

Supplementary Introduction for the Mendelian Randomization Approach

In recent years, the Mendelian randomization (MR) approach has been widely utilized to investigate the risk factors of diseases (Smith and Ebrahim, 2003). The concept of MR was initially proposed by Katan in 1986 and further developed by others, introducing instrumental variables (IVs) from econometrics (Katan, 1986). Within the MR framework, genetic variants serve as IVs to represent the exposure phenotypes of interest. If a genotype determines a certain phenotype, which in turn leads to the onset of a specific disease, then it can be inferred that the genotype influences the disease through the phenotype (Thomas and Conti, 2004). Due to the random assortment at meiosis and fixed allocation at conception for genetic variants, the MR design is less susceptible to biases from confounders and reverse causality. Therefore, genetic variations (single nucleotide polymorphisms, SNPs) can be utilized as IVs to deduce causal relationships between phenotypes and disease risk (Burgess et al., 2013). IVs in the MR framework must satisfy three assumptions: i) robust association with the exposure phenotype; ii) no association with potential confounders; iii) influence on the outcome solely through the exposure phenotype (Emdin et al., 2017). The first assumption is known as the 'relevance' assumption, while the second ('exclusiveness') and third ('independence') assumptions together are referred to as independence from horizontal pleiotropy. Horizontal pleiotropy, also known as 'biological pleiotropy', occurs when an SNP is associated with multiple exposure phenotypes and affects the outcome independently of the risk factor but through other pathways. Violation of these fundamental assumptions can introduce bias in the MR analysis. To meet the first assumption, single nucleotide polymorphisms (SNPs) should be strongly associated with the exposure phenotype at genome-wide significance ($p < 5 \times 10^{-8}$) (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 Mendelian randomization (MR)-Egger regression can be used to detect horizontal pleiotropy. Specifically, an intercept with a p-value > 0.05 suggests the rejection of the 'non-zero intercept' hypothesis, indicating no pleiotropy detected (Burgess and Thompson, 2017).

The present work conducted 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 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 SNP quality control and complementary statistical methods were employed to detect and correct any potential pleiotropy.

References

- Burgess, S., Butterworth, A., Thompson, S.G., 2013. Mendelian randomization analysis with multiple genetic variants using summarized data. *Genet. Epidemiol.* 37, 658-665.
- Burgess, S., Thompson, S.G., 2011. Avoiding bias from weak instruments in Mendelian randomization studies. *Int. J. Epidemiol.* 40, 755-764.
- Burgess, S., Thompson, S.G., 2017. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur. J. Epidemiol.* 32, 377-389.
- Emdin, C.A., Khera, A.V., Kathiresan, S., 2017. Mendelian Randomization. *JAMA* 318, 1925-1926.
- Katan, M.B., 1986. Apolipoprotein E isoforms, serum cholesterol, and cancer. *Lancet* i, 507-508.
- Smith, G.D., Ebrahim, S., 2003. 'Mendelian randomization': can genetic epidemiology contribute to understanding environmental determinants of disease? *Int. J. Epidemiol.* 32, 1-22.
- Thomas, D.C., Conti, D.V., 2004. Commentary: the concept of 'Mendelian Randomization'. *Int. J. Epidemiol.* 33, 21-25.

Supplementary Table S1. Detailed description of exposure phenotypes in the present study.

Phenotypes	PMID	Sample size	Ancestry	Definition
Education attainment	30038396	257,841	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.)
Physical activity				
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	34737426	453,838	European(U.K.)	<p>Participants were asked "How many times in the last 4 weeks did you go walking for pleasure?"</p> <p>SELECT one of 8 from</p> <p>1 :Once in the last 4 weeks</p> <p>2 :2-3 times in the last 4 weeks</p> <p>3 :Once a week</p> <p>4 :2-3 times a week</p> <p>5 :4-5 times a week</p> <p>6 :Every day</p> <p>-1 :Do not know</p> <p>-3 :Prefer not to answer</p> <p>And"Each time you went walking for pleasure, about how long did you spend doing it?"</p> <p>SELECT one of 9 from</p> <p>1 :Less than 15 minutes</p> <p>2 :Between 15 and 30 minutes</p> <p>3 :Between 30 minutes and 1 hour</p> <p>4 :Between 1 hour and 1½ hours</p> <p>5 :Between 1½ hours and 2 hours</p> <p>6 :Between 2 and 3 hours</p> <p>7 :Over 3 hours</p> <p>-1 :Do not know</p> <p>-3 :Prefer not to answer</p>

				<p>If the participant activated the Help button they were shown the message:</p> <p>Strenuous sports include sports that make you sweat or breathe hard.</p> <p>Heavy DIY includes chopping wood, home or car maintenance, lifting heavy objects or using heavy tools.</p> <p>If the participant are unsure, please provide an estimate or select Do not know.</p>
--	--	--	--	--

<p>Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)</p>	<p>34737426</p>	<p>453,838</p>	<p>European(U.K.)</p>	<p>Participants were asked "How many times in the last 4 weeks did you do other exercises such as swimming, cycling, keep fit?"</p> <p>And"Each time you did other exercises such as swimming, cycling, keep fit, about how long did you spend doing them?"</p> <p>It was collected from all participants who indicated that they spent time doing other exercises (e.g. swimming, cycling, keep fit, bowling) in the previous 4 weeks, as defined by their answers to Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)</p> <p>If the participant activated the Help button they were shown the message:</p> <p>Strenuous sports include sports that make you sweat or breathe hard.</p> <p>Heavy DIY includes chopping wood, home or car maintenance, lifting heavy objects or using heavy tools.</p> <p>If the participant are unsure, please provide an estimate or select Do not know.</p>
<p>Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)</p>	<p>34737426</p>	<p>453,838</p>	<p>European(U.K.)</p>	<p>Participants were asked "How many times in the last 4 weeks did you do strenuous sports?"</p> <p>And"Each time you did strenuous sports, about how long did you spend doing it?"</p> <p>It was collected from all participants who indicated that they spent time doing strenuous sports in the previous 4 weeks, as defined by their answers to Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)</p> <p>If the participant activated the Help button they were shown the message:</p> <p>Strenuous sports include sports that make you sweat or breathe hard.</p> <p>Heavy DIY includes chopping wood, home or car maintenance, lifting heavy objects or using heavy tools.</p>

				<p>If the participant are unsure, please provide an estimate or select Do not know.</p>
<p>Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)</p>	34737426	453,838	European(U.K.)	<p>Participants were asked "How many times in the last 4 weeks did you do light DIY?"</p> <p>And"Each time you did light DIY, about how long did you spend doing it?"</p> <p>It was collected from all participants who indicated that they spent time doing light DIY (e.g. pruning, watering the lawn) in the previous 4 weeks, as defined by their answers to Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)</p> <p>If the participant activated the Help button they were shown the message:</p> <p>Strenuous sports include sports that make you sweat or breathe hard.</p> <p>Heavy DIY includes chopping wood, home or car maintenance, lifting heavy objects or using heavy tools.</p> <p>If the participant are unsure, please provide an estimate or select Do not know.</p>

Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	34737426	453,838	European(U.K.)	<p>Participants were asked "How many times in the last 4 weeks did you do heavy DIY?"</p> <p>And"Each time you did heavy DIY, about how long did you spend doing it?"</p> <p>It was collected from all participants who indicated that they spent time doing heavy DIY (e.g. weeding, lawn mowing, carpentry, digging) in the previous 4 weeks, as defined by their answers to Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)</p> <p>If the participant activated the Help button they were shown the message:</p> <p>Strenuous sports include sports that make you sweat or breathe hard.</p> <p>Heavy DIY includes chopping wood, home or car maintenance, lifting heavy objects or using heavy tools.</p> <p>If the participant are unsure, please provide an estimate or select Do not know.</p>
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

				<p>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?”</p>
Smoking initiation	30643251	1,232,091	European	<p>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 everyday for at least a month?” or “Have you ever smoked regularly?”.</p>
Sleeping behaviors				
Insomnia	ukb-b-3957	462,341	European	<p>UK biobank phenotype:</p> <p>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.</p>

Long sleep duration	30846698	339,926 (Female 56.1%; 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	446,118 (Female 53.1%; 106,192 cases vs. 305,742 controls).	European	Short sleep duration was defined as sleeping for 6hor less relative to 7-8h sleep duration (set as controls).
Sleep duration	30846698	446,118 (Female 54.1%)	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 hor 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.
--	--	--	--	---

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

Supplementary Table SII. Detailed descriptions for GWAS data of endometriosis

Disorder	Endometriosis
Total sample sizes	16,588 cases/111,583 controls
Percentage of European	100%
Diagnosis criteria	<p>Using structured</p> <p>diagnostic instruments,</p> <p>a lifetime diagnosis of</p> <p>endometriosis was established</p> <p>on the basis of international</p> <p>consensus criteria (ICD-8/9/10).</p>

GWAS, genome-wide association study; ICD, International Classification of Diseases.

Supplementary Table SIII. Details of SNPs filtering procedures.

Exposure phenotypes	Number of SNPs available ¹	SNP filtering (number of SNPs remained ²)			
		Step 1	endometriosis		
			Step 2	Step 3	Step 4
Educational attainment	146	124	121	98	95
Physical activity					
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	20	13	13	11	9
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	17	12	12	11	11
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	8	4	3	2	2
Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)	7	6	6	5	5
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	7	6	5	5	5
Smoking behaviors					
Age of initiation of regular smoking	7	6	6	6	6
Number of cigarettes per day	23	16	16	15	15
Smoking cessation	8	7	7	6	6
Smoking initiation	96	74	73	61	60
Sleeping behaviors					
Insomnia	42	39	39	30	30
Long sleep duration	10	10	9	7	7
Short sleep duration	26	16	16	14	14

Sleep duration	71	62	59	51	50
----------------	----	----	----	----	----

SNP, single nucleotide polymorphisms;

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.

