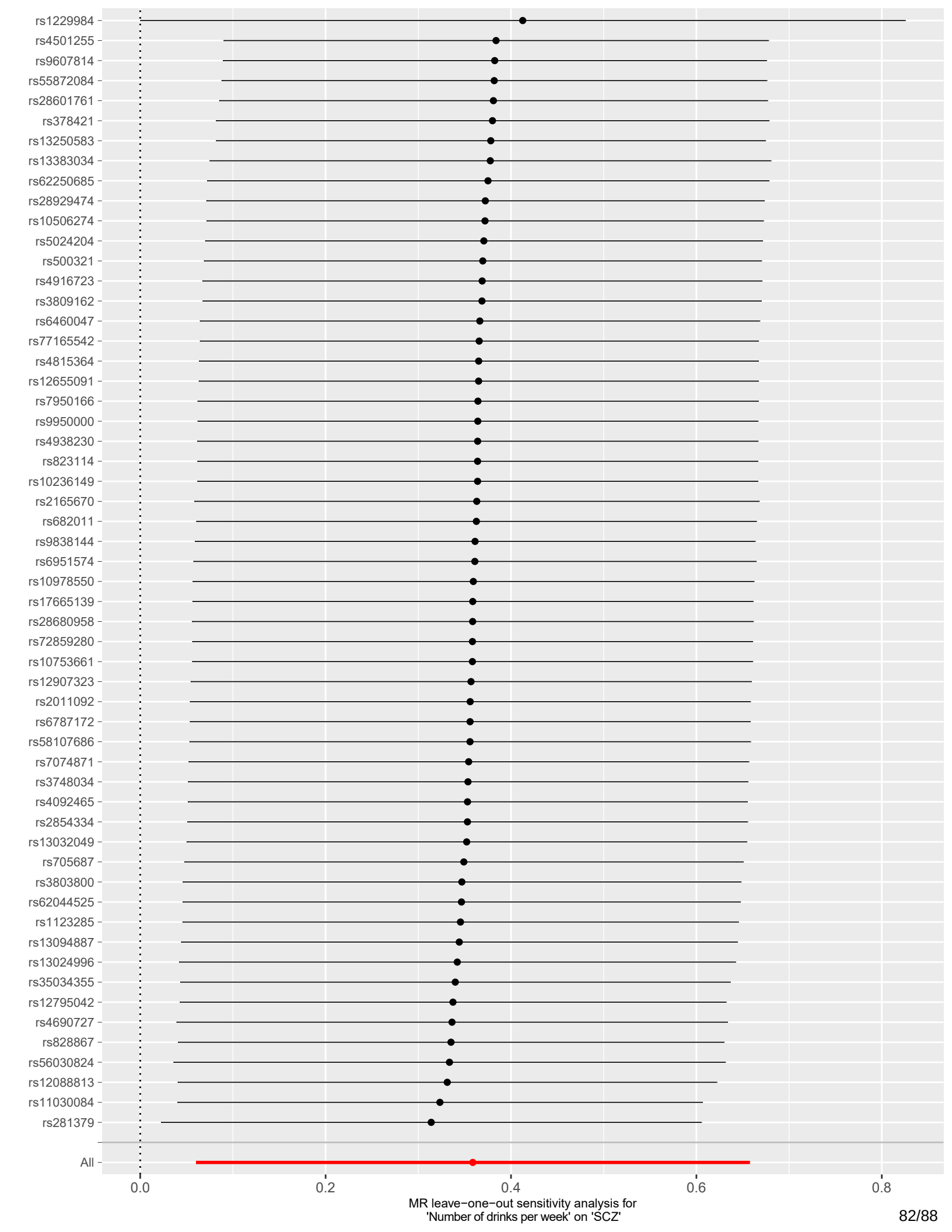
rs61533748
rs1109480
rs4837631
rs2173019
rs71592686
rs6438436
rs12022778
rs11594623
rs748832
rs6948707
rs2155646
rs6265
All
0.0
0.2
0.4
0.6
MR leave−one−out sensitivity analysis for
'Smoking initiation' on 'SCZ'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rs5024204
rs500321
rs4916723
rs3809162
rs6460047
rs77165542
rs4815364
rs12655091
rs7950166
rs9950000
rs4938230
rs823114
rs10236149
rs2165670
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rs4690727
rs828867
rs56030824
