

### **Supplementary file 3**

MR results of localized pain on risk of sleeplessness/insomnia,  
anxiety/panic attacks and depression with scatter plots

**Single-variable MR results of localized pain on risk of sleeplessness/insomnia, anxiety/panic attacks and depression**

Exposure	Method	Sleeplessness / insomnia			Anxiety/panic attacks			Depression		
		N SNV	OR (95%CI)	P value	N SNV	OR (95%CI)	P value	N SNV	OR (95%CI)	P value
Headache	IVW (FEM)	45	1.14 (1.05-1.24)	0.003	45	1.00 (0.99-1.02)	0.56	45	1.06 (1.03-1.08)	<0.001
	IVW (REM)	45	1.14 (1.01-1.28)	0.04	45	1.00 (0.99-1.02)	0.63	45	1.06 (1.02-1.09)	<0.001
	Weighted median	45	1.15 (1.02-1.31)	0.03	45	1.00 (0.98-1.03)	0.69	45	1.04 (1.01-1.08)	0.02
	MR Egger	45	0.92 (0.65-1.30)	0.62	45	1.00 (0.95-1.05)	0.91	45	1.01 (0.93-1.11)	0.77
Facial pain*	IVW (FEM)	16	1.31 (0.69-2.49)	0.41	16	1.00 (0.90-1.11)	0.98	16	1.13 (0.95-1.35)	0.16
	IVW (REM)	16	1.31 (0.68-2.54)	0.42	16	1.00 (0.88-1.14)	0.99	16	1.13 (0.94-1.36)	0.18
	Weighted median	16	2.01 (0.82-4.91)	0.13	16	1.01 (0.87-1.17)	0.91	16	1.08 (0.84-1.39)	0.55
	MR Egger	16	5.22 (0.30-90.81)	0.28	16	0.80 (0.45-1.41)	0.45	16	1.08 (0.47-2.45)	0.86
Neck or shoulder pain	IVW (FEM)	6	1.95 (1.50-2.54)	<0.001	6	1.00 (0.96-1.04)	0.96	6	1.09 (1.01-1.17)	0.02
	IVW (REM)	6	1.95 (1.03-3.68)	0.03	6	1.00 (0.96-1.04)	0.96	6	1.09 (1.00-1.18)	0.04
	Weighted median	6	1.97 (1.32-2.94)	<0.001	6	1.00 (0.95-1.06)	0.95	6	1.10 (1.01-1.21)	0.04
	MR Egger	6	2.39 (0.11-50.76)	0.61	6	1.07 (0.89-1.30)	0.50	6	1.07 (0.73-1.58)	0.73
Back pain	IVW (FEM)	20	1.40 (1.22-1.60)	<0.001	20	1.00 (0.98-1.02)	0.94	19	1.08 (1.04-1.13)	<0.001
	IVW (REM)	20	1.40 (1.18-1.65)	<0.001	20	1.00 (0.98-1.02)	0.94	19	1.08 (1.03-1.14)	0.002
	Weighted median	20	1.26 (1.04-1.54)	0.02	20	1.01 (0.98-1.05)	0.41	19	1.06 (1.00-1.11)	0.03
	MR Egger	20	1.14 (0.60-2.20)	0.69	20	0.97 (0.89-1.06)	0.51	19	0.90 (0.71-1.13)	0.37
Stomach and abdominal pain*	IVW (FEM)	30	1.79 (1.44-2.23)	<0.001	30	1.03 (1.00-1.07)	0.06	28	1.19 (1.12-1.25)	<0.001
	IVW (REM)	30	1.79 (1.25-2.56)	0.001	30	1.03 (0.99-1.08)	0.13	28	1.19 (1.11-1.26)	<0.001
	Weighted median	30	2.10 (1.50-2.95)	<0.001	30	1.03 (0.98-1.09)	0.24	28	1.17 (1.07-1.28)	<0.001
	MR Egger	30	0.44 (0.14-1.37)	0.17	30	0.91 (0.79-1.06)	0.23	28	1.14 (0.86-1.50)	0.37
Hip pain	IVW (FEM)	4	2.29 (1.18-4.45)	<0.001	4	1.01 (0.97-1.05)	0.83	4	1.17 (1.03-1.33)	0.01
	IVW (REM)	4	2.29 (1.46-3.60)	0.01	4	1.01 (0.94-1.08)	0.69	4	1.17 (0.94-1.46)	0.16
	Weighted median	4	1.76 (0.97-3.17)	0.06	4	0.99 (0.91-1.07)	0.81	4	1.13 (0.95-1.33)	0.17
	MR Egger	4	22.35 (1.12-447.57)	0.17	4	1.12 (0.75-1.67)	0.62	4	1.37 (0.32-5.89)	0.71
Knee pain	IVW (FEM)	11	1.19 (0.99-1.42)	0.09	11	0.99 (0.97-1.01)	0.44	11	1.07 (1.03-1.12)	0.004
	IVW (REM)	11	1.19 (0.83-1.71)	0.35	11	0.99 (0.96-1.02)	0.29	11	1.07 (1.02-1.13)	<0.001
	Weighted median	11	0.99 (0.76-1.30)	0.96	11	0.99 (0.95-1.03)	0.55	11	1.08 (1.01-1.15)	0.02
	MR Egger	11	0.41 (0.08-2.16)	0.32	11	1.01 (0.88-1.17)	0.84	11	1.10 (0.86-1.39)	0.47
None of above	IVW (FEM)	37	0.62 (0.56-0.67)	<0.001	37	0.98 (0.97-1.00)	0.01	37	0.92 (0.90-0.95)	<0.001
	IVW (REM)	37	0.62 (0.54-0.70)	<0.001	37	0.98 (0.97-1.00)	0.02	37	0.92 (0.90-0.95)	<0.001
	Weighted median	37	0.68 (0.59-0.79)	<0.001	37	0.97 (0.95-0.99)	0.005	37	0.92 (0.89-0.96)	<0.001
	MR Egger	37	0.90 (0.40-2.07)	0.81	37	0.97 (0.88-1.08)	0.61	37	1.00 (0.86-1.17)	0.96

Abbreviations: MR, mendelian randomization; N SNV, number of single-nucleotide variants; IVW, inverse-variance weighted; FEM, fixed effects models; REM, random effects models; OR, odds ratio; GWAS, genome-wide association studies.

Genetic instruments selected from localized pain GWASs, selection threshold  $P$  less than  $5 \times 10^{-8}$ , pruned at linkage disequilibrium  $R^2$  less than 0.001 (10 000 kilobase pair window).

\* If the number of SNPs available for analysis is less than 3, the selection threshold  $P$  will be adjusted to  $5 \times 10^{-6}$ .

SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82

### MR Test



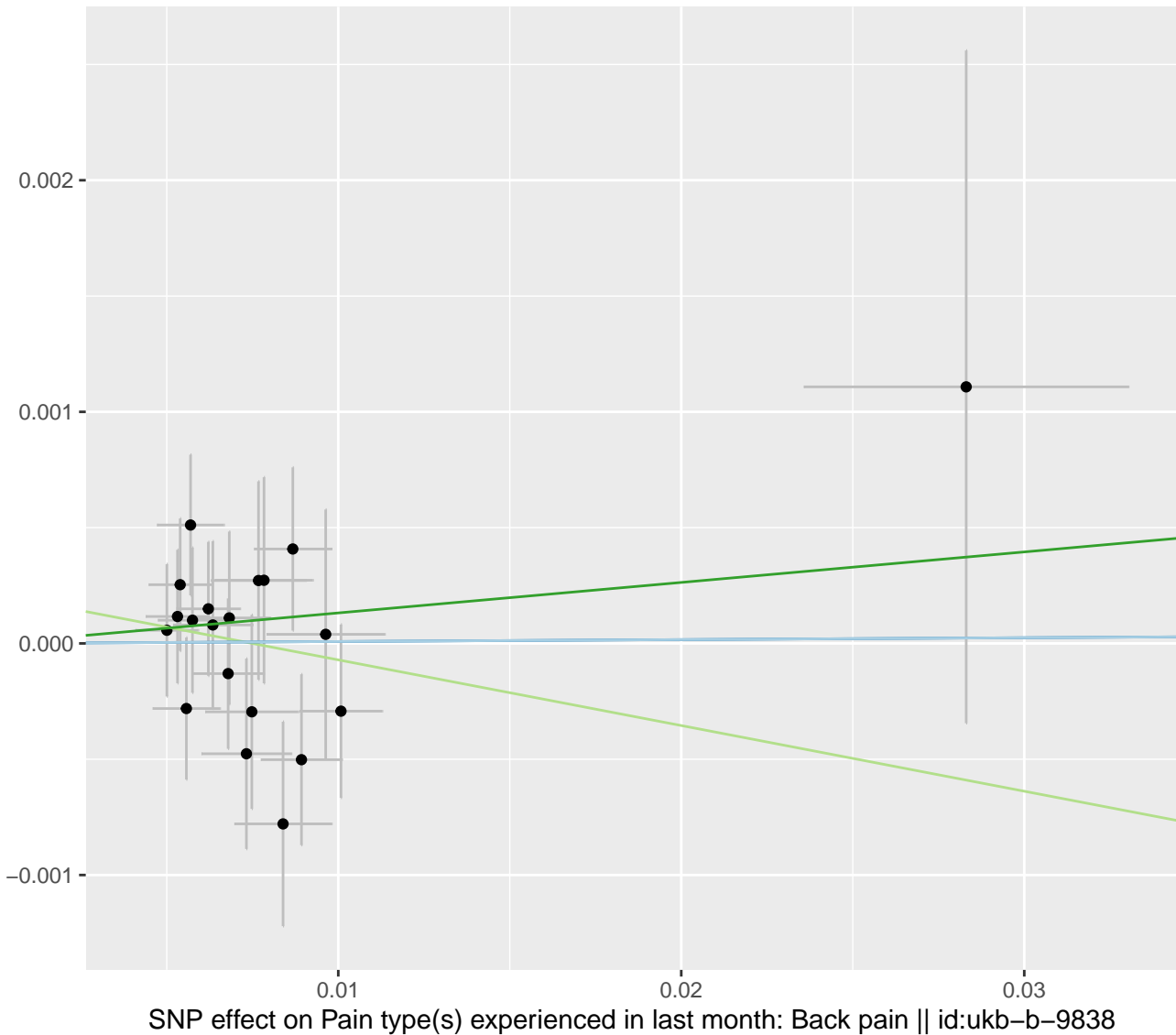
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)