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

SNPs	Exposures
rs2014830	Educational attainment
rs314280	Menarche
rs9607805	Insomnia
rs1691471	Physical activity
rs56180486	Educational attainment
rs11989077	Physical activity
rs11774212	Educational attainment
rs479018	Educational attainment
rs11793831	Insomnia
rs11693702	Smoking
rs26046	Smoking initiation
rs10129426	Insomnia
rs11605348	Insomnia
rs9930063	Smoking initiation
rs4937860	Insomnia
rs11915747	Educational attainment
rs11725618	educational attainment
rs7951365	Smoking cessation
rs7928017	Educational attainment
rs56113850	Smoking cessation
rs2424888	Insomnia
rs12133063	Educational attainment
rs1004787	Smoking cessation, Educational attainment
rs1565735	Smoking cessation
rs9651873	Smoking cessation
rs3741499	Educational attainment
rs9540731	Educational attainment
rs11643113	Insomnia

rs76608582	Educational attainment
rs6141759	Educational attainment
rs2186122	Smoking initiation
rs12567114	Educational attainment
rs2820313	Educational attainment
rs1380703	Sleep duration
rs2014830	Educational attainment, Insomnia
rs17005118	Insomnia
rs13107325	Insomnia, Educational attainment
rs12518468	Educational attainment
rs12963463	Insomnia
rs12567114	Sleep duration, Educational attainment
rs75539574	Sleep duration
rs2079070	Short sleep duration
rs7915425	Insomnia
rs4767550	Insomnia
rs11621908	Short sleep duration
rs205024	Sleep duration
rs12042107	Educational attainment, Smoking initiation
rs2246873	Educational attainment
rs1927902	Insomnia
rs1939153	Smoking initiation
rs613872	Short sleep duration, Educational attainment
rs362307	Educational attainment
rs13135092	Insomnia, Educational attainment
rs12571549	Educational attainment
rs35683183	Educational attainment

SNP, single nucleotide polymorphisms.

Supplementary Table SV. 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 than the IVW and weighted median methods, but is larger than that of MR Egger regression.

Supplementary Table SVI. Mendelian randomization estimates for the association of life behaviors with endometriosis derived from different models.

Exposures	Outcomes	Number of SNPs	Number of proxies	Inverse variance weighted		MR-Egger		Weighted median		Weighted mode		MR Steiger Test	
				OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	Causal direction	p
Educational attainment	Endometriosis	95	0	0.85(0.73 - 1.00)	0.050	0.91(0.42 - 1.98)	0.815	0.95(0.77 - 1.15)	0.591	1.03(0.61 - 1.74)	0.918	TRUE	0.203
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	Endometriosis	9	0	1.07(0.64 - 1.78)	0.809	3.97(0.20 - 79.75)	0.398	1.12(0.69 - 1.83)	0.645	1.19(0.50 - 2.86)	0.707	TRUE	6.692
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	Endometriosis	9	0	0.65(0.38 - 1.09)	0.017	0.06(0.001 - 3.87)	0.228	0.61(0.38 - 0.97)	0.037	0.54(0.26 - 1.09)	0.124	TRUE	0.486
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	Endometriosis	2	0	0.90(0.62 - 1.32)	0.606	NA	NA	NA	NA	NA	NA	TRUE	0.281
Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)	Endometriosis	5	0	1.11(0.68 - 1.79)	0.679	1.756(0.29 - 10.54)	0.581	0.99(0.56 - 1.74)	0.970	0.94 (0.44 - 1.99)	0.875	TRUE	0.204
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	Endometriosis	5	0	1.20 (0.79 - 1.81)	0.395	2.94 (0.05 - 169.86)	0.638	1.14 (0.69 - 1.88)	0.619	1.03(0.48 - 2.20)	0.946	TRUE	0.254
Age of initiation of regular smoking	Endometriosis	6	0	1.60 (0.86 - 2.96)	0.138	2.49 (0.45 - 13.71)	0.354	1.75 (0.84 - 3.62)	0.132	2.01(0.67 - 6.06)	0.270	TRUE	0.296
Number of cigarettes per day	Endometriosis	15	0	1.21 (0.98 - 1.49)	0.080	1.45(1.03 - 2.06)	0.054	1.34 (1.04 - 1.72)	0.021	1.34(1.03 - 1.73)	0.047	TRUE	0.140
Smoking cessation	Endometriosis	6	0	0.48(0.24 - 0.96)	0.038	0.35(0.03 - 4.64)	0.472	0.84(0.35 - 2.00)	0.698	0.91 (0.20 - 4.05)	0.902	TRUE	0.383
Smoking initiation	Endometriosis	60	0	1.08 (0.71 - 1.66)	0.721	1.31 (0.17 - 10.31)	0.801	0.89 (0.55 - 1.43)	0.628	0.79 (0.26 - 2.43)	0.678	TRUE	0.681
Insomnia	Endometriosis	30	0	1.48 (0.94 - 2.30)	0.088	0.41 (0.13 - 1.29)	0.139	1.22 (0.65 - 2.30)	0.538	0.61 (0.22 - 1.65)	0.336	TRUE	0.329
Long sleep duration	Endometriosis	7	0	0.03 (2.77e-03 - 0.29)	0.003	0.001(1.23e-06 - 1.54)	0.125	0.02 (8.90e-04 - 0.31)	0.006	0.02 (3.36e-04 - 0.69)	0.075	TRUE	0.301

Short sleep duration	Endometriosis	14	0	1.96 (0.55 - 0.70)	0.293	2344.89(8.42 6.53e+05)	- 0.019	1.64(0.34 - 0.78)	0.554	0.28 (0.01 - 0.67)	0.477	TRUE	0.371
Sleep duration	Endometriosis	50	0	0.90 (0.68 - 1.19)	0.452	0.62(0.22 - 1.80)	0.388	0.73 (0.50 - 1.07)	0.102	0.62 (0.34 - 1.12)	0.126	TRUE	0.351

NA,not applicable.

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

Exposures	endometriosis		
	R ² (%)	F-statistics	Power (%)
Educational attainment	1.60e-02	29.79-91.51	100
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	7.27E-03	30.24-38.99	91
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	7.97E-03	30.13-53.52	100
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	8.66E-03	34.17-48.27	91
Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)	9.15E-03	29.84-80.37	99
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	7.80E-03	29.96--39.68	100
Age of initiation of regular smoking	1.06e-02	31.24-46.51	100
Number of cigarettes per day	3.11e-02	29.93-965.05	100
Smoking cessation	7.77e-03	19.55-74.34	100
Smoking initiation	2.71e-03	15.48---105.63	97
Insomnia	9.75e-03	29.85-199.34	100
Long sleep duration	1.15e-02	29.89-52.98	100
Short sleep duration	8.25e-03	29.90-77.04	100
Sleep duration	9.04e-03	29.62--220.87	99

R² 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 $R^2 \times (N - 2) / (1 - R^2)$.

Supplementary Table SVIII. Heterogeneity and pleiotropy assessment for all results.

Exposures	Outcomes	Directional pleiotropy		Heterogeneity test					
		MR-Egger		MR-Egger			Inverse-variance weighted		
		Intercept	P	Q	Q_df	Q_pval	Q	Q_df	Q_pval
Educational attainment	endometriosis	-0.0014	0.86	132.67	93	0.004	132.71	94	0.005
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	-0.0392	0.41	20.70	7	0.004	22.95	8	0.003
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	0.0678	0.30	18.38	7	0.010	21.6950	8	0.005
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	endometriosis	NA	NA	NA	NA	NA	0.7233606	1	0.395
Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)	endometriosis	-0.0147	0.64	0.82	3	0.844	1.10	4	0.894
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	endometriosis	-0.0259	0.69	1.65	3	0.648	1.84	4	0.765
Age of initiation of regular smoking	endometriosis	-0.0112	0.61	6.24	4	0.182	6.71	5	0.243
Number of cigarettes per day	endometriosis	-0.0014	0.86	132.67	93	0.004	132.71	94	0.005
Smoking cessation	endometriosis	0.0058	0.82	5.87	4	0.209	5.96	5	0.311
Smoking initiation	endometriosis	-0.0022	0.86	122.35	58	1.69e-06	122.42	59	2.45e-06
Insomnia	endometriosis	0.0157	0.03	27.09	28	0.513	32.63	29	0.293
Long sleep duration	endometriosis	0.0191	0.41	2.77	5	0.735	3.57	6	0.734
Short sleep duration	endometriosis	-0.0476	0.03	11.41	12	0.494	17.73	13	0.168
Sleep duration	endometriosis	0.0063	0.49	66.43	48	0.040	67.11	49	0.044

NA,not applicable.

