

Supplementary Material

Supplementary Table SI. Details of studies included in the Mendelian randomization analyses

Exposures/outcome	GWAS ID	Consortium	Participants	SNPs number	Population	Year
Major depression	ieu-b-102	UKB, PGC	500,199	8,482,942	European	2019
Broad depression	ebi-a-GCST005902	UKB	322,580	7,624,934	European	2018
Depressed affect	ebi-a-GCST006475	UKB, 23andMe, GPC	357,957	10,828,862	European	2018
Anxious feelings	ukb-b-6519	UKB	450,765	9,851,867	European	2018
Worry	ebi-a-GCST006478	UKB, 23andMe, GPC	348,219	10,828,862	European	2018
Sleep duration	ukb-b-4424	UKB	460,099	9,851,867	European	2018
Sleeplessness	ukb-a-13	UKB	336,965	10,894,596	European	2017
Constipation	finn-b-K11_CONSTIPATION	FinnGen	218,792	16,380,466	European	2021

* UKB: the United Kingdom Biobank; PGC: the Psychiatric Genomics Consortium; GPC: the Genetics of Personality Consortium.

Supplementary Table SII. The causal associations of depression, anxiety, and sleep disorders with constipation

Exposure	Sample size	Method	SNPs	OR (95% CI)	P-value
Major depression	500,199	IVW (fixed effects)	46	1.28 (1.12-1.46)	2.68E-04
		Maximum likelihood	46	1.29 (1.13-1.47)	2.42E-04
		MR-RAPS	46	1.29 (1.12-1.48)	4.93E-04
		MR-PRESSO	46	1.28 (1.13-1.46)	4.39E-04
Broad depression	322,580	IVW (fixed effects)	16	3.72 (1.55-8.97)	3.31E-03
		Maximum likelihood	16	3.88 (1.58-9.51)	3.00E-03
		MR-RAPS	16	3.92 (1.38-11.13)	1.03E-02
		MR-PRESSO	16	3.63 (1.39-9.48)	1.87E-02
Depressed affect	357,957	IVW (fixed effects)	57	1.41 (1.13-1.76)	2.65E-03
		Maximum likelihood	57	1.42 (1.13-1.79)	2.47E-03
		MR-RAPS	57	1.48 (1.14-1.91)	2.81E-03
		MR-PRESSO(outlier)	57	1.45 (1.14-1.83)	3.12E-03
Anxious feelings	450,765	IVW (random effects)	63	1.29 (0.74-2.23)	3.72E-01
		Maximum likelihood	63	1.29 (0.80-2.10)	3.01E-01
		MR-RAPS	63	1.34 (0.78-2.30)	2.84E-01
		MR-PRESSO	63	1.41 (0.72-2.76)	2.10E-01
Worry	348,219	IVW (fixed effects)	59	1.42 (1.13-1.77)	2.11E-03
		Maximum likelihood	59	1.43 (1.14-1.79)	1.89E-03
		MR-RAPS	59	1.37 (1.09-1.72)	7.82E-03
		MR-PRESSO	59	1.34 (1.07-1.66)	1.18E-02
Sleep duration	460,099	IVW (random effects)	67	0.92 (0.65-1.30)	6.25E-01
		Maximum likelihood	67	0.91 (0.68-1.22)	5.49E-01
		MR-RAPS	67	0.88 (0.61-1.26)	4.88E-01
		MR-PRESSO	67	0.94 (0.67-1.32)	7.07E-01
Sleeplessness	336,965	IVW (random effects)	29	1.31 (0.82-2.10)	2.59E-01
		Maximum likelihood	29	1.32 (0.89-1.97)	1.72E-01