MR Egger

Weighted median

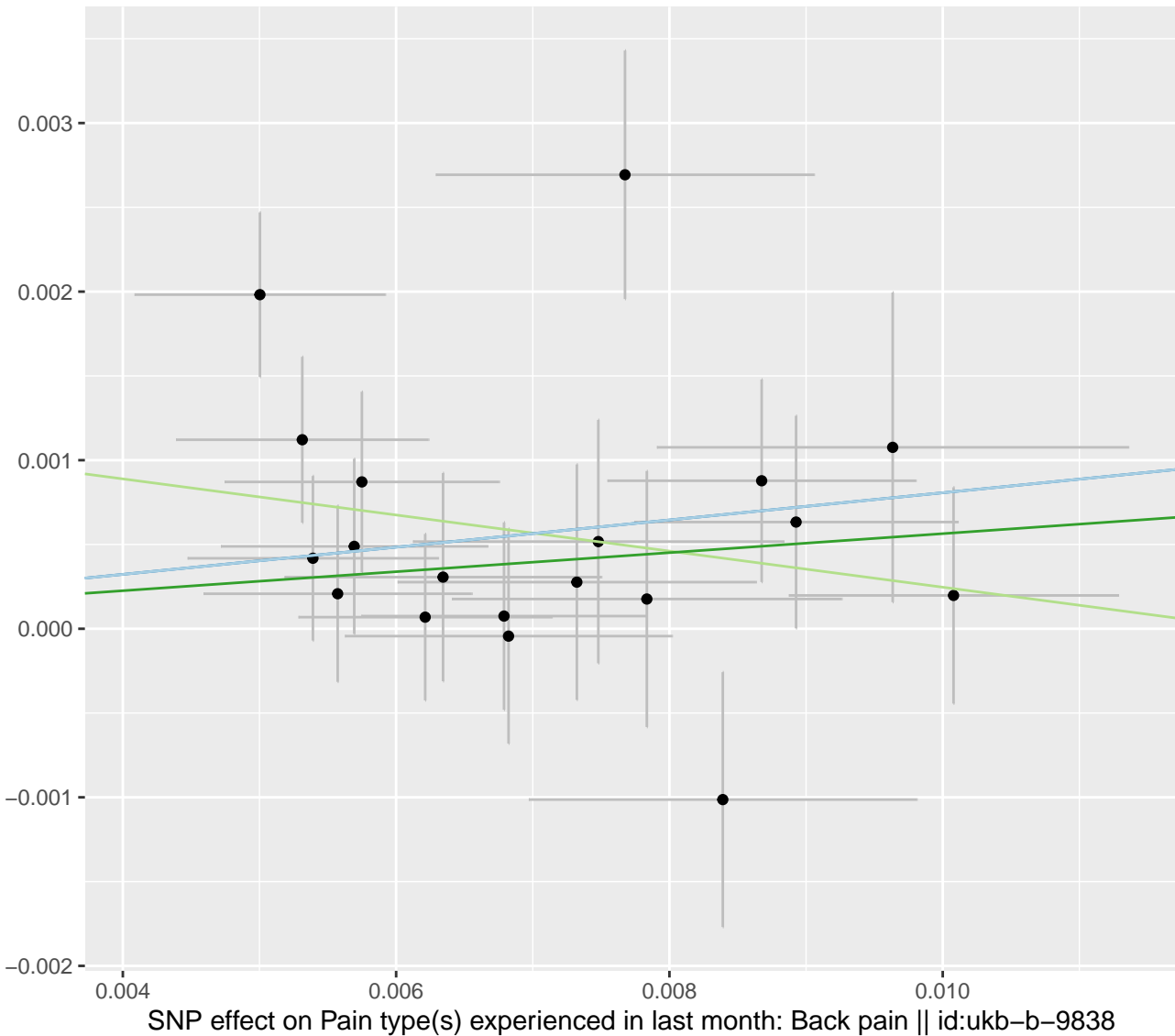


MR Test

Inverse variance weighted (fixed effects)  
Inverse variance weighted (multiplicative random effects)