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

Phenotype in the present study	Outcome	SNP	Confounders
insomnia	endometriosis	rs2014830	Years of educational attainment
insomnia	endometriosis	rs705219	Smoking status
insomnia	endometriosis	rs314280	Menarche (age at onset)
Short sleep duration	endometriosis	rs2186122	Smoking initiation
Short sleep duration	endometriosis	rs12567114	Educational attainment
Short sleep duration	endometriosis	rs2820313	Educational attainment (years of education)
Short sleep duration	endometriosis	rs1380703	Sleep duration (oversleepers vs undersleepers)
Short sleep duration	endometriosis	rs2014830	Educational attainment (years of education), insomnia
Short sleep duration	endometriosis	rs17005118	Insomnia
Short sleep duration	endometriosis	rs13107325	Body mass index, alcohol consumption (drinks per week), insomnia, educational attainment (years of education)
Short sleep duration	endometriosis	rs12518468	Educational attainment
Short sleep duration	endometriosis	rs2517827	Body mass index
Short sleep duration	endometriosis	rs12963463	Insomnia
Sleep duration	endometriosis	rs12567114	Short sleep duration, educational attainment
Sleep duration	endometriosis	rs75539574	Short sleep duration
Sleep duration	endometriosis	rs2079070	Short sleep duration
Sleep duration	endometriosis	rs7915425	Insomnia
Sleep duration	endometriosis	rs4767550	Insomnia
Sleep duration	endometriosis	rs11621908	Short sleep duration
Sleep duration	endometriosis	rs9940128	Body mass index
Sleep duration	endometriosis	rs205024	Short sleep duration
Sleep duration	endometriosis	rs2072727	chronotype measurement Morning person
Age of initiation of regular smoking	endometriosis	rs11915747	Educational attainment (years of education), body mass index, Whole body fat mass
Number of cigarettes per day	endometriosis	rs11725618	Cognitive ability, years of educational attainment or schizophrenia
Number of cigarettes per day	endometriosis	rs215600	Cognitive ability

Number of cigarettes per day	endometriosis	rs7951365	Smoking cessation
Number of cigarettes per day	endometriosis	rs7928017	Educational attainment (years of education)
Number of cigarettes per day	endometriosis	rs56356382	Body mass index, Predicted visceral adipose tissue
Number of cigarettes per day	endometriosis	rs56113850	Smoking cessation, chronotype
Number of cigarettes per day	endometriosis	rs2424888	Insomnia
Smoking cessation	endometriosis	rs9607805	Insomnia
Smoking initiation	endometriosis	rs301806	Ease of getting up in the morning, waist-hip ratio, systemic lupus erythematosus (MTAG), irritable bowel syndrome (MTAG)
Smoking initiation	endometriosis	rs6690398	Body mass index
Smoking initiation	endometriosis	rs7525548	Age at first sexual intercourse
Smoking initiation	endometriosis	rs12133063	Noncognitive aspects of educational attainment
Smoking initiation	endometriosis	rs2046850	Lifetime smoking
Smoking initiation	endometriosis	rs1004787	Alcohol consumption, smoking cessation (MTAG), alcohol consumption (drinks per week), educational attainment
Smoking initiation	endometriosis	rs993700	Age at first sexual intercourse
Smoking initiation	endometriosis	rs4352629	Ayurvedic vata prakriti specific rheumatoid arthritis
Smoking initiation	endometriosis	rs4044321	Lifetime smoking
Smoking initiation	endometriosis	rs10498846	Number of sexual partners
Smoking initiation	endometriosis	rs11768481	Lifetime smoking index
Smoking initiation	endometriosis	rs1565735	Smoking cessation, lifetime smoking
Smoking initiation	endometriosis	rs4543592	Lifetime smoking index
Smoking initiation	endometriosis	rs6265	Body mass index, waist-hip ratio, lifetime smoking
Smoking initiation	endometriosis	rs9651873	Smoking cessation
Smoking initiation	endometriosis	rs3741499	Educational attainment (years of education)
Smoking initiation	endometriosis	rs7969559	Lifetime smoking
Smoking initiation	endometriosis	rs9540731	Educational attainment
Smoking initiation	endometriosis	rs11643113	Insomnia
Smoking initiation	endometriosis	rs62098013	Lifetime smoking index
Smoking initiation	endometriosis	rs76608582	Educational attainment (years of education), lifetime smoking index
Smoking initiation	endometriosis	rs6141759	Educational attainment

Educational attainment	endometriosis	rs2352974	Waist-hip ratio
Educational attainment	endometriosis	rs1906252	Household income
Educational attainment	endometriosis	rs13107325	Body mass index
Educational attainment	endometriosis	rs11793831	Insomnia symptoms (never/rarely vs. sometimes/usually)
Educational attainment	endometriosis	rs8054299	Waist-hip ratio
Educational attainment	endometriosis	rs34811474	Menarche (age at onset), body mass index, age at first sexual intercourse
Educational attainment	endometriosis	rs10189857	Leisure screen time
Educational attainment	endometriosis	rs2239647	Body mass index, predicted visceral adipose tissue, whole body fat mass
Educational attainment	endometriosis	rs3735478	Ease of getting up in the morning
Educational attainment	endometriosis	rs11693702	Smoking status
Educational attainment	endometriosis	rs26046	Smoking initiation
Educational attainment	endometriosis	rs10129426	Insomnia
Educational attainment	endometriosis	rs9683585	chronotype measurement
Educational attainment	endometriosis	rs11079849	Body mass index, drinks per week, sex hormone-binding globulin levels, body fat percentage, whole body fat mass
Educational attainment	endometriosis	rs80170948	Menarche (age at onset)
Educational attainment	endometriosis	rs11605348	Insomnia
Educational attainment	endometriosis	rs12441495	Waist-to-hip ratio adjusted for BMI
Educational attainment	endometriosis	rs6798941	Body mass index
Educational attainment	endometriosis	rs9930063	Smoking initiation
Educational attainment	endometriosis	rs4937860	Insomnia
Educational attainment	endometriosis	rs7312770	Polycystic ovary syndrome, hypothyroidism
Educational attainment	endometriosis	rs11259916	Waist circumference adjusted for body mass index
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs12042107	Smoking status (ever vs never smokers), educational attainment, smoking initiation, number of sexual partners in opposite-sex sexual behavior, number of sexual partners
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs2246873	Educational attainment (years of education)

Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs1927902	Insomnia
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs4755720	Menarche (age at onset) , waist-hip ratio
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs1939153	Smoking initiation
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs34898535	Waist circumference variance, hip circumference variance, body fat percentage
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	rs613872	Body mass index, educational attainment (years of education), short sleep duration
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	rs1691471	Moderate-to-vigorous intensity physical activity during leisure time
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	rs56180486	Educational attainment (years of education)
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	rs11989077	Moderate-to-vigorous intensity physical activity during leisure time (MTAG)
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	rs11774212	Educational attainment
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	rs479018	Educational attainment (years of education)
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	endometriosis	rs2526388	Intelligence (MTAG)
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	endometriosis	rs362307	General cognitive ability, educational attainment, drinks per week
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	endometriosis	rs13135092	Insomnia, bitter alcoholic beverage consumption, educational attainment, body mass index,whole body fat mass

Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	endometriosis	rs12571549	Educational attainment (years of education)
Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)	endometriosis	rs35626515	Body mass index, drinks per week
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	endometriosis	rs35683183	Educational attainment

SNP, single nucleotide polymorphisms.

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

Exposures	Outcomes	IVW analysis		
		OR	95% CI	<i>p</i> values
Educational attainment	endometriosis	0.85	0.73-1.00	0.050
Types of physical activity in last 4 weeks: Walking for pleasure (not as a means of transport) (UKB data field 6164_1)	endometriosis	1.07	0.64-1.78	0.809
Types of physical activity in last 4 weeks: Other exercises (eg: swimming, cycling, keep fit, bowling) (UKB data field 6164_2)	endometriosis	0.65	0.38-1.09	0.095
Types of physical activity in last 4 weeks: Strenuous sports (UKB data field 6164_3)	endometriosis	0.90	0.62-1.32	0.606
Types of physical activity in last 4 weeks: Light DIY (eg: pruning, watering the lawn) (UKB data field 6164_4)	endometriosis	1.11	0.68-1.79	0.679
Types of physical activity in last 4 weeks: Heavy DIY (eg: weeding, lawn mowing, carpentry, digging) (UKB data field 6164_5)	endometriosis	1.20	0.79-1.81	0.395
Age of initiation of regular smoking	endometriosis	1.60	0.86-2.96	0.233
Number of cigarettes per day	endometriosis	1.21	0.98-1.49	0.080
Smoking cessation	endometriosis	0.48	0.24-0.96	0.038
Smoking initiation	endometriosis	1.08	0.71-1.66	0.721
Insomnia	endometriosis	1.48	0.94-2.31	0.088
Long sleep duration	endometriosis	35.24	3.43-361.45	0.002
Short sleep duration	endometriosis	1.96	0.55-7.03	0.293
Sleep duration	endometriosis	0.90	0.68-1.19	0.452

SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

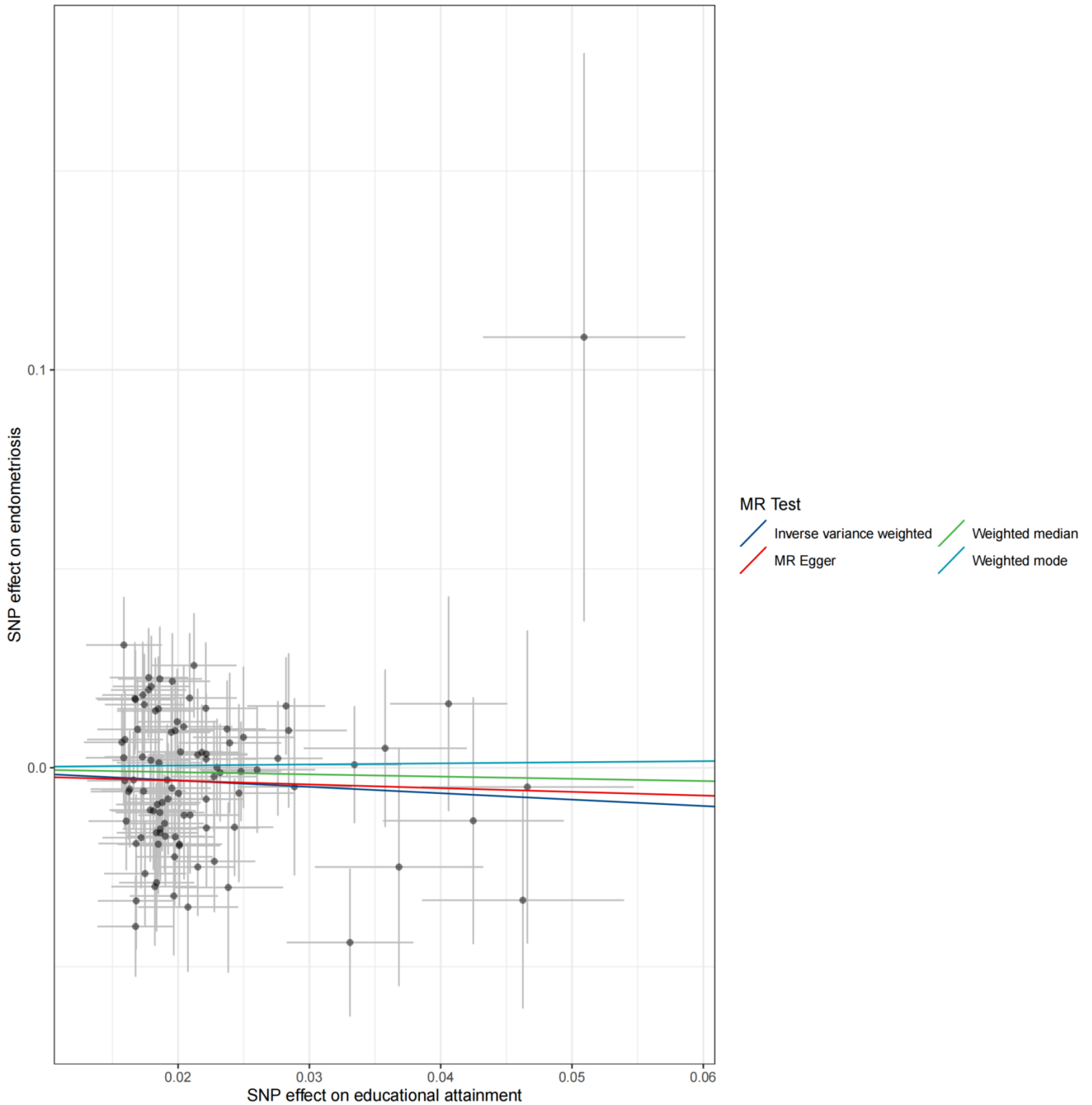
Supplementary Figure S1. Scatter plots showing robust genetic associations of life behaviors with endometriosis.

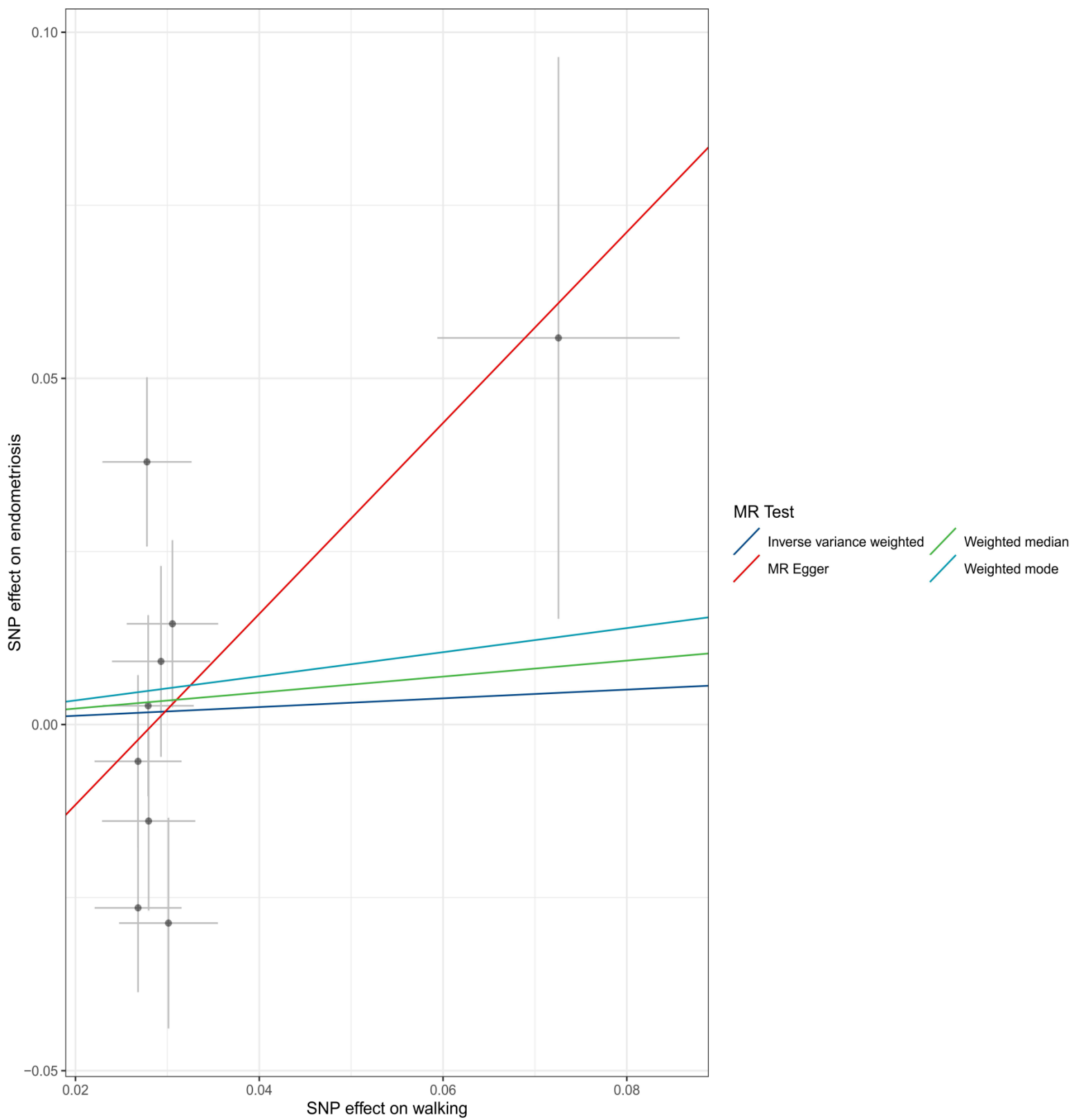
Each of the SNPs associated with exposures is represented by a black dot with the error bar depicting

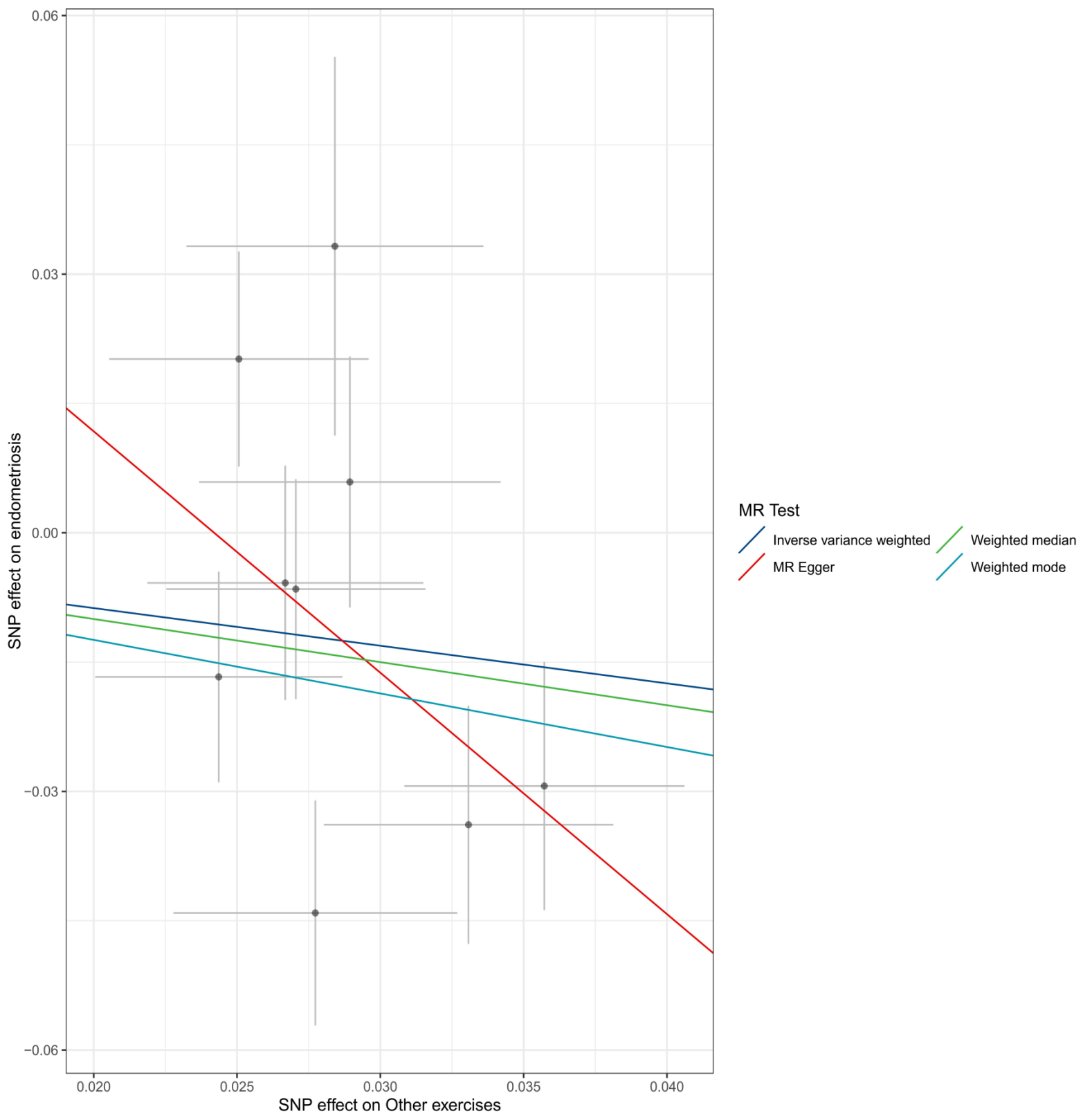
the standard error of its association with a specific exposure (horizontal) and endometriosis