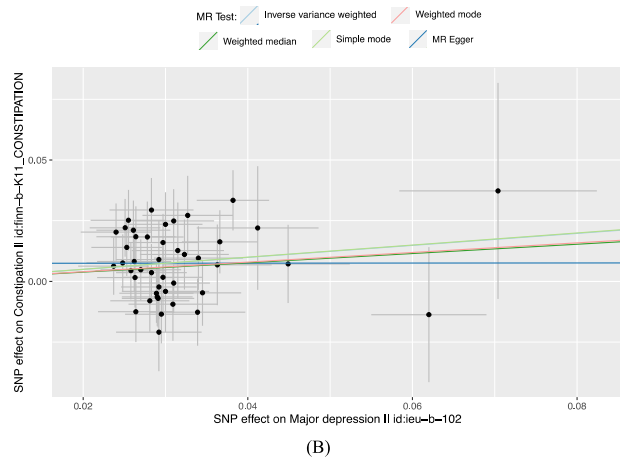
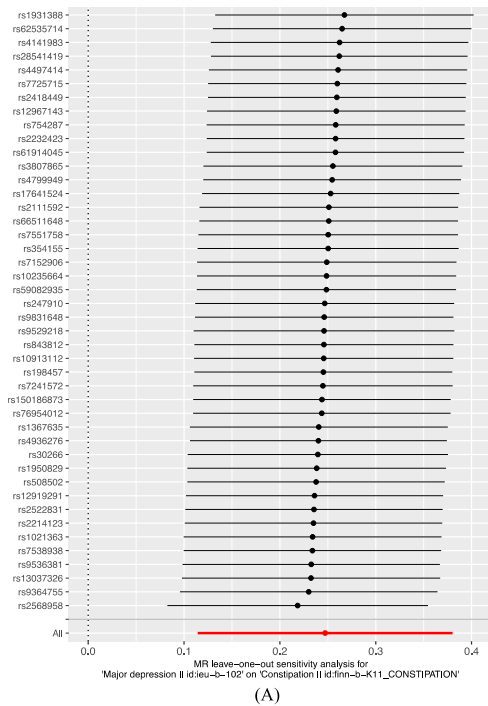
	MR-RAPS	29	1.16 (0.77-1.74)	4.79E-01
	MR-PRESSO	29	1.27 (0.81-1.98)	3.02E-01

*IVW, inverse-variance weighted; MR-RAPS, Mendelian Randomization robust adjusted profile score; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

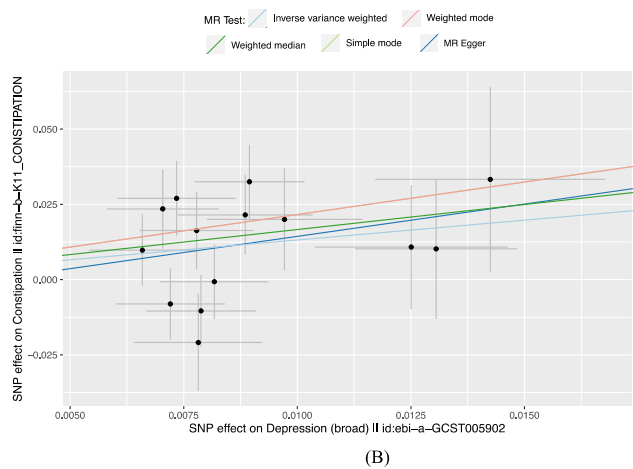
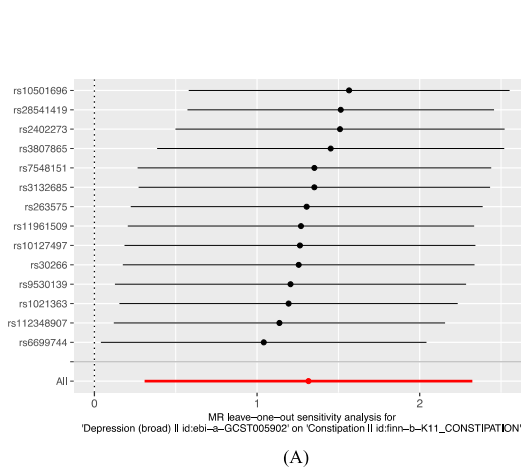
Supplementary Table SIII. The causal associations of constipation with depression, anxiety, and sleep disorders