MR Egger  
Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064



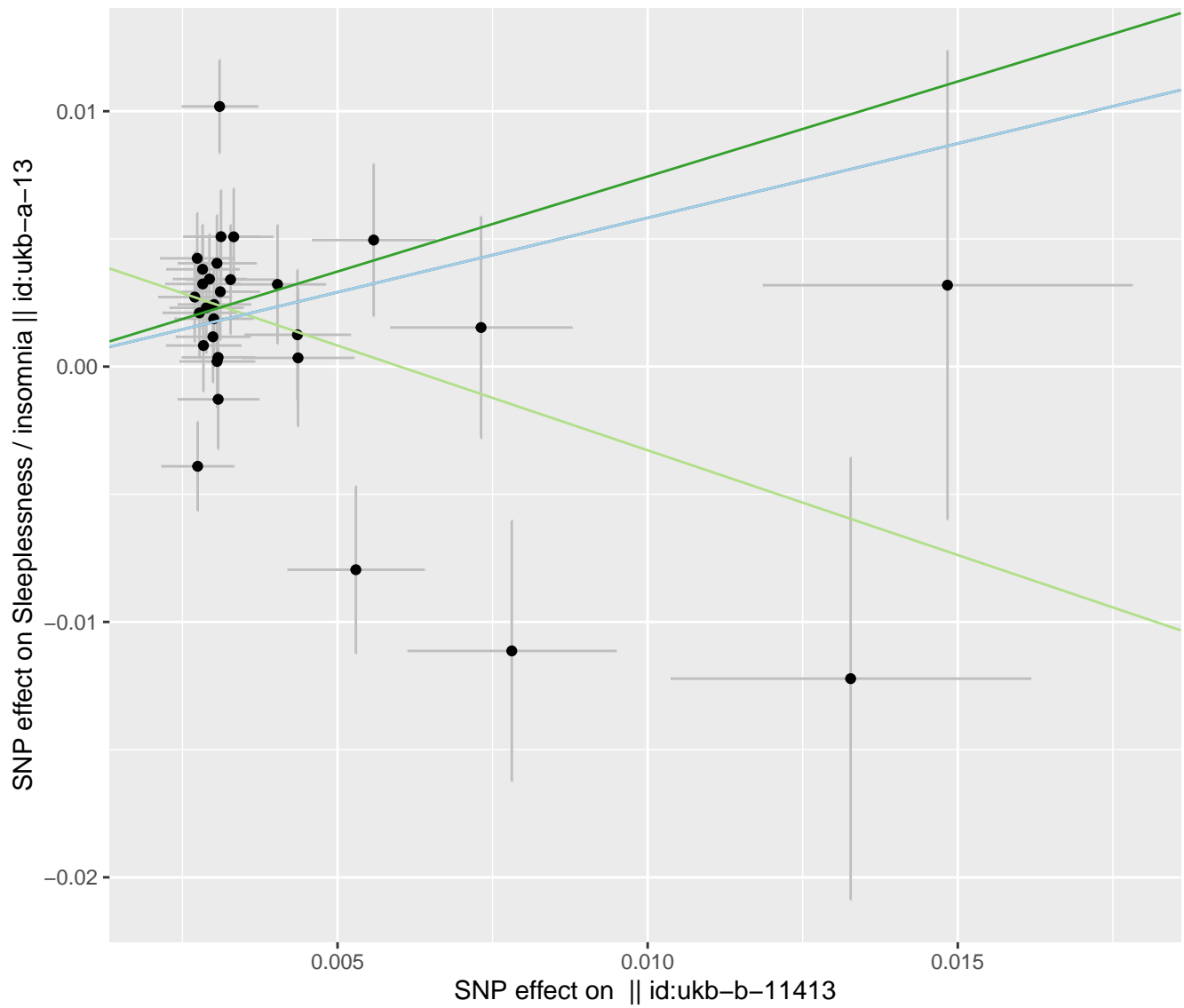
### MR Test

Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median



SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82

MR Test



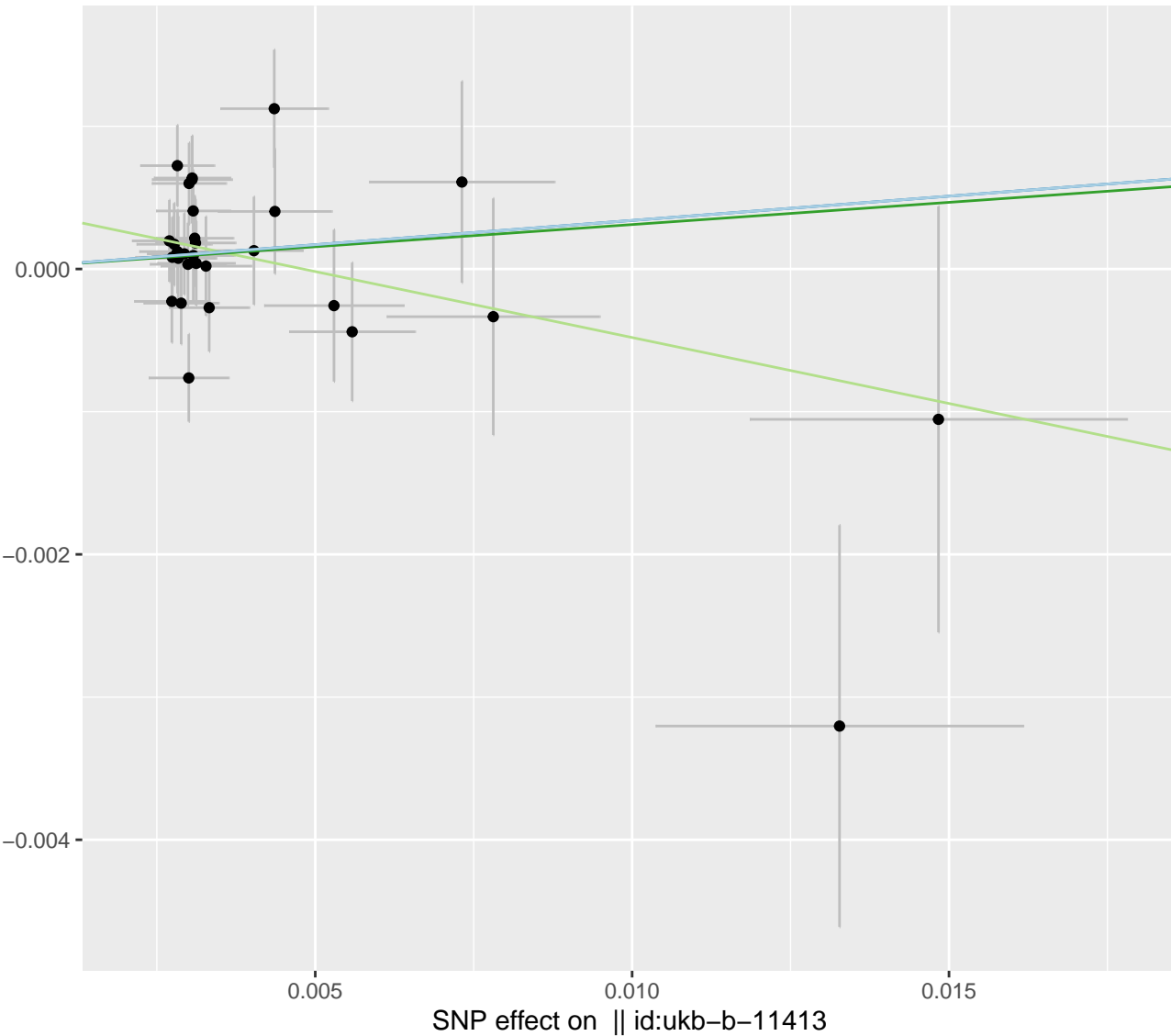
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)



MR Egger

Weighted median



MR Test

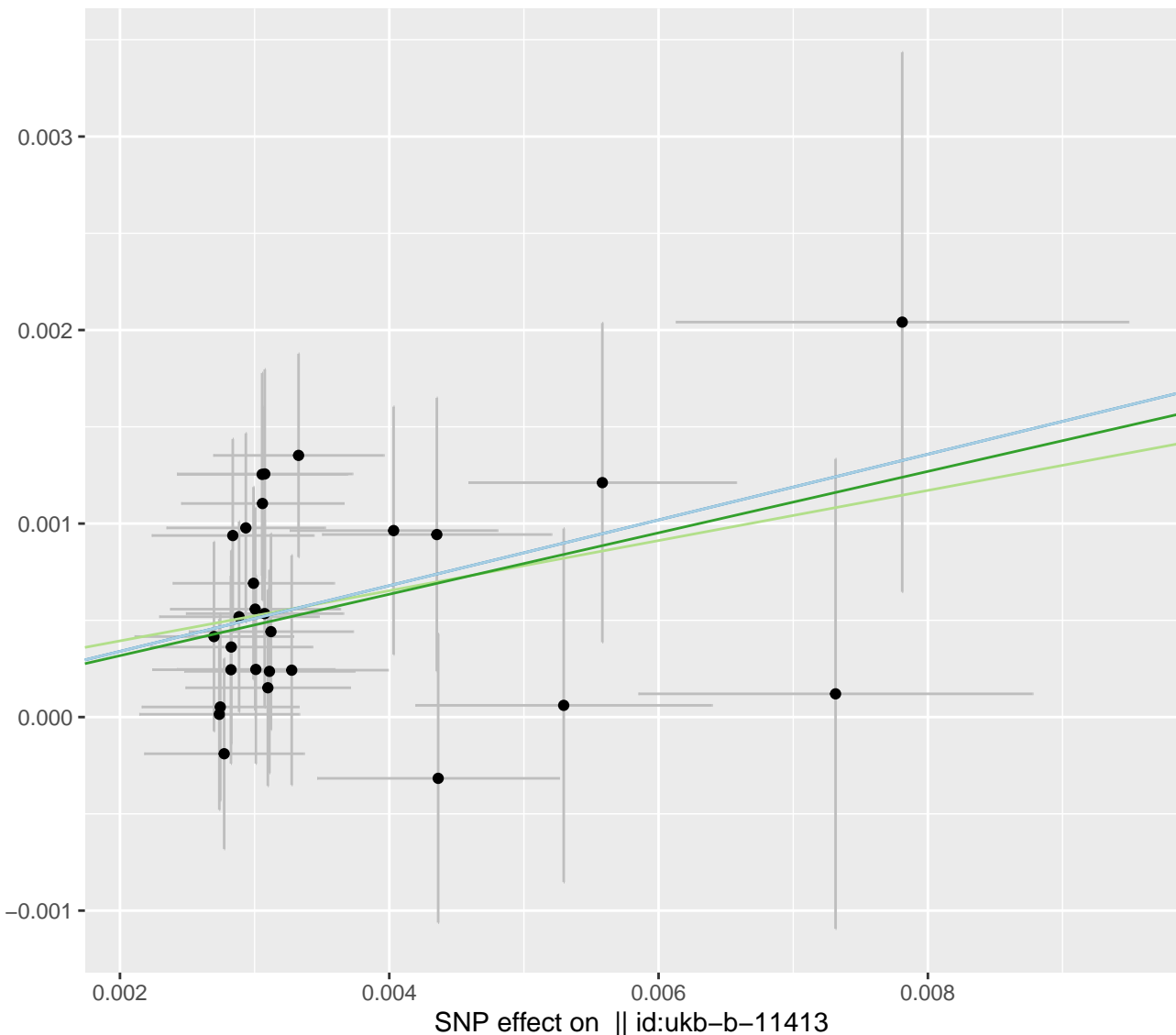
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064