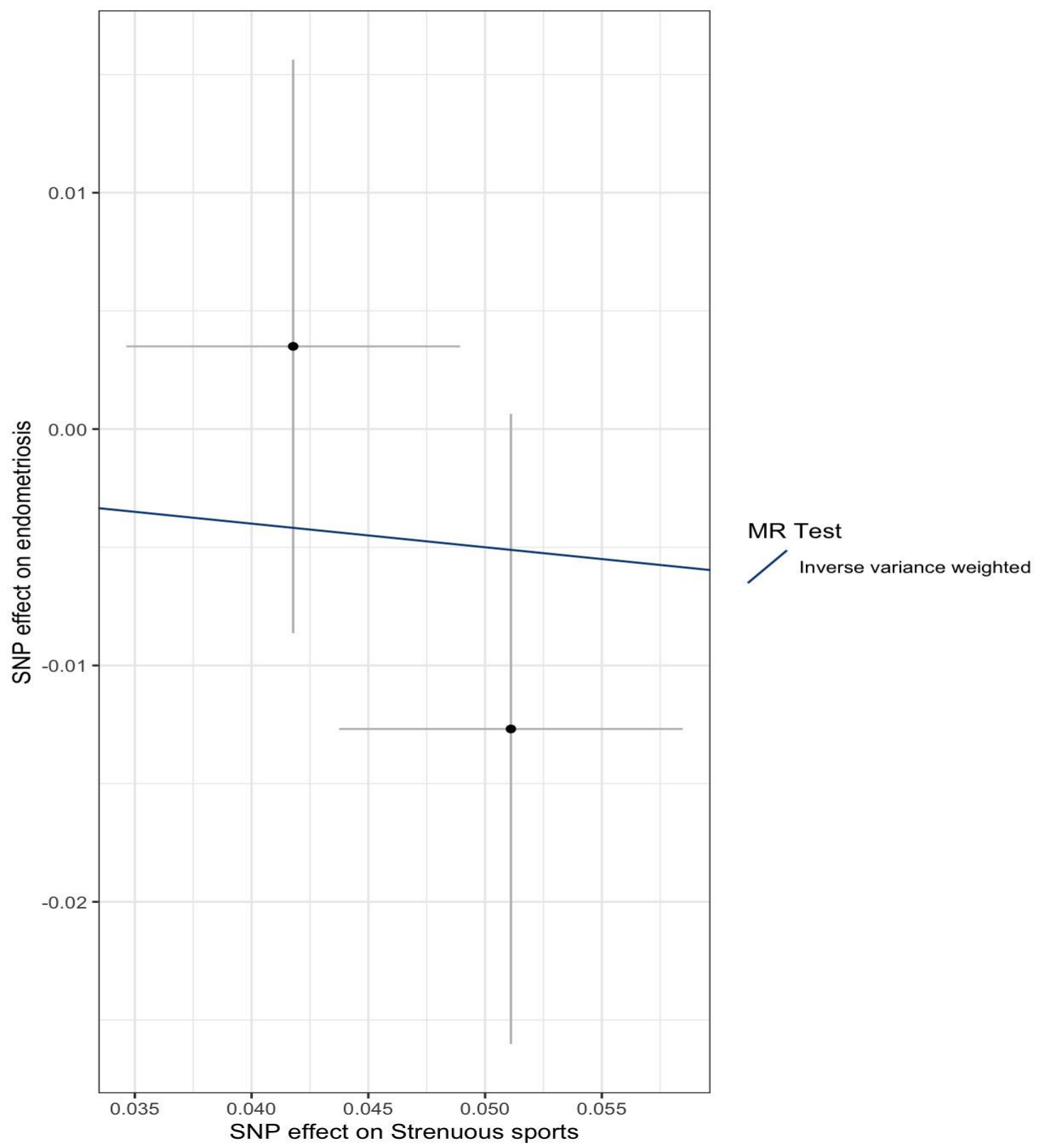
(vertical). The slopes of each line represent the causal association for each Mendelian randomization

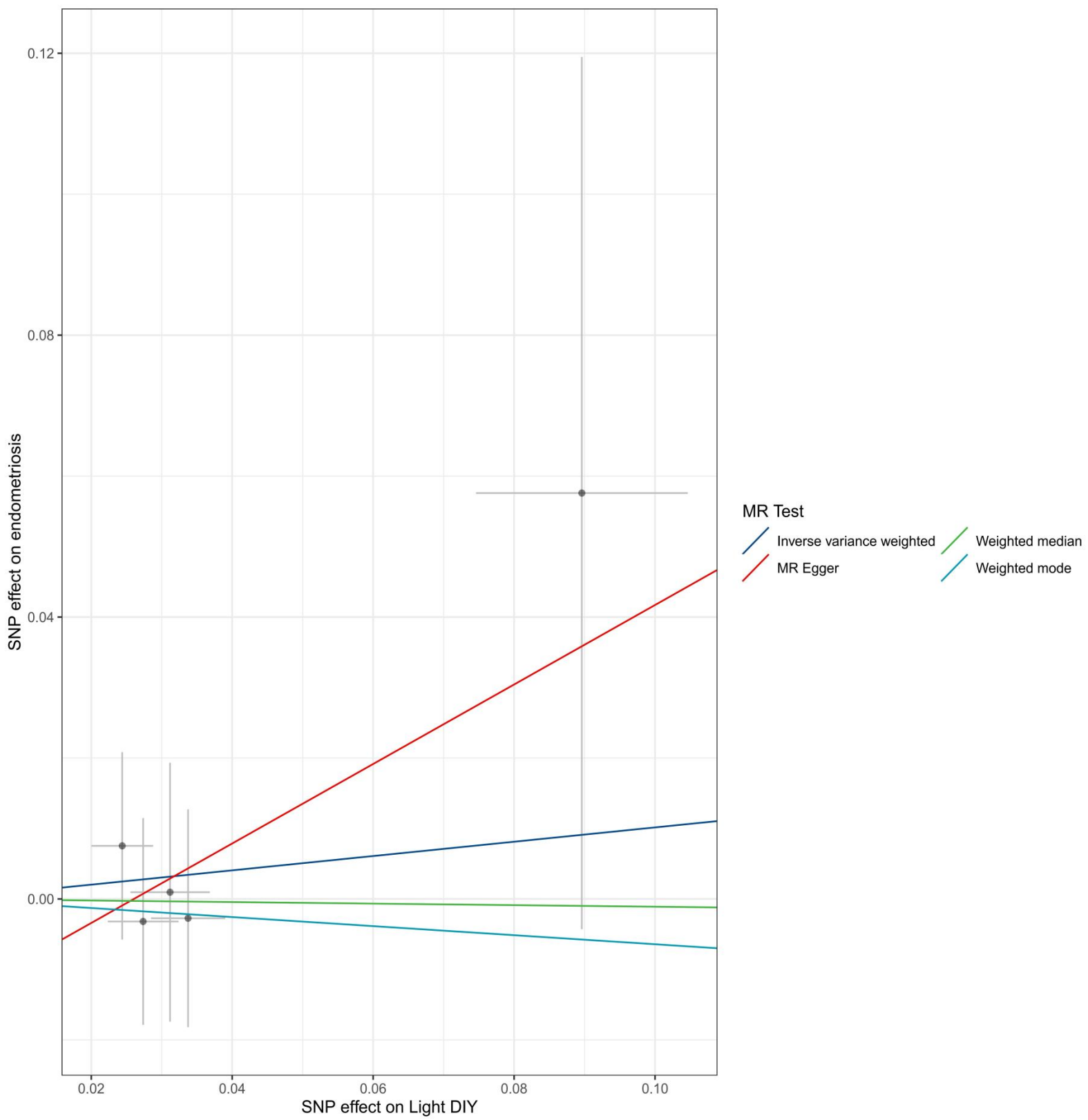
method.