Outcome	Sample size	Method	SNPs	OR (95% CI)	P-value
Major depression	218,792	IVW (fixed effects)	17	1.03 (1.00-1.06)	8.29E-02
		Maximum likelihood	17	1.03 (1.00-1.06)	8.50E-02
		MR-RAPS	17	1.03 (0.99-1.06)	1.11E-01
		MR-PRESSO	17	1.03 (1.00-1.06)	1.06E-01
Broad depression	218,792	IVW (fixed effects)	15	1.01 (1.00-1.02)	1.58E-01
		Maximum likelihood	15	1.01 (1.00-1.02)	1.65E-01
		MR-RAPS	15	1.01 (1.00-1.02)	1.50E-01
		MR-PRESSO	15	1.01 (1.00-1.02)	2.13E-01
Depressed affect	218,792	IVW (fixed effects)	13	1.00 (0.98-1.02)	9.73E-01
		Maximum likelihood	13	1.00 (0.98-1.02)	9.72E-01
		MR-RAPS	13	1.00 (0.98-1.02)	8.40E-01
		MR-PRESSO(outlier)	13	1.00 (0.98-1.02)	9.79E-01
Anxious feelings	218,792	IVW (random effects)	16	1.00 (0.99-1.01)	8.45E-01
		Maximum likelihood	16	1.00 (0.99-1.10)	7.71E-01
		MR-RAPS	16	1.00 (0.99-1.01)	9.05E-01
		MR-PRESSO	16	1.00 (0.99-1.01)	8.48E-01
Worry	218,792	IVW (fixed effects)	12	1.00 (0.98-1.02)	8.92E-01
		Maximum likelihood	12	1.00 (0.98-1.02)	8.94E-01
		MR-RAPS	12	1.01 (0.99-1.03)	4.99E-01
		MR-PRESSO	12	1.01 (0.99-1.04)	4.12E-01
Sleep duration	218,792	IVW (fixed effects)	17	1.00 (0.99-1.01)	8.73E-01
		Maximum likelihood	17	1.00 (0.99-1.01)	8.69E-01
		MR-RAPS	17	1.00 (0.99-1.02)	8.39E-01
		MR-PRESSO	17	1.00 (0.99-1.01)	8.85E-01
Sleeplessness	218,792	IVW (fixed effects)	17	1.01 (1.00-1.02)	1.82E-01
		Maximum likelihood	17	1.01 (1.00-1.02)	1.76E-01
		MR-RAPS	17	1.00 (0.99-1.02)	2.29E-01
		MR-PRESSO	17	1.01 (1.00-1.02)	2.24E-01

*IVW, inverse-variance weighted; MR-RAPS, Mendelian Randomization robust adjusted profile score; MR-PRESSO, Mendelian randomization pleiotropy residual sum and outlier; SNPs, single nucleotide polymorphisms; OR, odds ratio; CI, confidence interval.