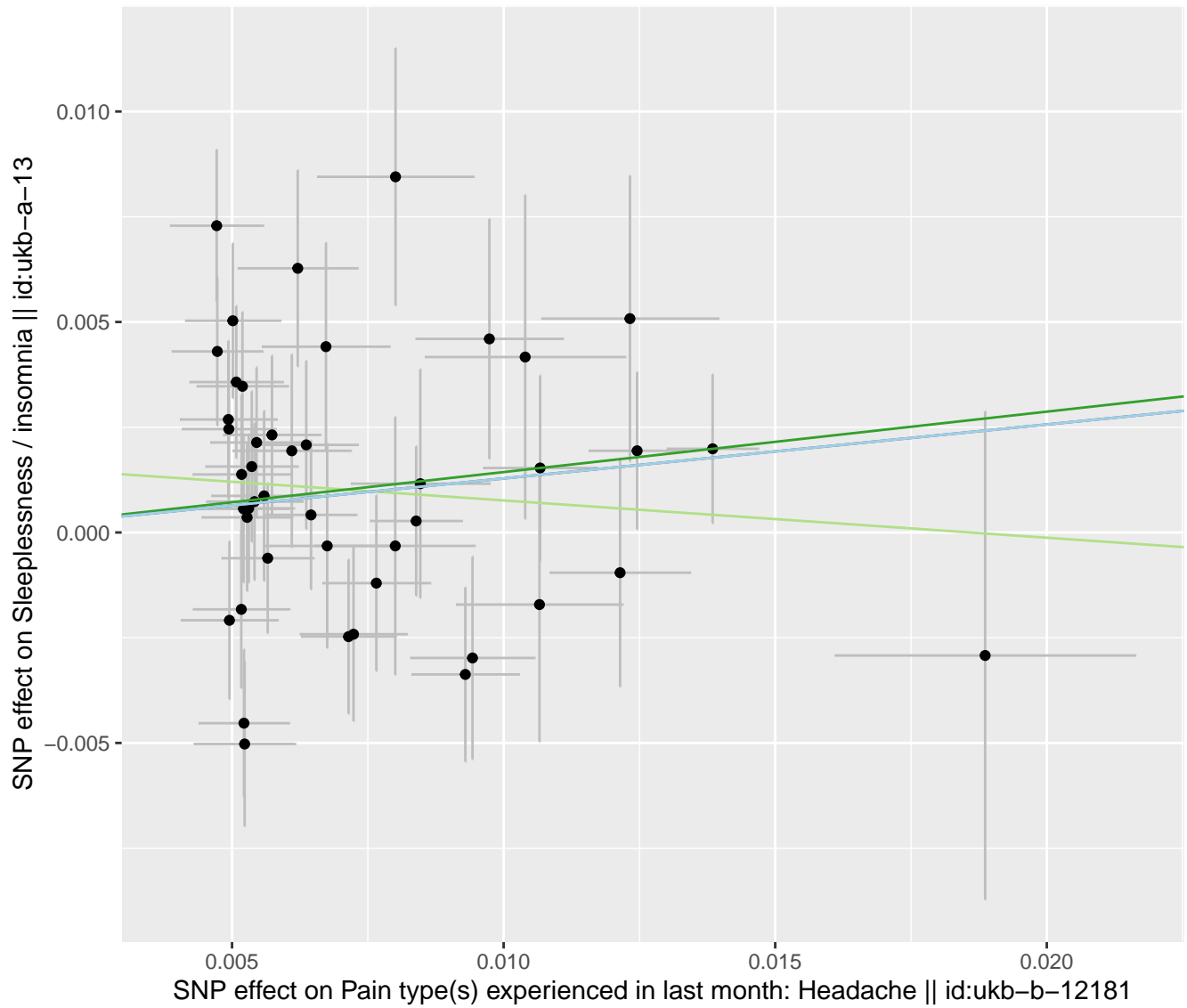
MR Test

Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median



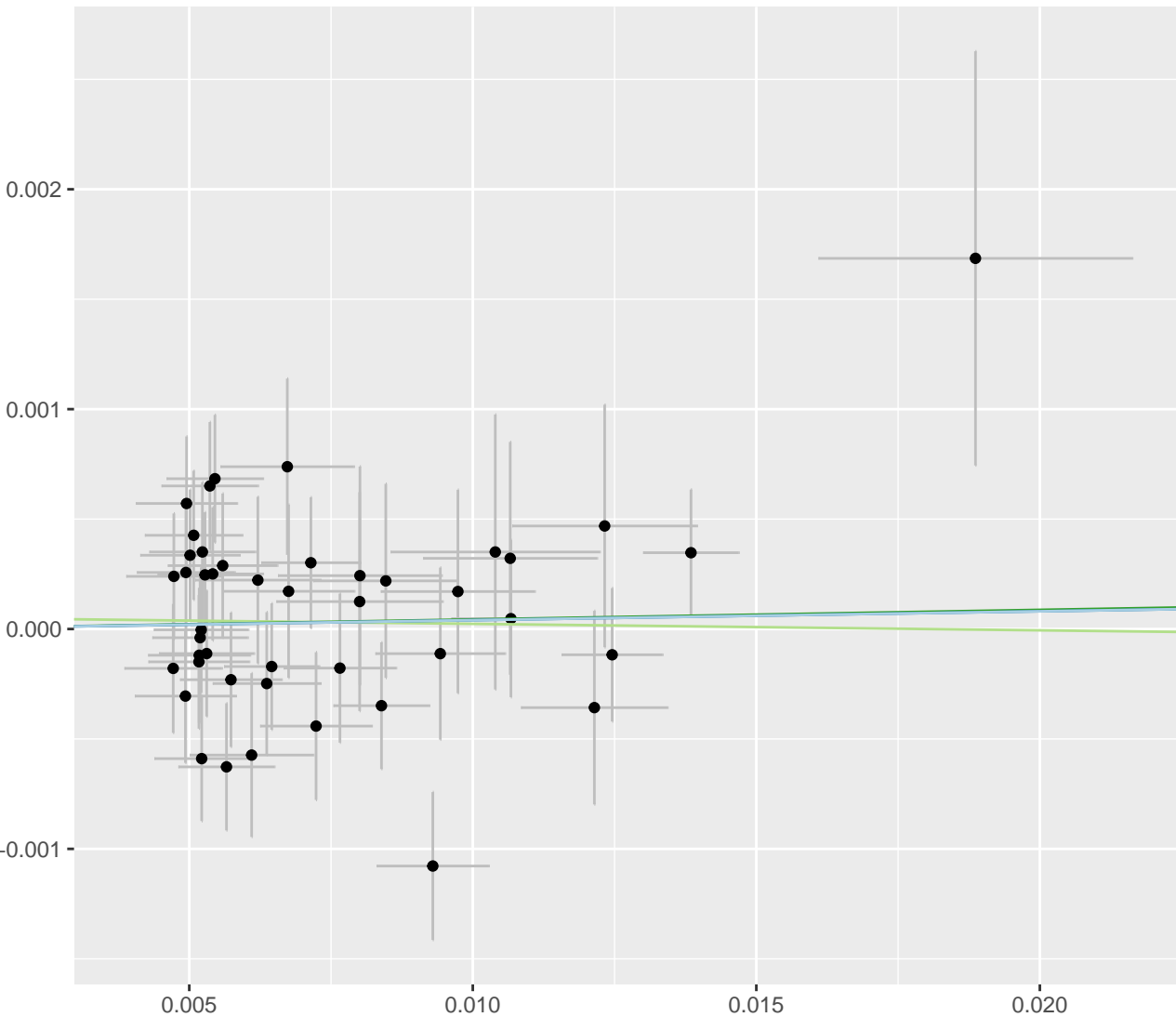


MR Test

- Inverse variance weighted (fixed effects)
- Inverse variance weighted (multiplicative random effects)