rs12088813
rs11030084
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All
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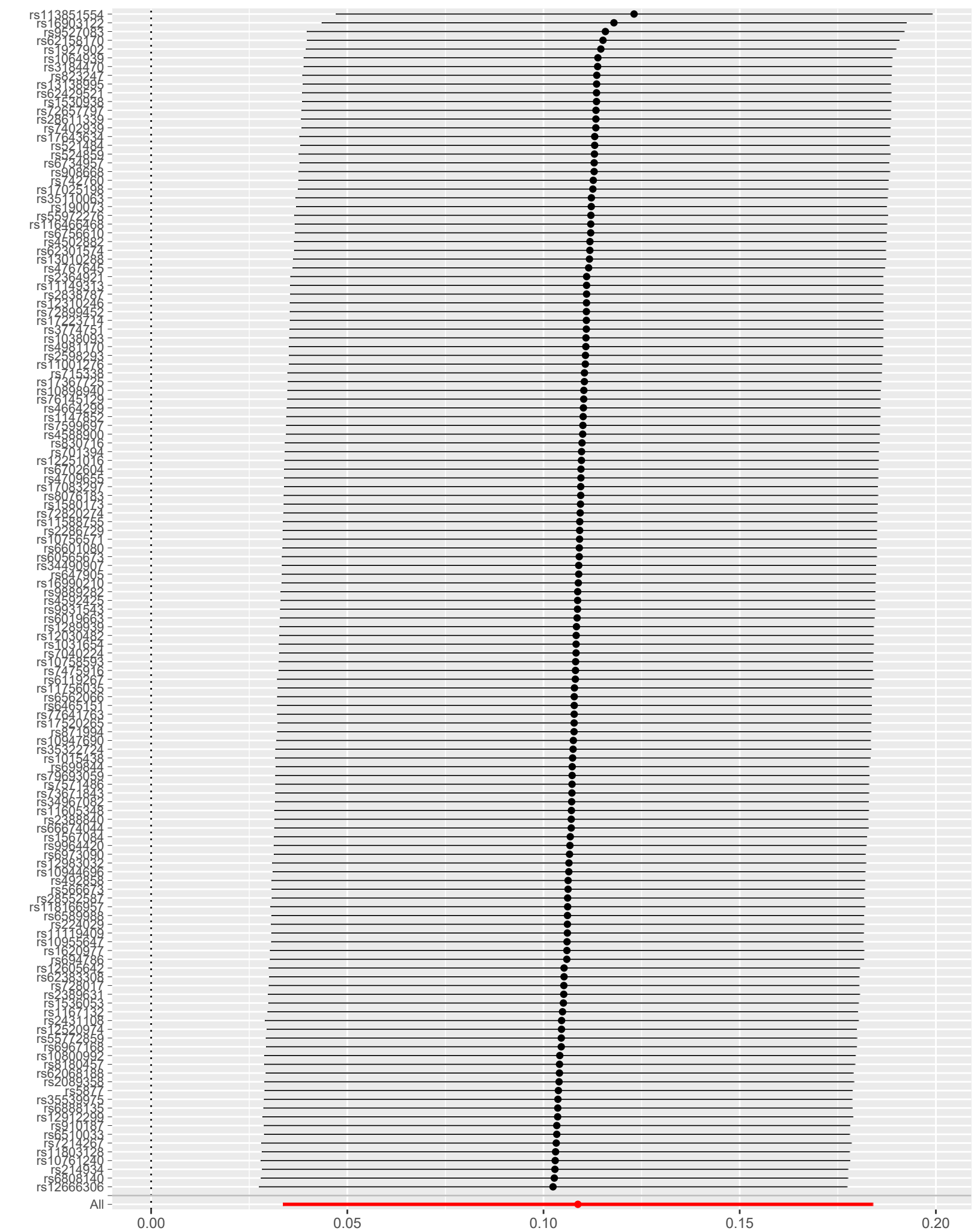
0.2
0.4
0.6
0.8
MR leave−one−out sensitivity analysis for
'Number of drinks per week' on 'SCZ'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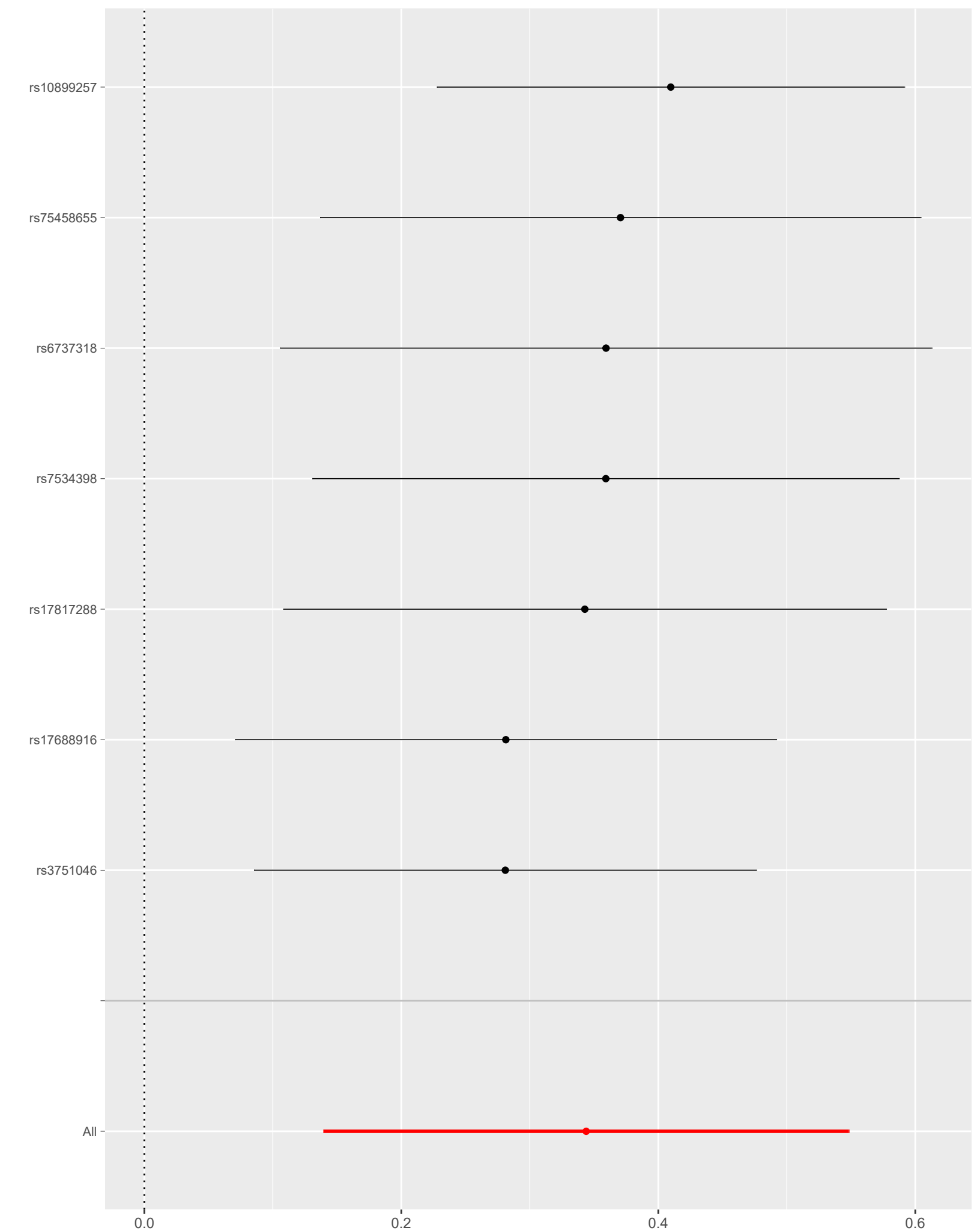
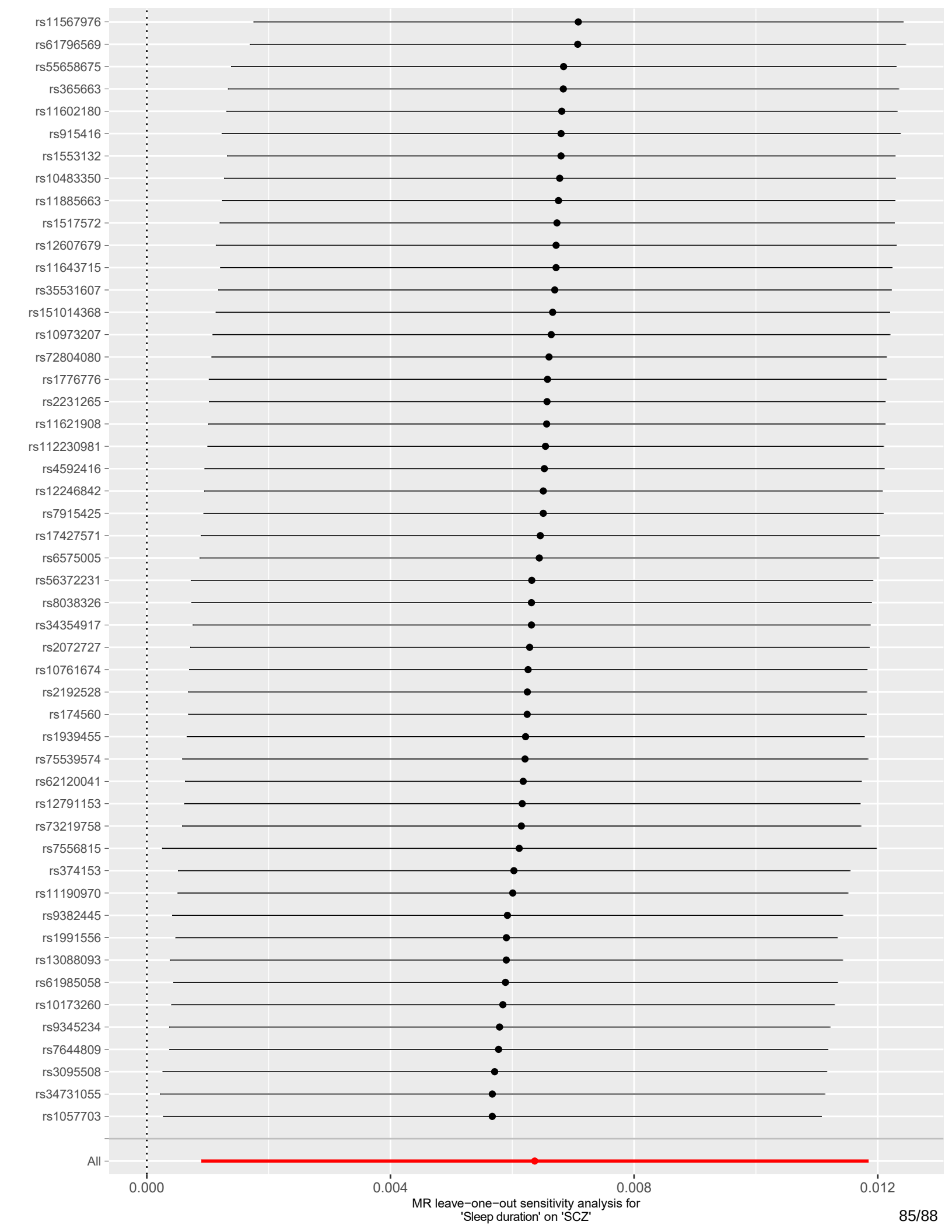
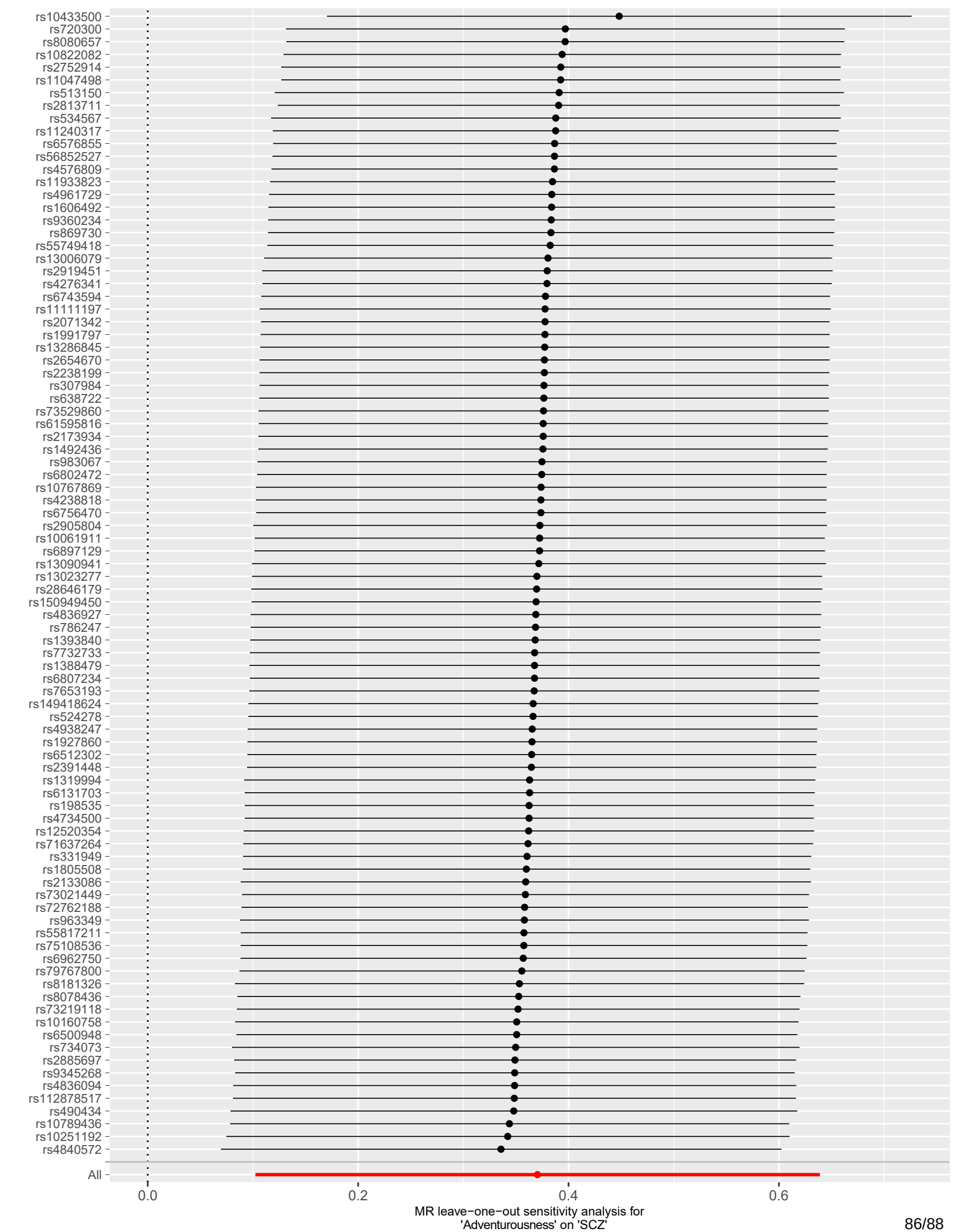
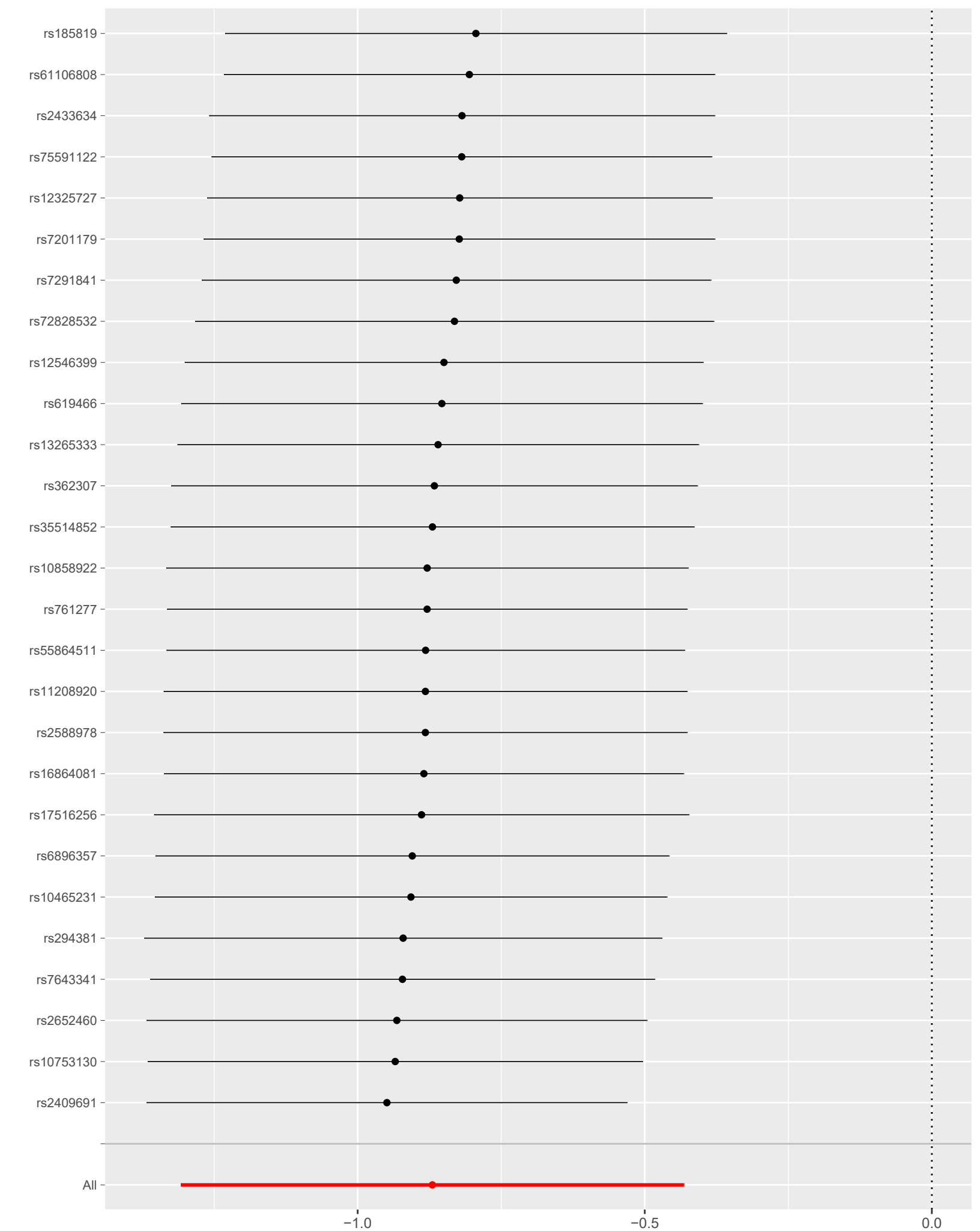
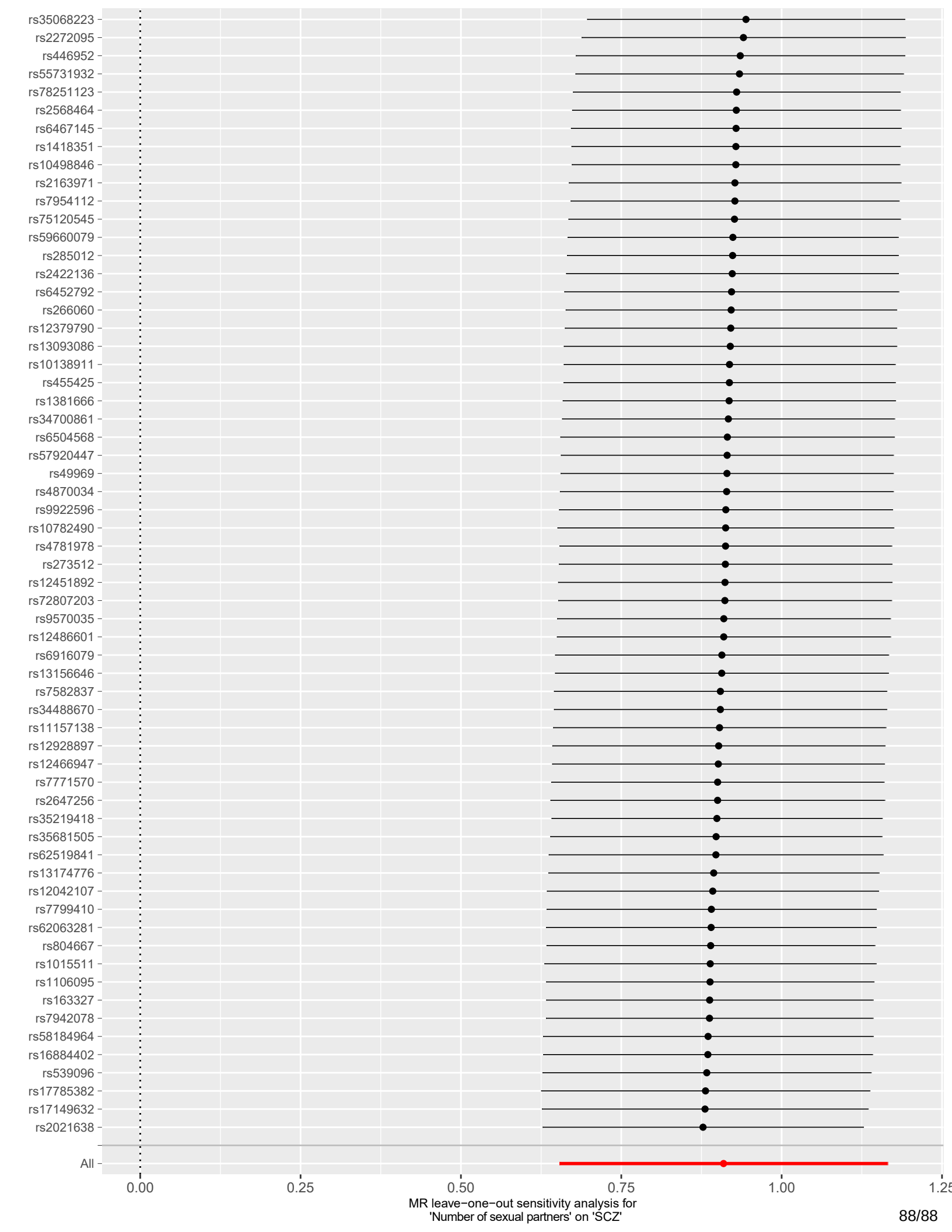