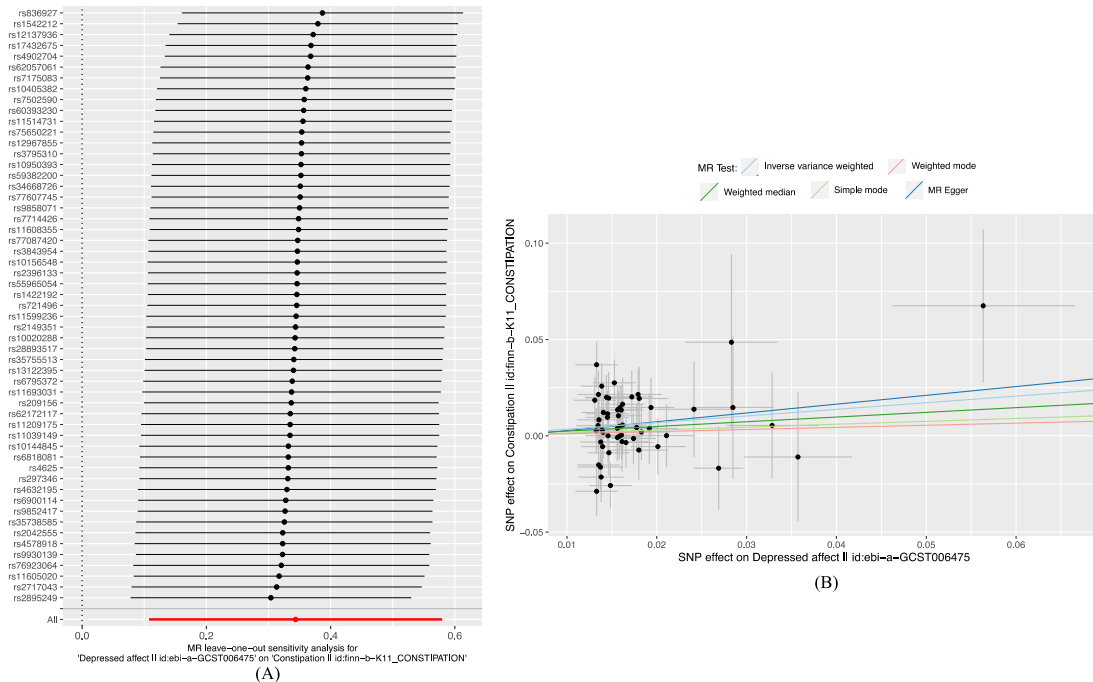


Supplementary Figure S1. Forest plot and scatter plot of the effect of major depression on constipation. (A) Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the correlation between major depression and constipation. The slope of each line corresponds to the estimated correlation of different MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.

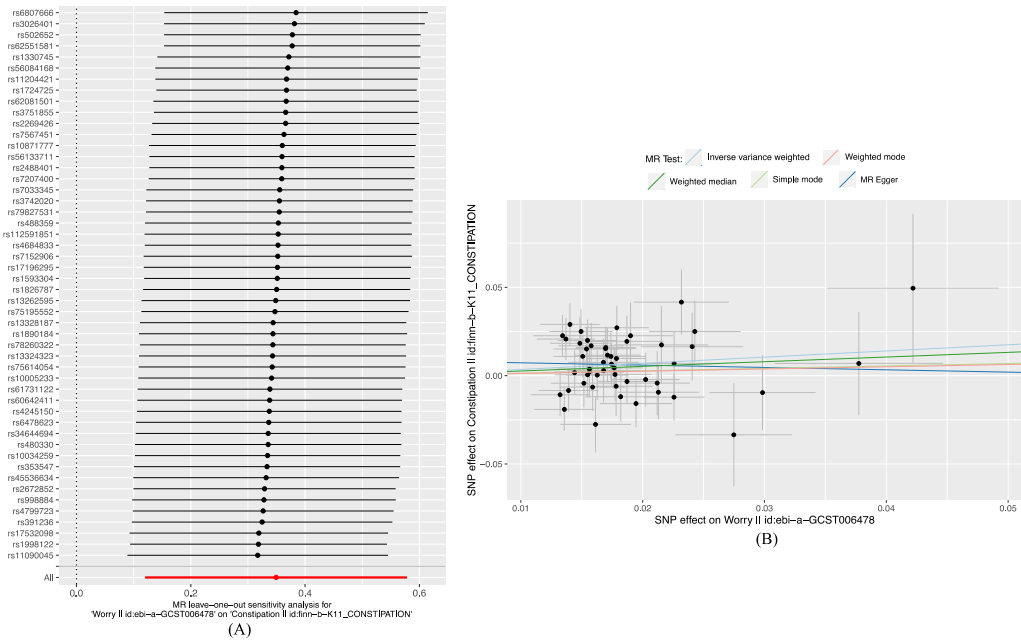


Supplementary Figure S2. Forest plot and scatter plot of the effect of broad depression on constipation. (A) Forest plot shows

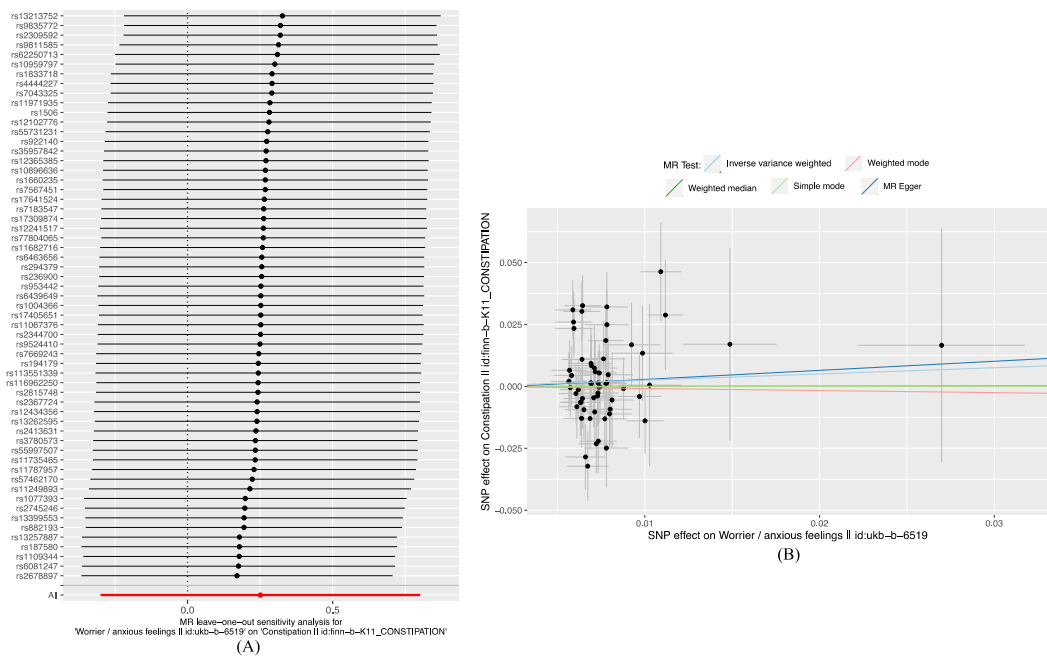
the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the correlation between broad depression and constipation. The slope of each line corresponds to the estimated correlation of different MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.