- MR Egger
- Weighted median

SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82



MR Test

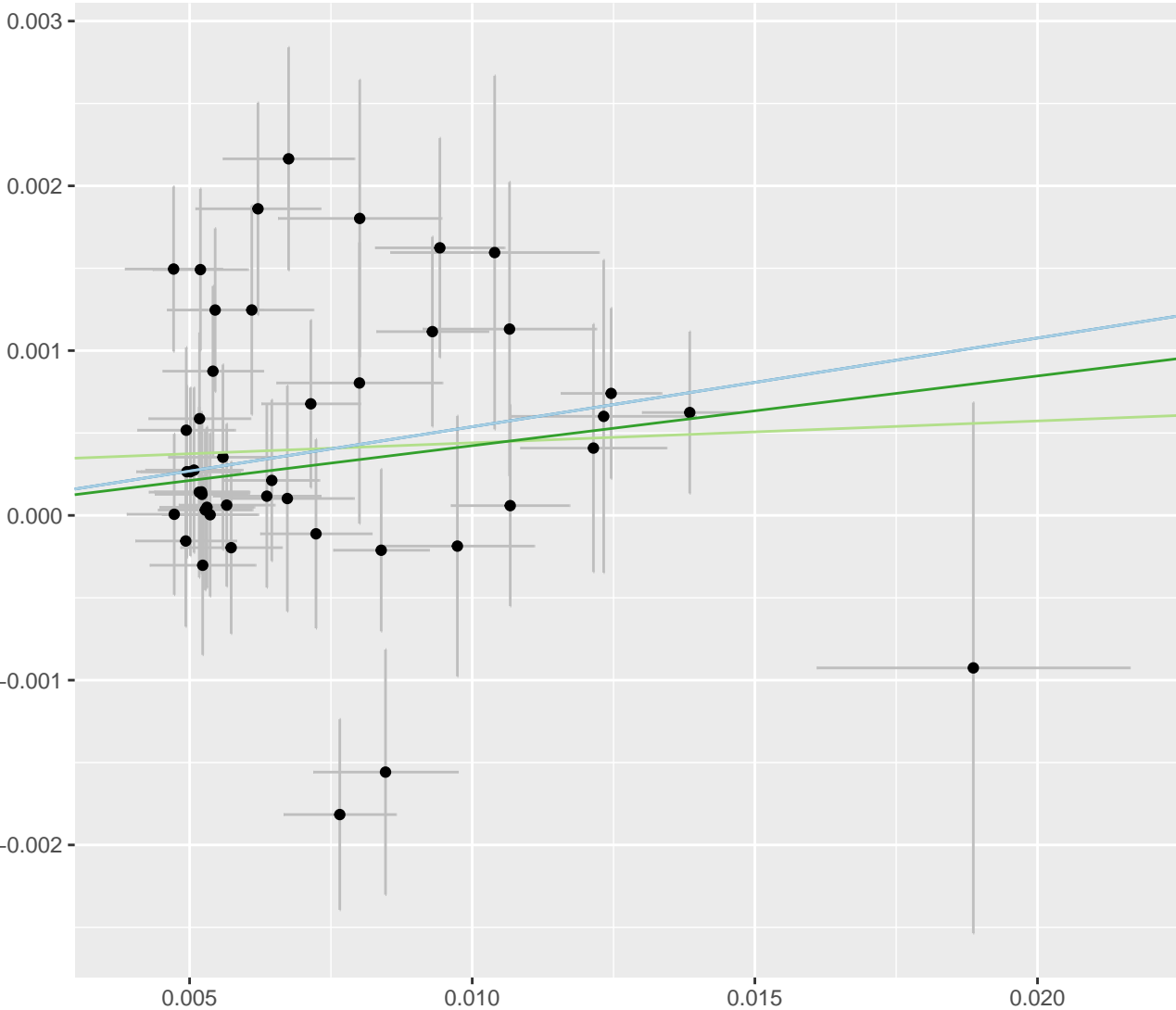
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064