rs5877
rs35539975
rs6888135
rs12912299
rs910187
rs6510033
rs7214287
rs11803758
rs10761240
rs214934
rs6808140
rs12666306
All
0.00
0.05
0.10
0.15
0.20
MR leave−one−out sensitivity analysis for
'Insomnia' on 'SCZ'


rs10899257
rs75458655
rs6737318
rs7534398
rs17817288
rs17688916
rs3751046
All
0.0
0.2
0.4
0.6
MR leave−one−out sensitivity analysis for
'Long sleep duration' on 'SCZ'


rs11567976
rs61796569
rs55658675
rs365663
rs11602180
rs915416
rs1553132
rs10483350
rs11885663
rs1517572
rs12607679
rs11643715
rs35531607
rs151014368
rs10973207
rs72804080
rs1776776
rs2231265
rs11621908
rs112230981
rs4592416
rs12246842
rs7915425
rs17427571
rs6575005
rs56372231
rs8038326
rs34354917
rs2072727
rs10761674
rs2192528
rs174560
rs1939455
rs75539574
rs62120041
rs12791153
rs73219758
rs7556815
rs374153
rs11190970
rs9382445
rs1991556
rs13088093
rs61985058
rs10173260
rs9345234
rs7644809
rs3095508
rs34731055
rs1057703
All
0.000
0.004
0.008
0.012
MR leave−one−out sensitivity analysis for
'Sleep duration' on 'SCZ'


rs10433500
rs720300
rs8080657
rs10822082