Supplementary Figure S3. Forest plot and scatter plot of the effect of depressed affect on constipation. (A) Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the correlation between depressed affect and constipation. The slope of each line corresponds to the estimated correlation of different MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.

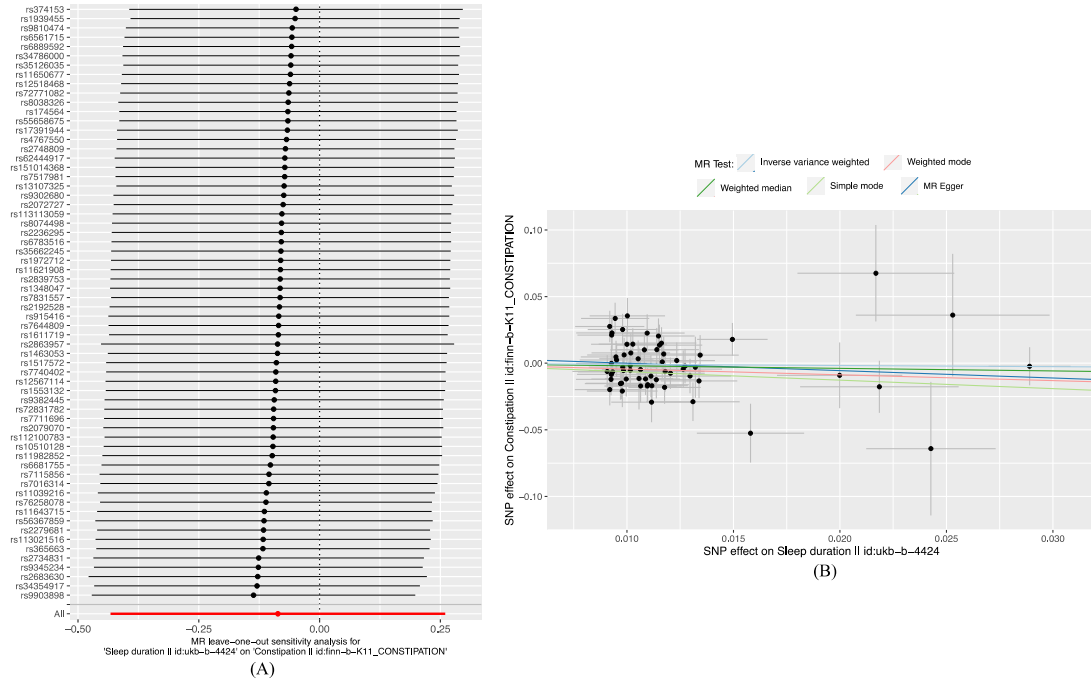


Supplementary Figure S4. Forest plot and scatter plot of the effect of worry on constipation. (A) Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the correlation between worry and constipation. The slope of each line corresponds to the estimated correlation of different MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.