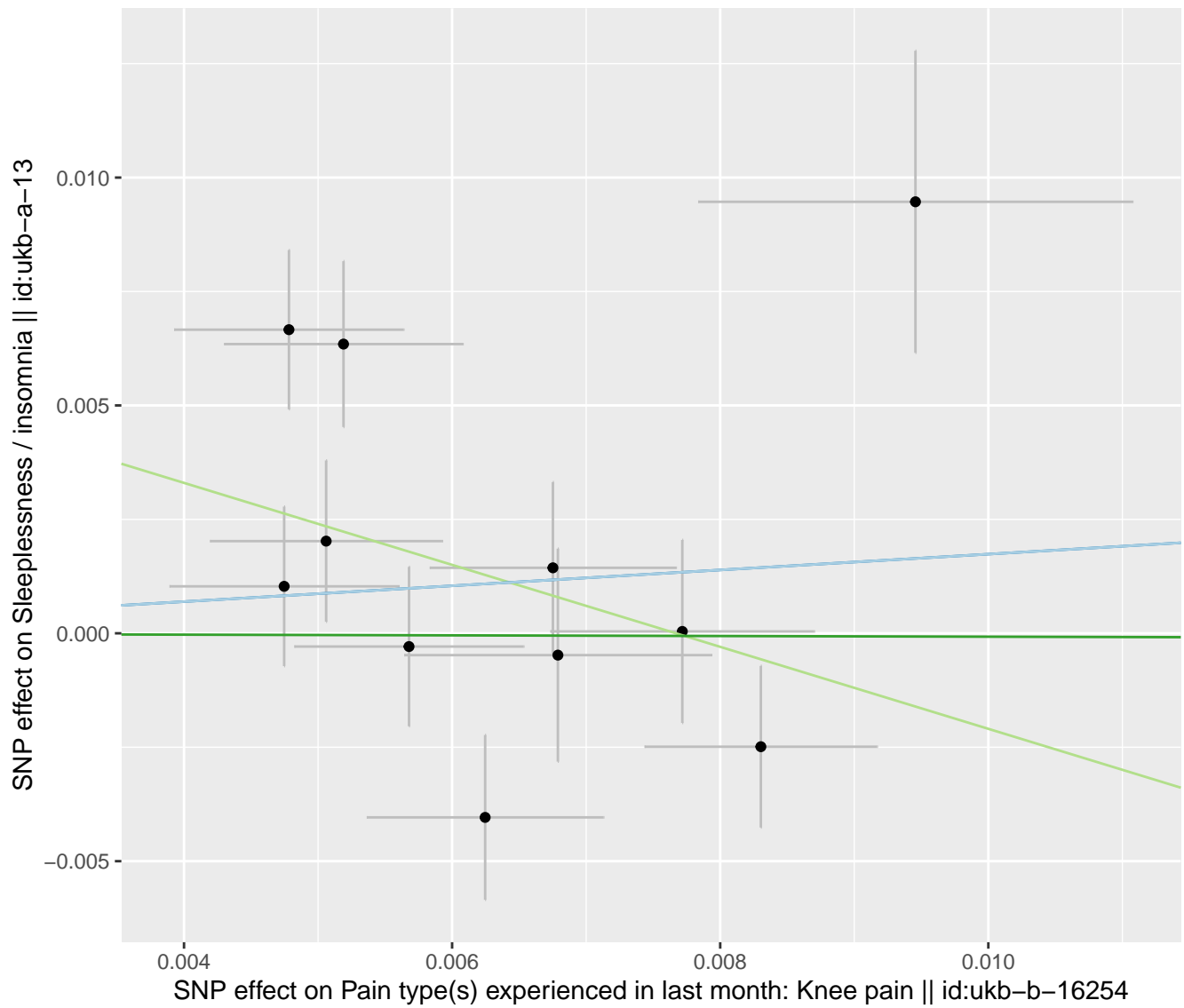
### MR Test

Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median



### MR Test

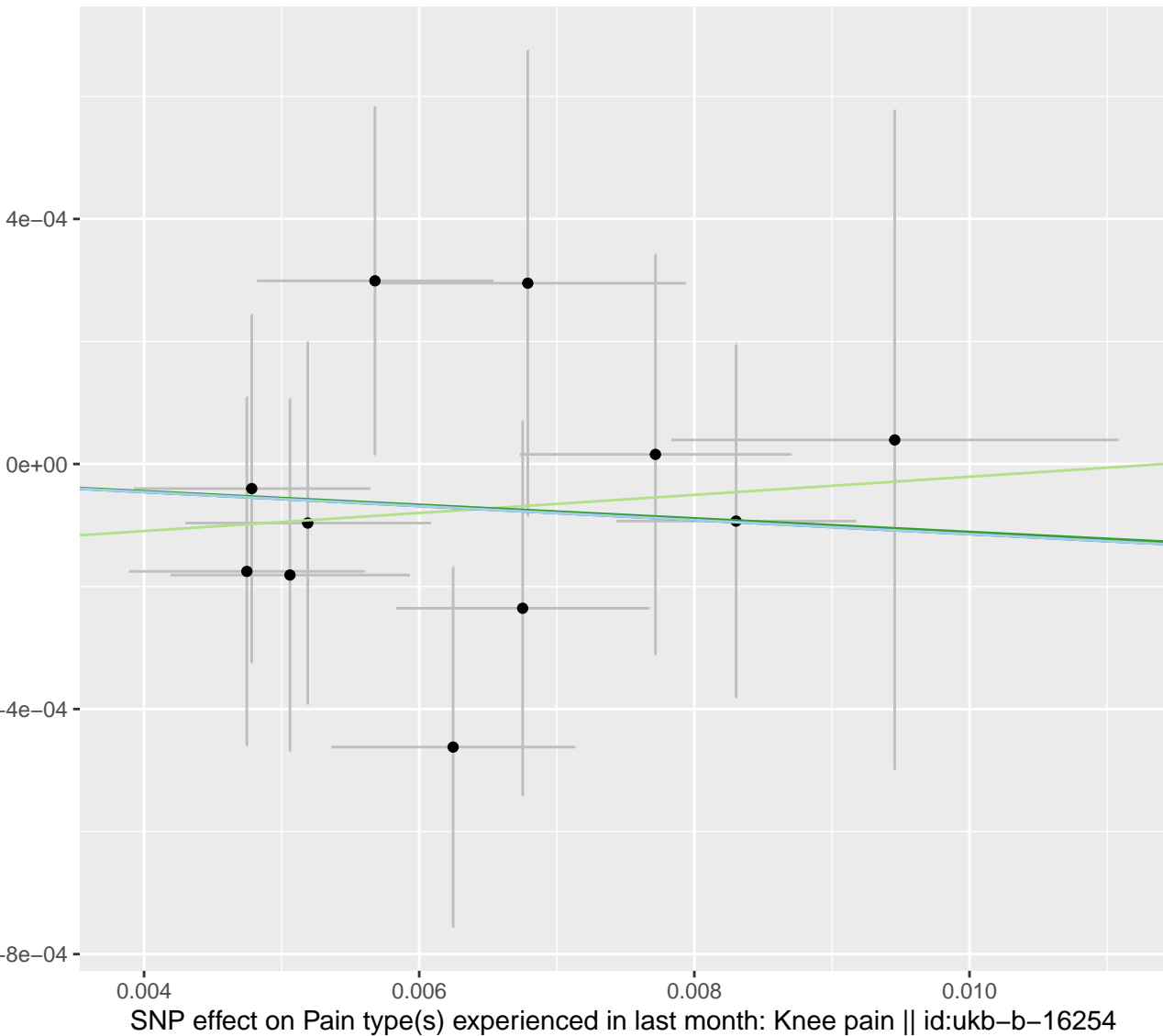
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82



MR Test

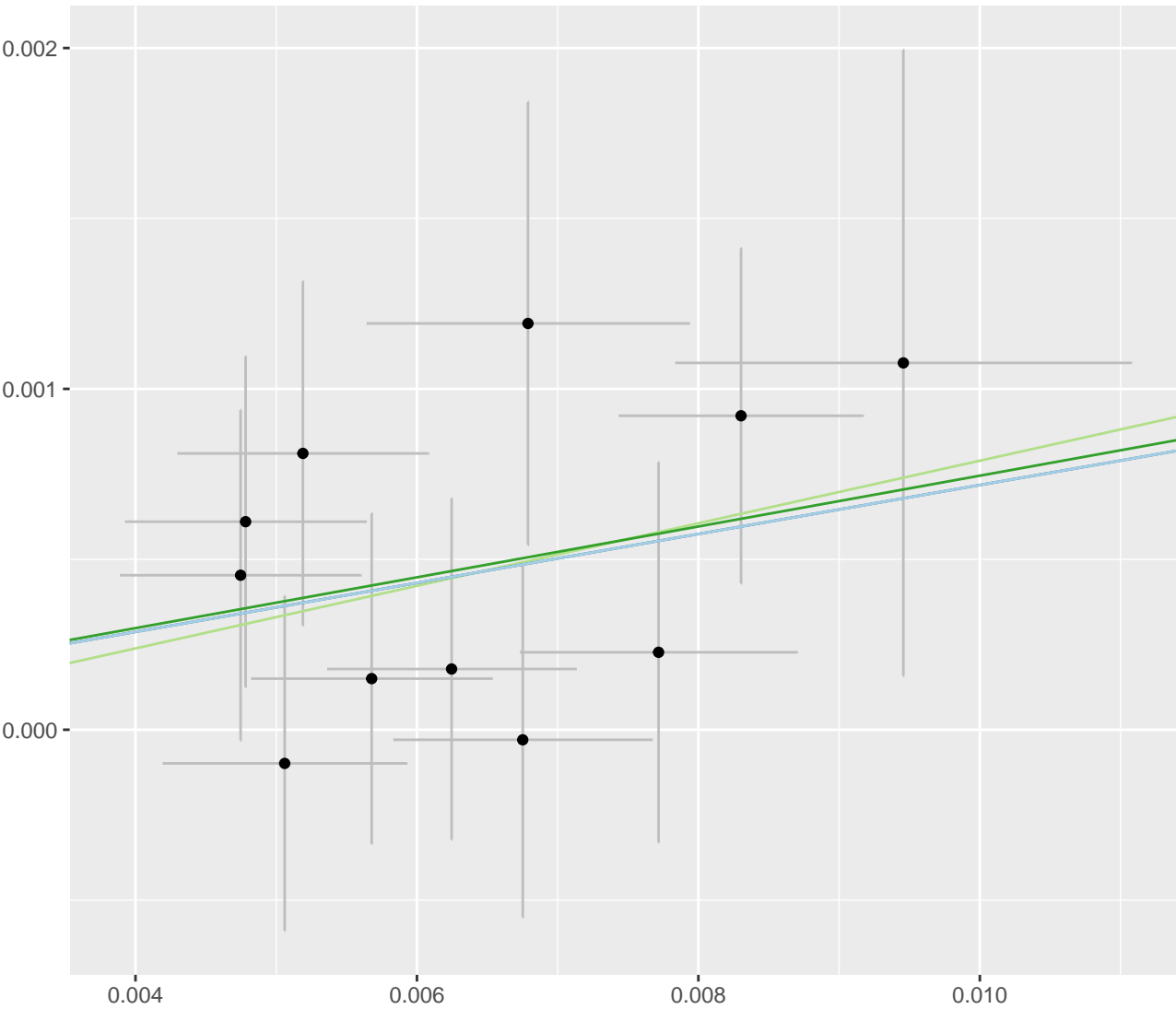
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064