rs2752914
rs11047498
rs513150
rs2813711
rs534567
rs11240317
rs6576855
rs56852527
rs4576809
rs11933823
rs4961729
rs1606492
rs9360234
rs869730
rs55749418
rs13006079
rs2919451
rs4276341
rs6743594
rs11111197
rs2071342
rs1991797
rs13286845
rs2654670
rs2238199
rs307984
rs638722
rs73529860
rs61595816
rs2173934
rs1492436
rs983067
rs6802472
rs10767869
rs4238818
rs6756470
rs2905804
rs10061911
rs6897129
rs13090941
rs13023277
rs28646179
rs150949450
rs4836927
rs786247
rs1393840
rs7732733
rs1388479
rs6807234
rs7653193
rs149418624
rs524278
rs4938247
rs1927860
rs6512302
rs2391448
rs1319994
rs6131703
rs198535
rs4734500
rs12520354
rs71637264
rs331949
rs1805508
rs2133086
rs73021449
rs72762188
rs963349
rs55817211
rs75108536
rs6962750
rs79767800
rs8181326
rs8078436
rs73219118
rs10160758
rs6500948
rs734073
rs2885697
rs9345268
rs4836094
rs112878517
rs490434
rs10789436
rs10251192
rs4840572
All
0.0
0.2
0.4
0.6
MR leave−one−out sensitivity analysis for
'Adventurousness' on 'SCZ'


rs185819
rs61106808
rs2433634
rs75591122
rs12325727
rs7201179
rs7291841
rs72828532