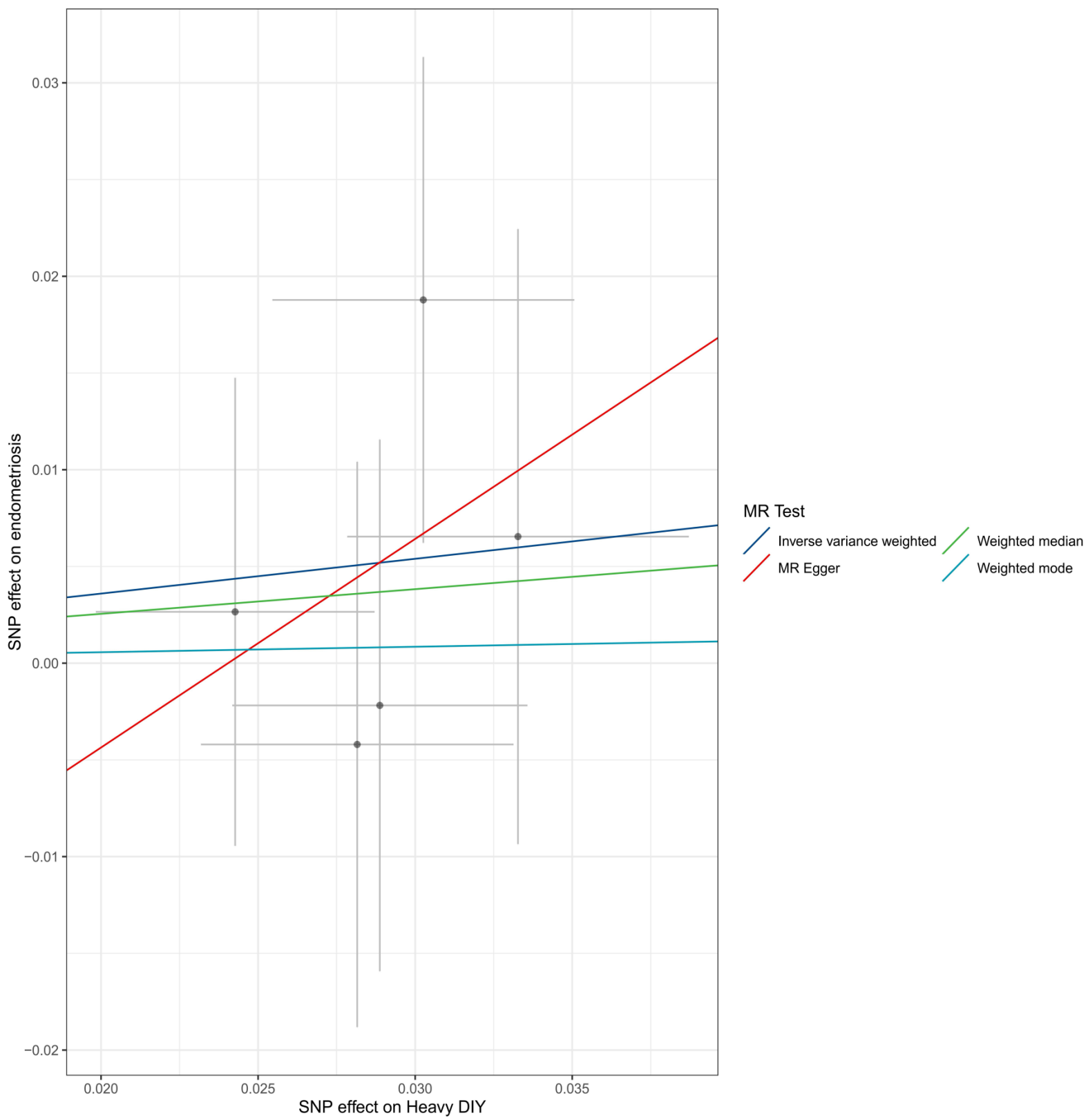


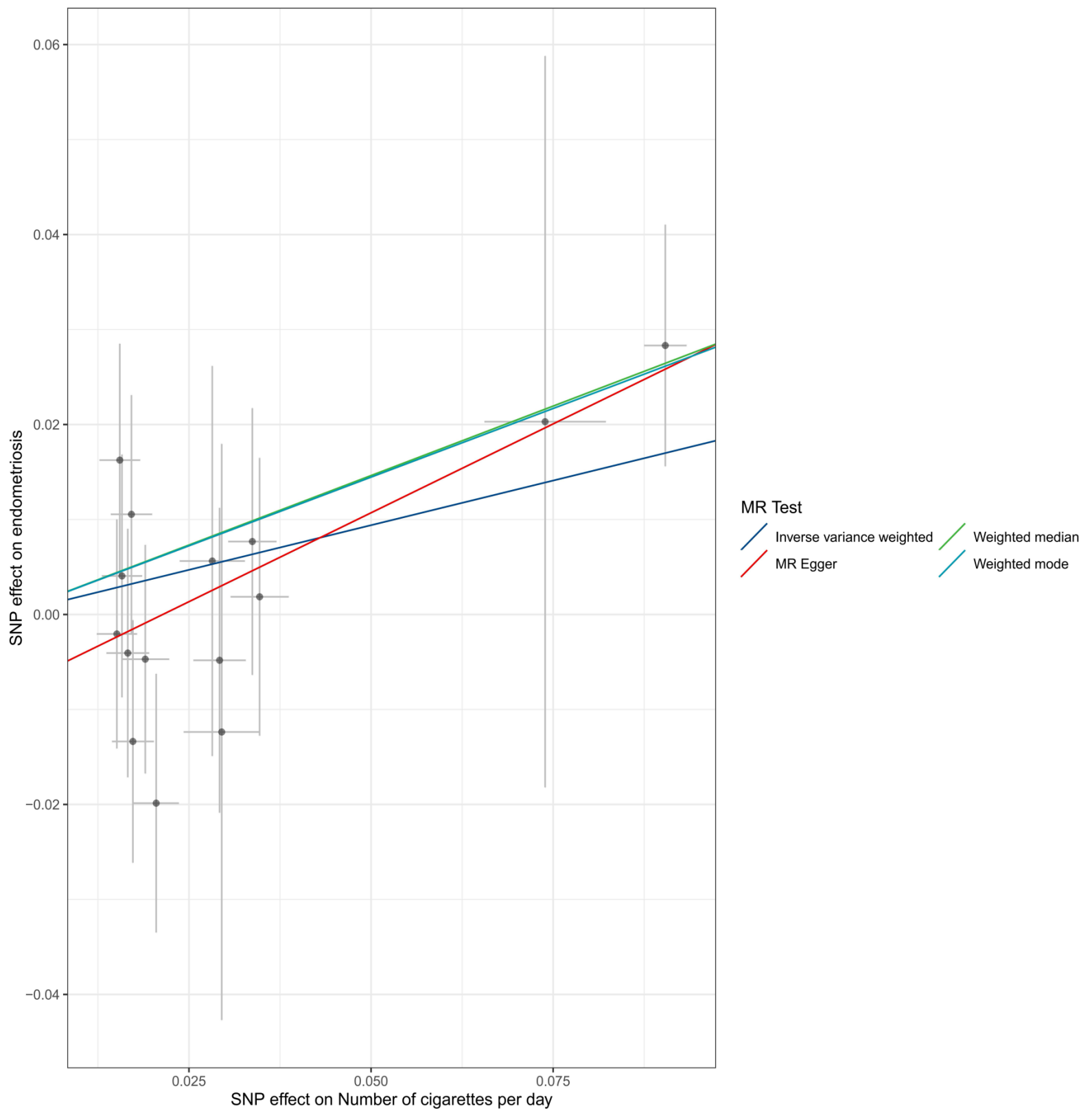


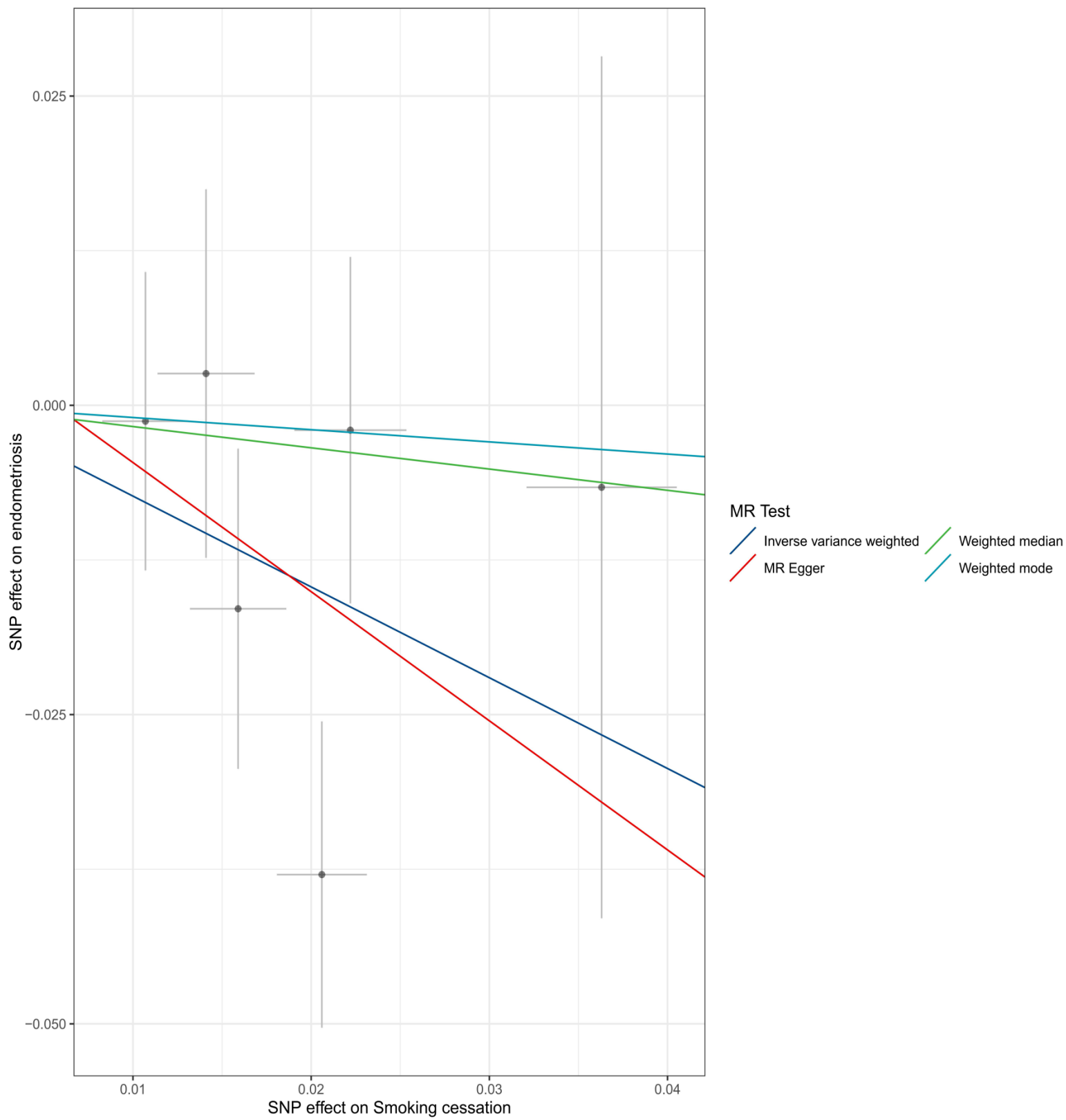


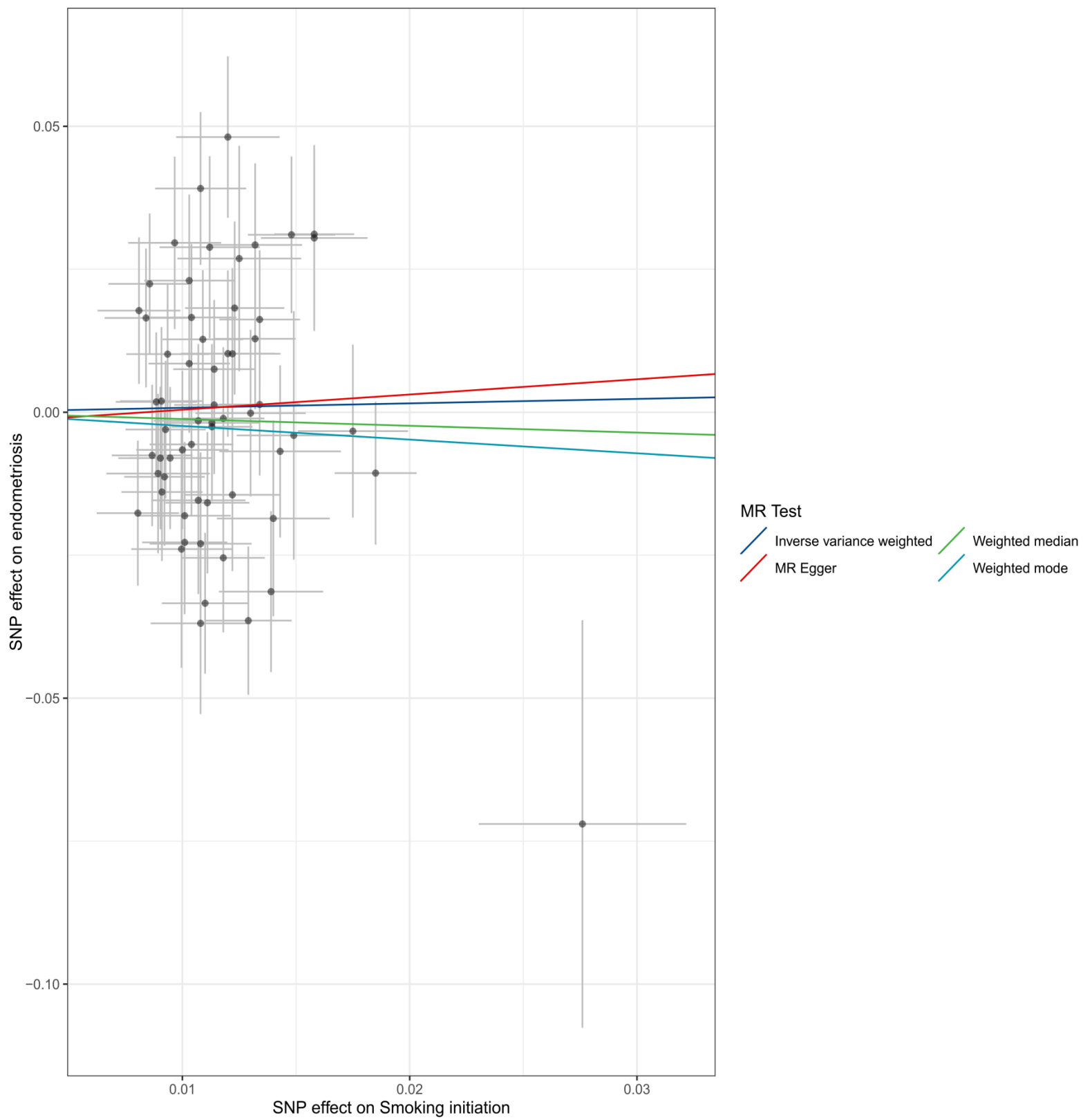


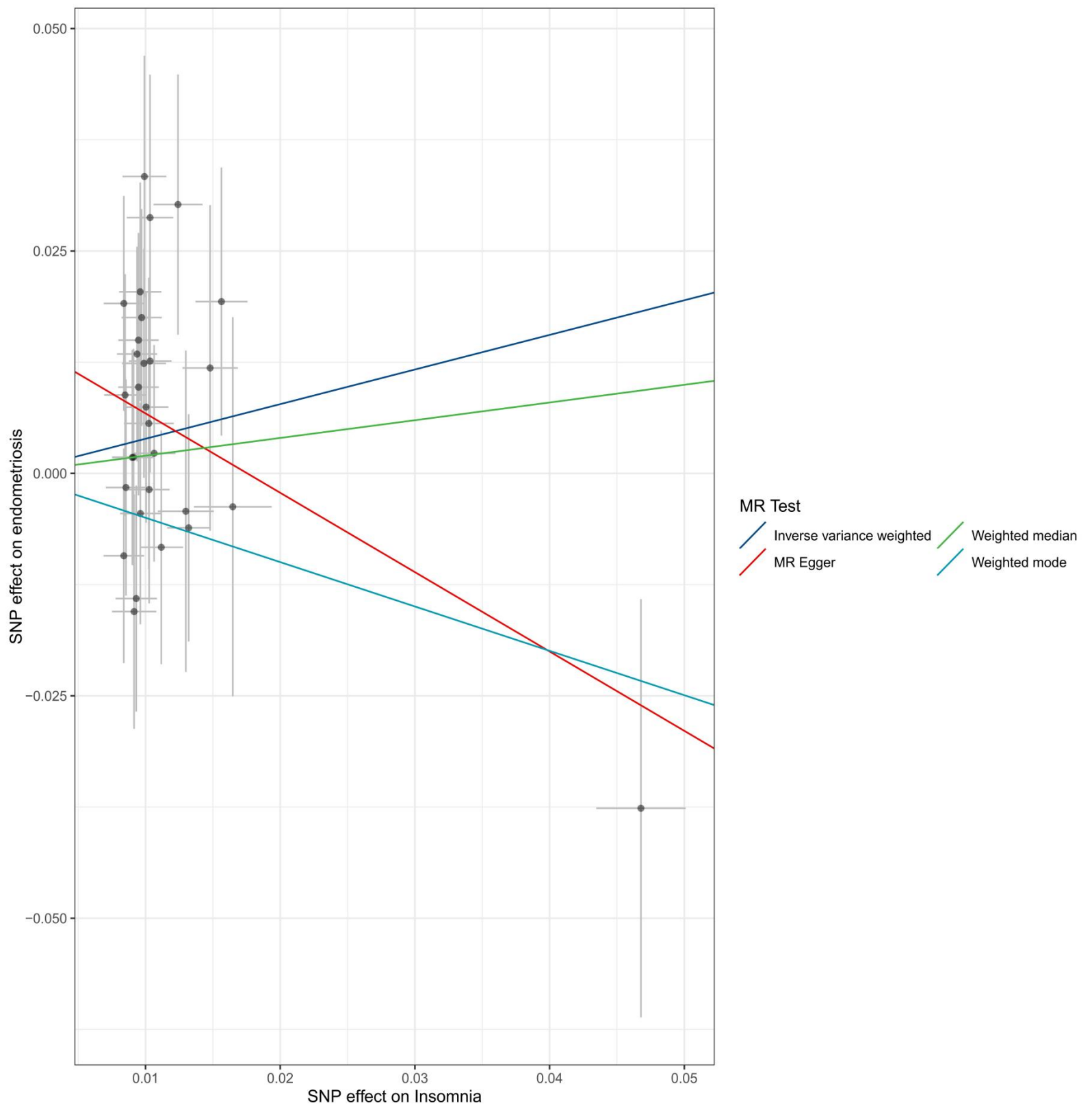