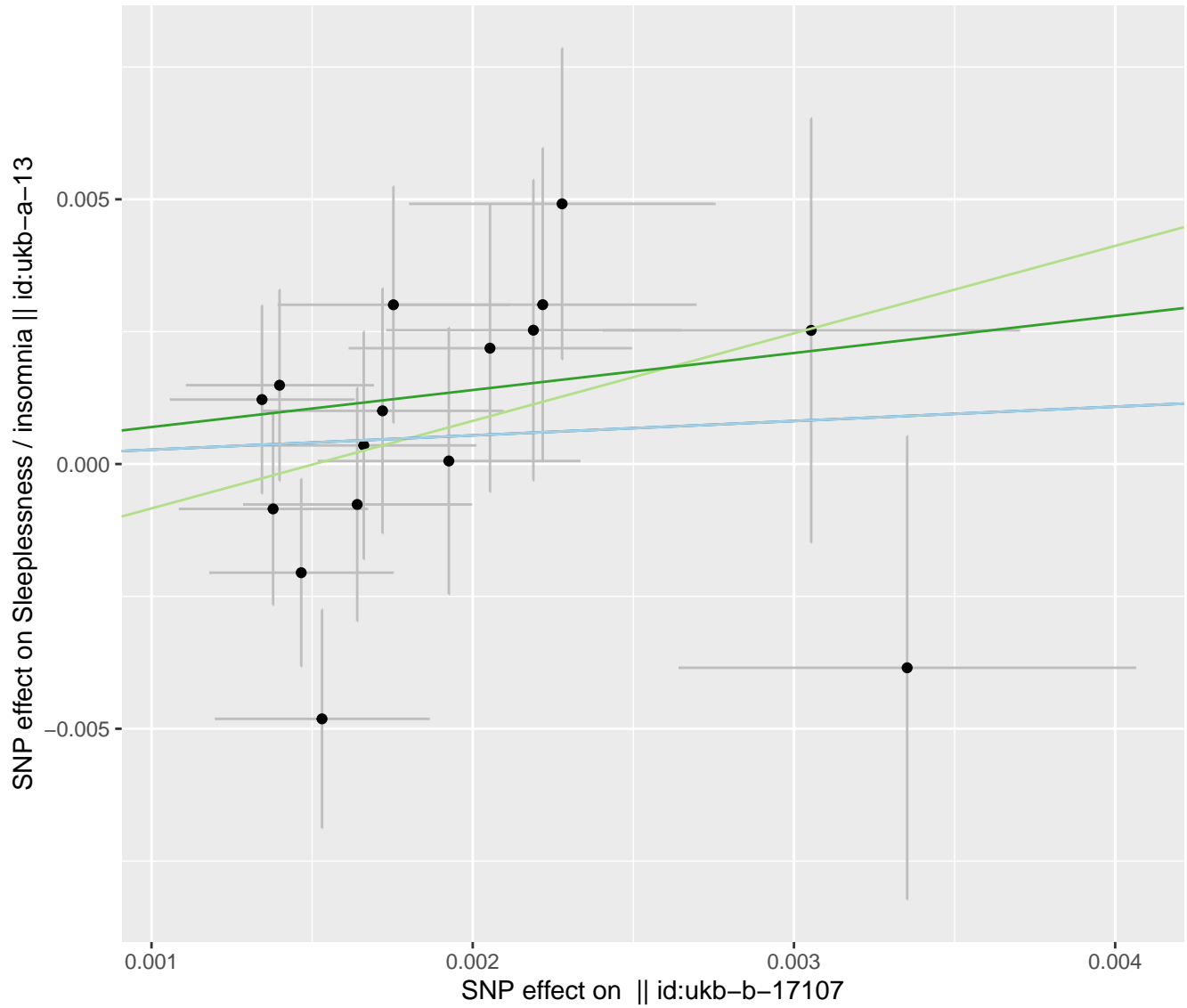


SNP effect on Pain type(s) experienced in last month: Knee pain || id:ukb-b-16254

### MR Test

Inverse variance weighted (fixed effects)  
Inverse variance weighted (multiplicative random effects)

MR Egger  
Weighted median

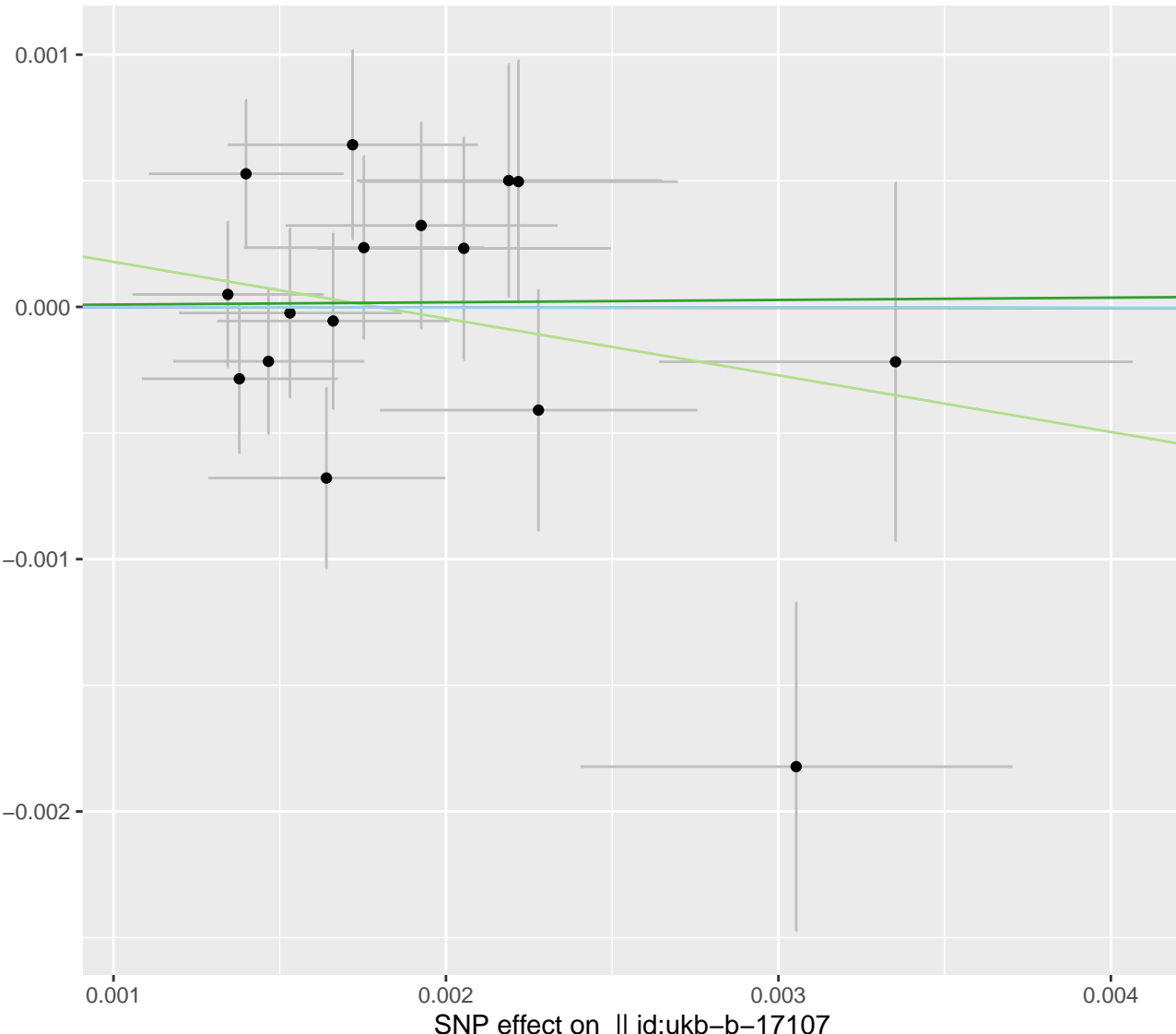


MR Test

- Inverse variance weighted (fixed effects)
- Inverse variance weighted (multiplicative random effects)

- MR Egger
- Weighted median

SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82



### MR Test

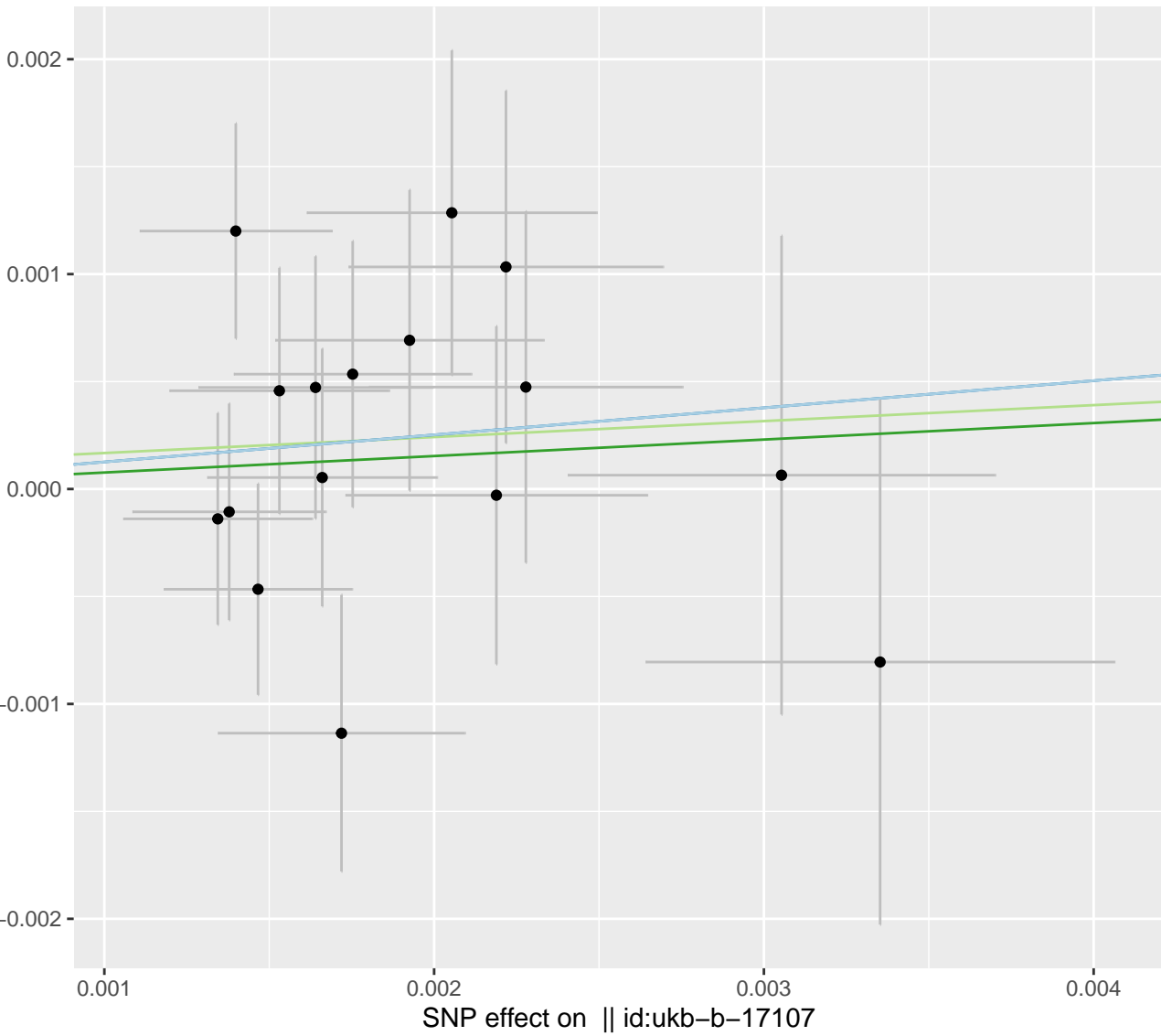
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