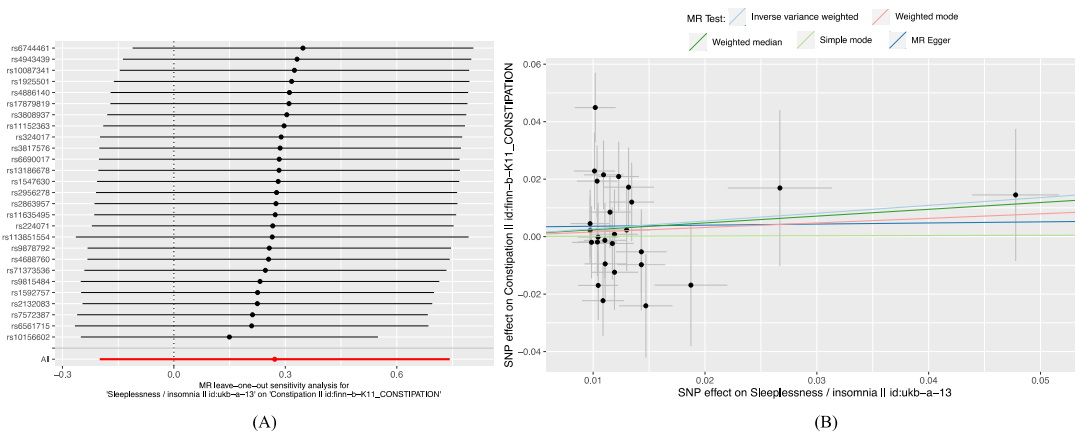


Supplementary Figure S5. Forest plot and scatter plot of the effect of anxious feelings on constipation. (A) Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the correlation between anxious feelings and constipation. The slope of each line corresponds to the estimated correlation of different

MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.

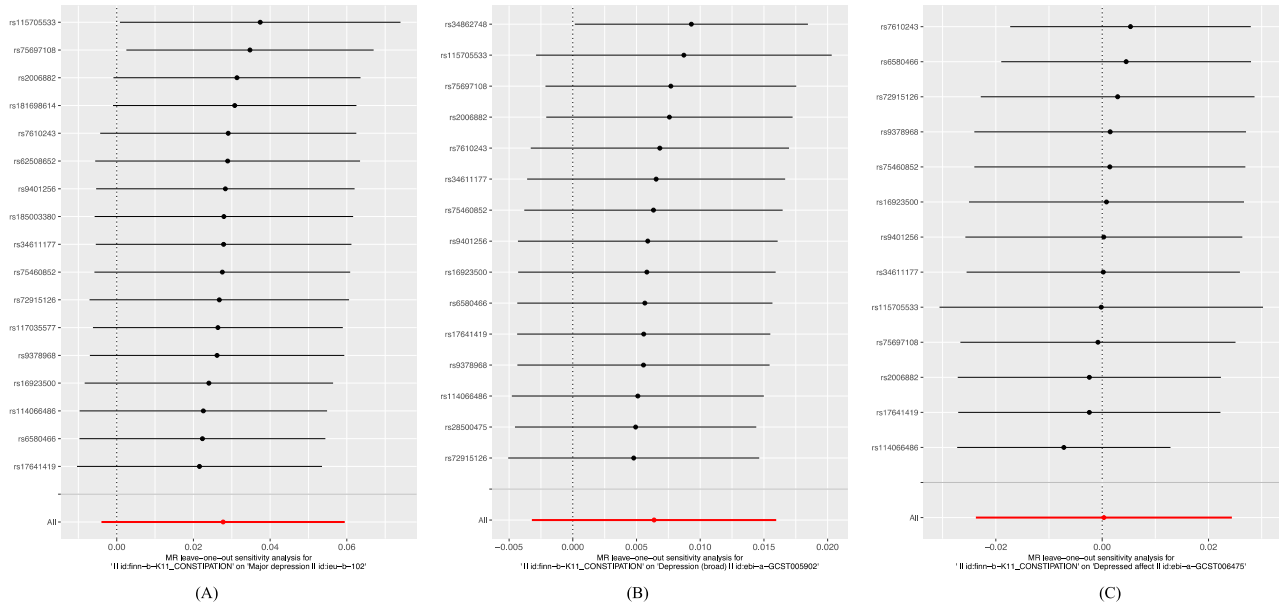


Supplementary Figure S6. Forest plot and scatter plot of the effect of sleep duration on constipation. (A) Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the correlation between sleep duration and constipation. The slope of each line corresponds to the estimated correlation of different MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.