rs12546399
rs619466
rs13265333
rs362307
rs35514852
rs10858922
rs761277
rs55864511
rs11208920
rs2588978
rs16864081
rs17516256
rs6896357
rs10465231
rs294381
rs7643341
rs2652460
rs10753130
rs2409691
All
−1.0
−0.5
0.0
MR leave−one−out sensitivity analysis for
'Automobile speeding propensity' on 'SCZ'


rs35068223
rs2272095
rs446952
rs55731932
rs78251123
rs2568464
rs6467145
rs1418351
rs10498846
rs2163971
rs7954112
rs75120545
rs59660079
rs285012
rs2422136
rs6452792
rs266060
rs12379790
rs13093086
rs10138911
rs455425
rs1381666
rs34700861
rs6504568
rs57920447
rs49969
rs4870034
rs9922596
rs10782490
rs4781978
rs273512
rs12451892
rs72807203
rs9570035
rs12486601
rs6916079
rs13156646
rs7582837
rs34488670
rs11157138
rs12928897
rs12466947
rs7771570
rs2647256
rs35219418
rs35681505
rs62519841
rs13174776
rs12042107
rs7799410
rs62063281
rs804667
rs1015511
rs1106095
rs163327
rs7942078
rs58184964
rs16884402
rs539096
rs17785382
rs17149632
rs2021638
All
0.00
0.25
0.50
0.75
1.00
1.25
MR leave−one−out sensitivity analysis for
'Number of sexual partners' on 'SCZ'
88/88