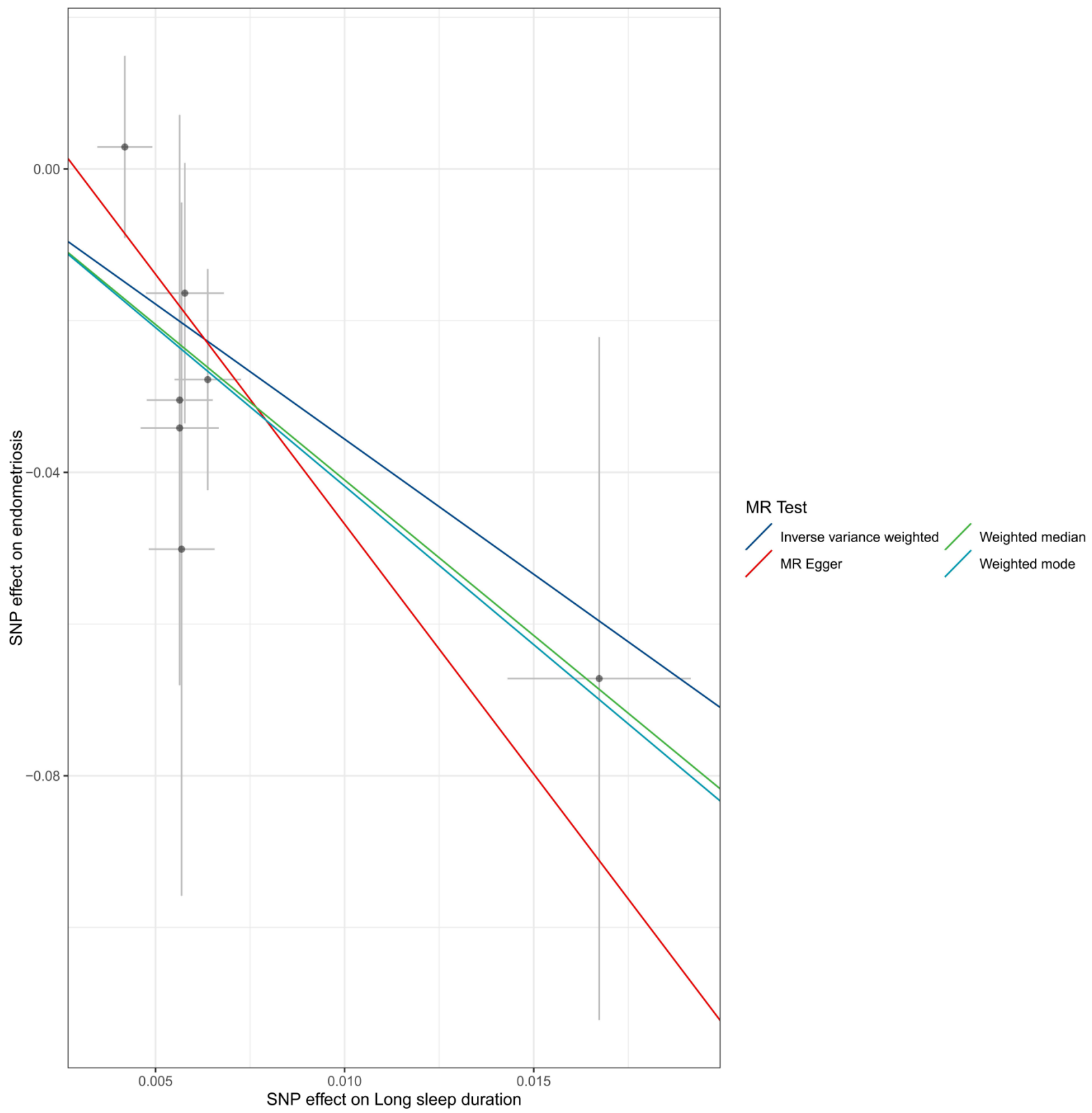


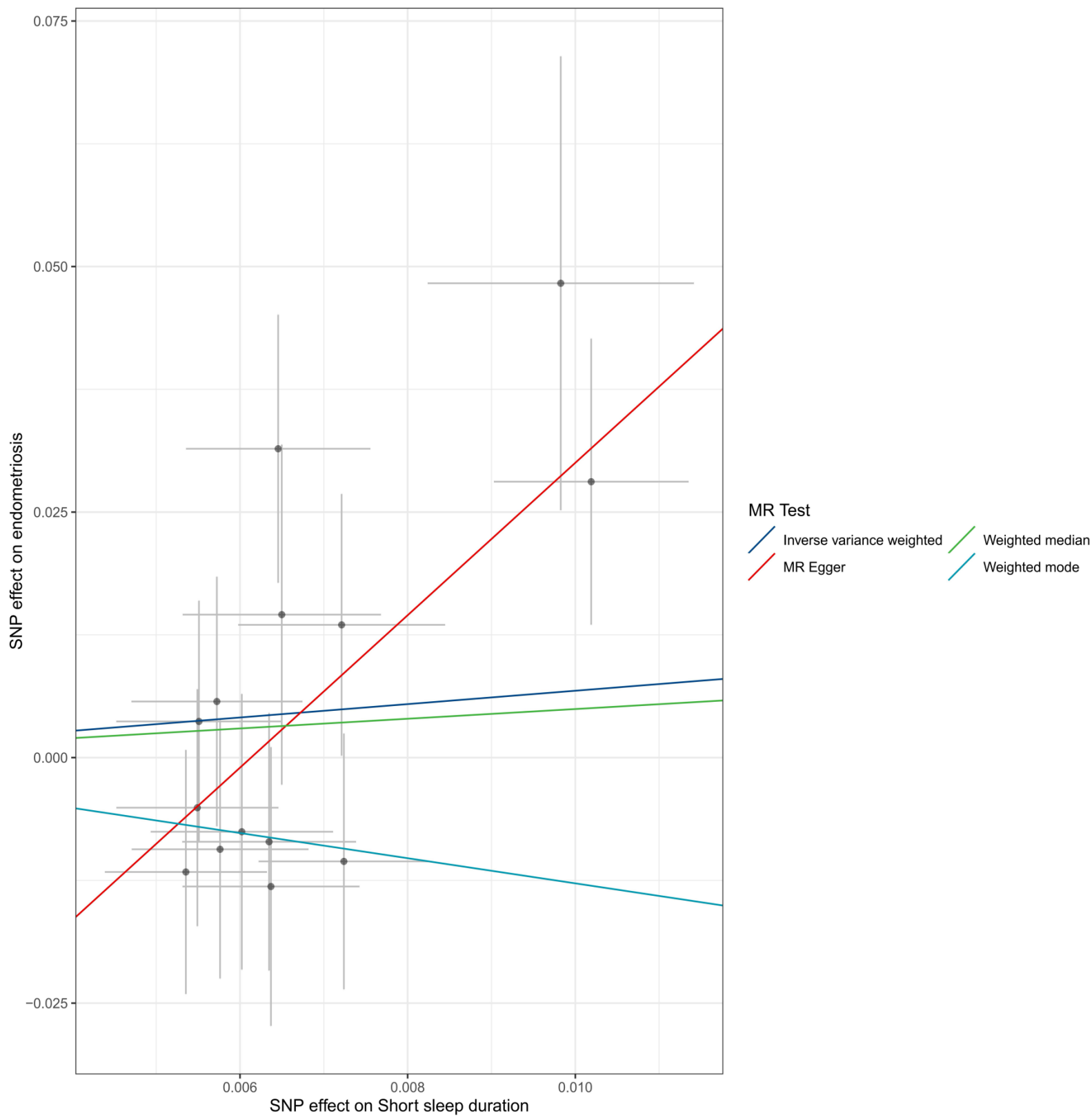


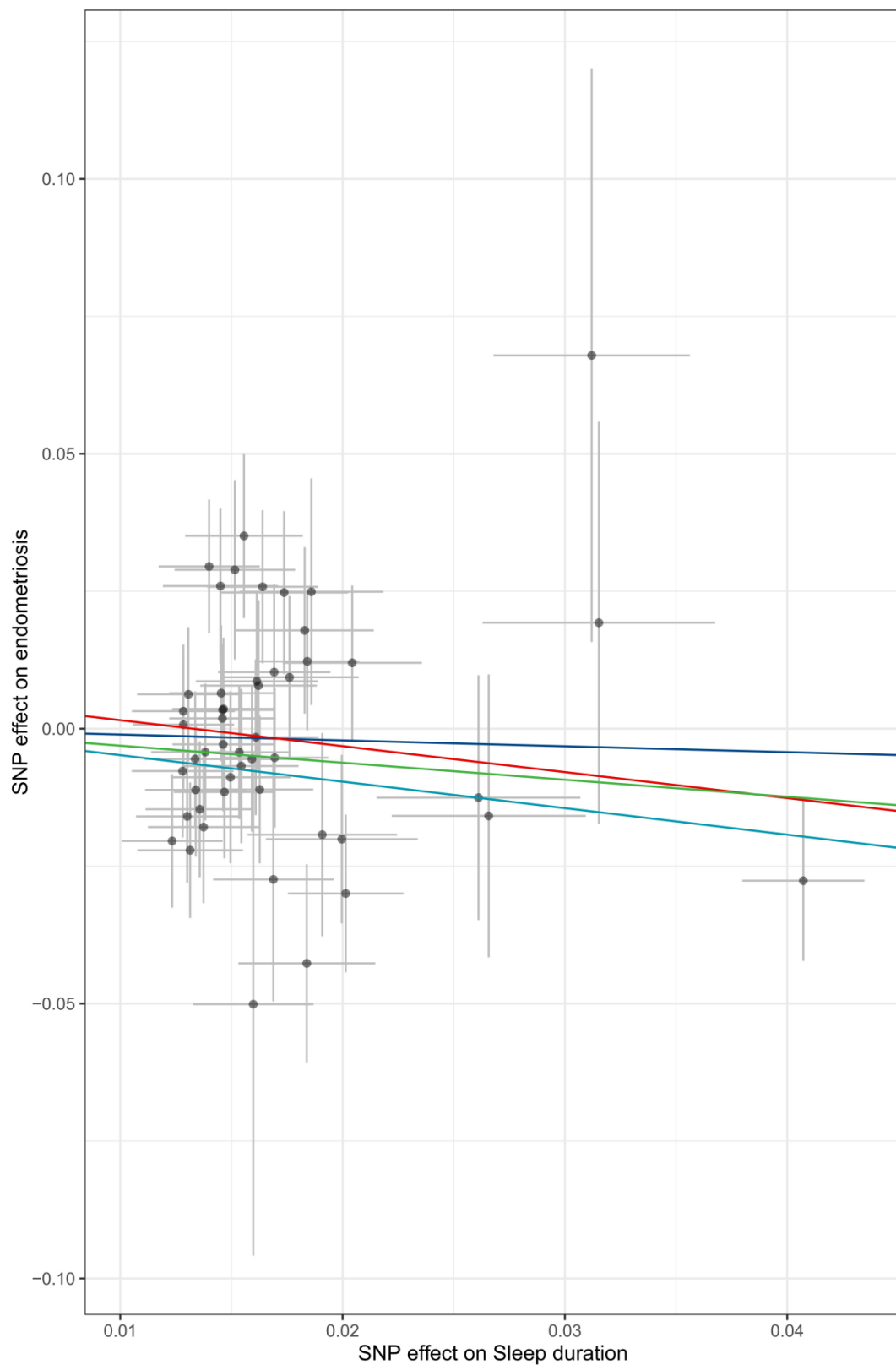












Supplementary Figure S2. Leave-one-out analysis for all causal relationships detected in primary analysis.

Within each panel, the black points represent the causal estimate of association between a specific exposure and endometriosis 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.