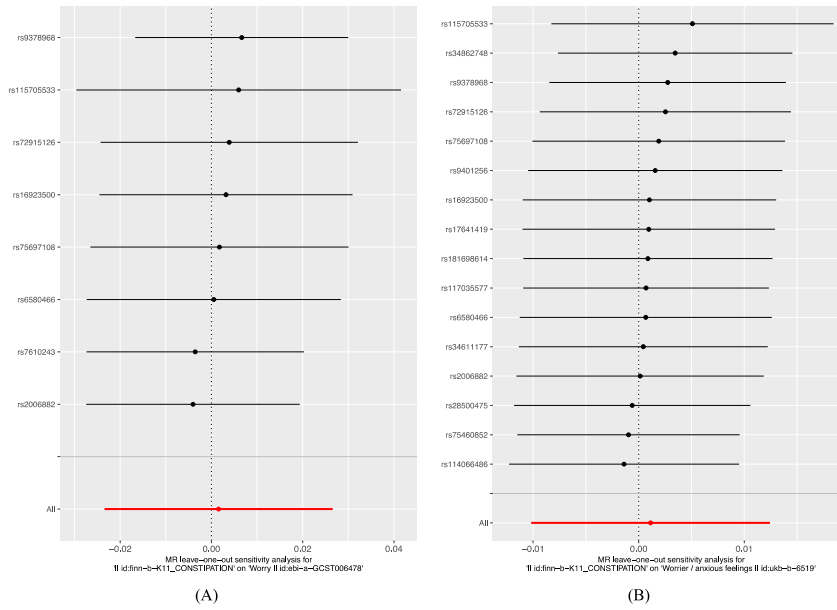


Supplementary Figure S7. Forest plot and scatter plot of the effect of sleeplessness on constipation. (A) Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (B) Scatter plot for MR analyses of the

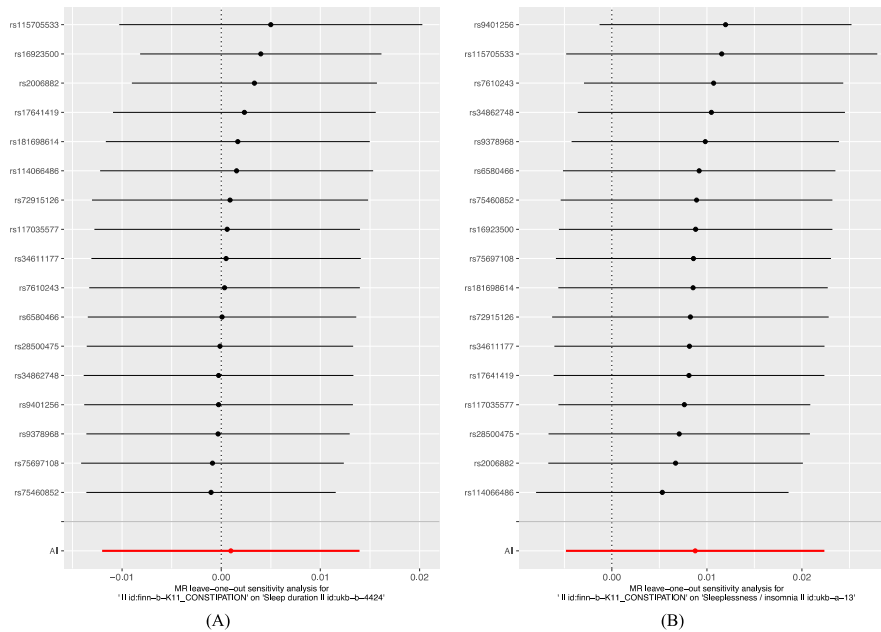
correlation between sleeplessness and constipation. The slope of each line corresponds to the estimated correlation of different MR methods; SNP, single nucleotide polymorphism; MR, Mendelian Randomization.



Supplementary Figure S8. Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (A) Forest plot of the effect of constipation on major depression. (B) Forest plot of the effect of constipation on broad depression. (C) Forest plot of the effect of constipation on depressed affect.



Supplementary Figure S9. Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (A) Forest plot of the effect of constipation on worry. (B) Forest plot of the effect of constipation on anxious feelings.



Supplementary Figure S10. Forest plot shows the odds ratio (OR) and 95% confidence interval (CI) of each SNP selected in the study; (A) Forest plot of the effect of constipation on sleep duration. (B) Forest plot of the effect of constipation on sleeplessness.