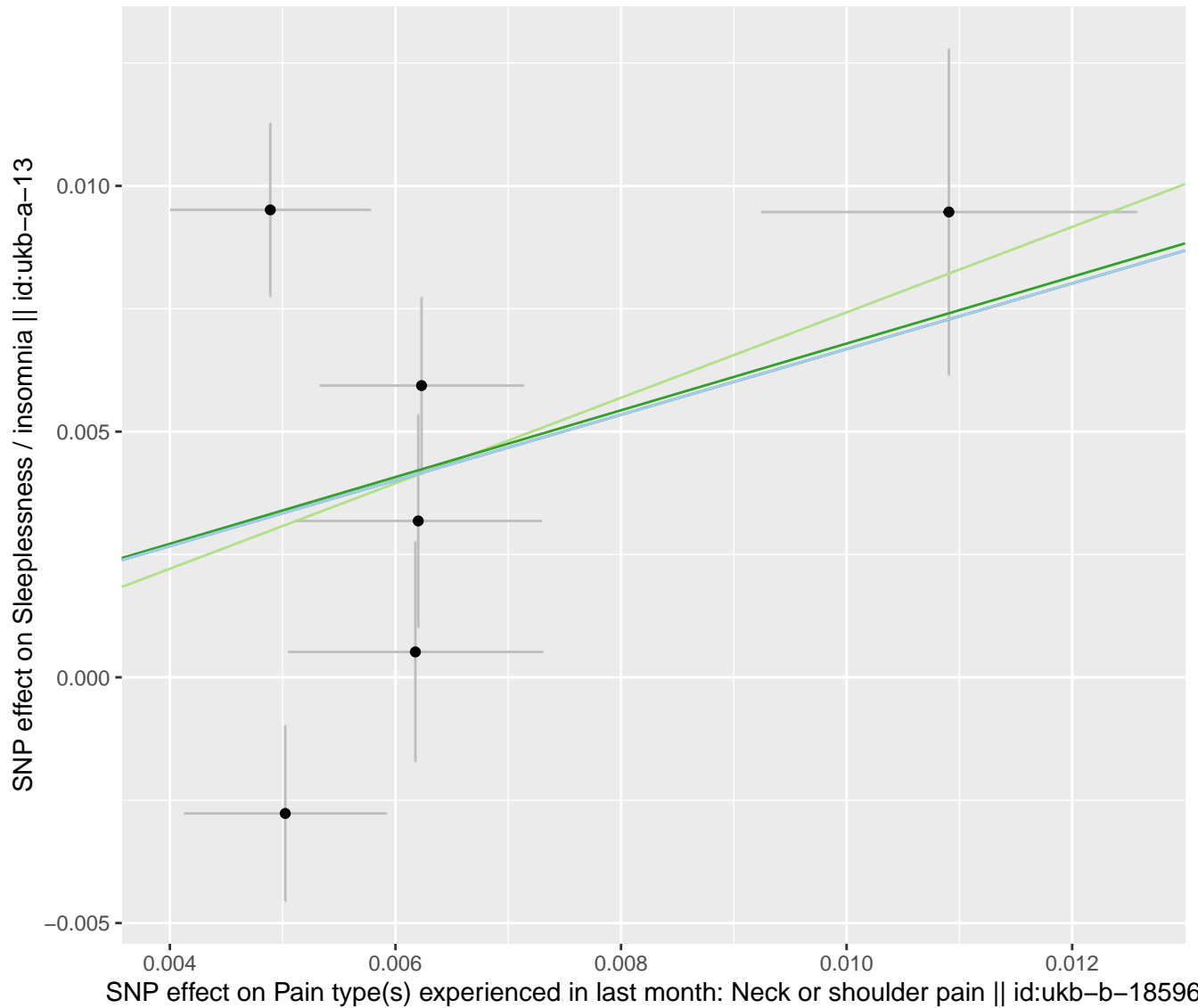
SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064





### MR Test

- Inverse variance weighted (fixed effects)
- Inverse variance weighted (multiplicative random effects)
- MR Egger
- Weighted median

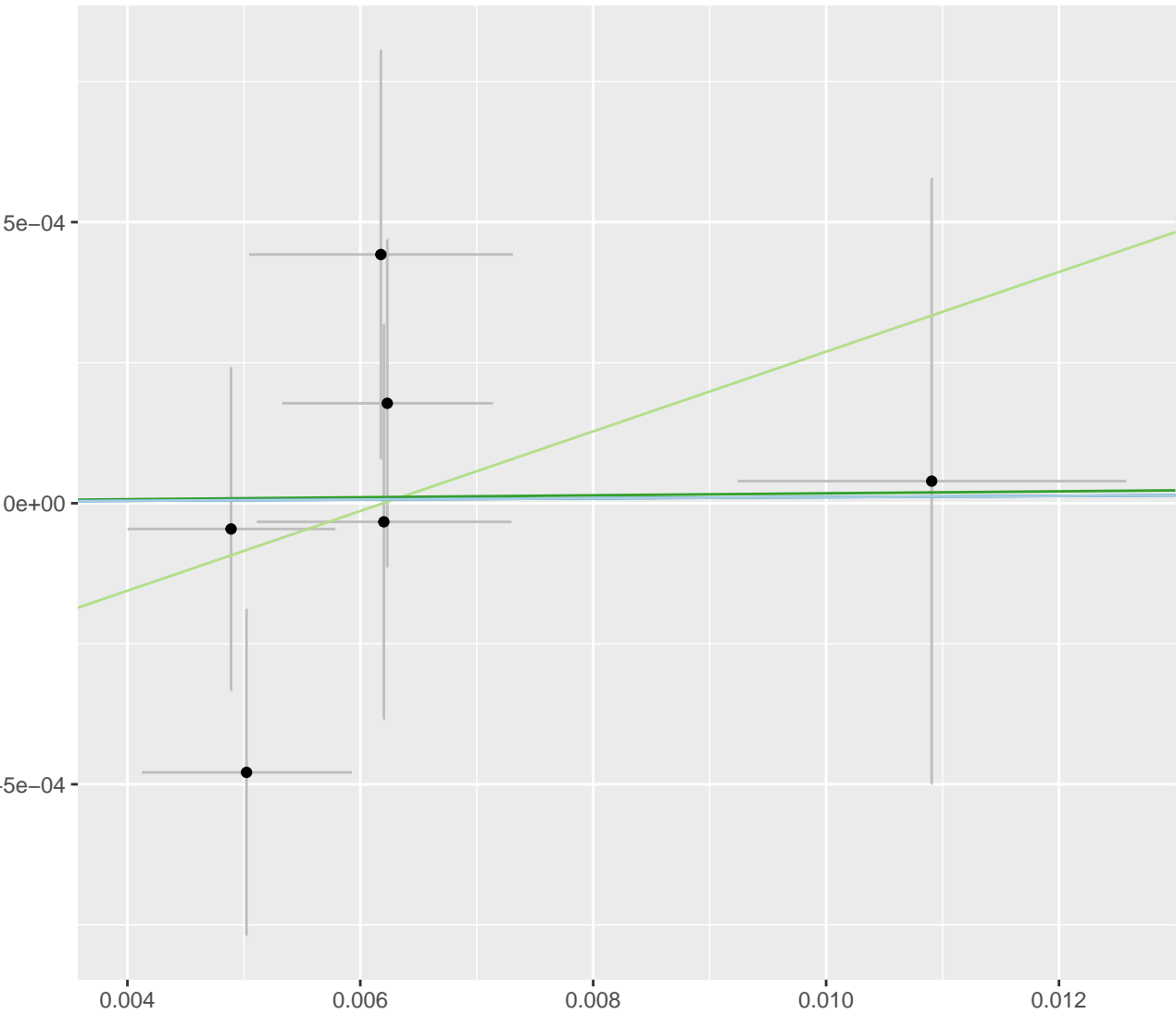


SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82

### MR Test

Inverse variance weighted (fixed effects)  
Inverse variance weighted (multiplicative random effects)

MR Egger  
Weighted median



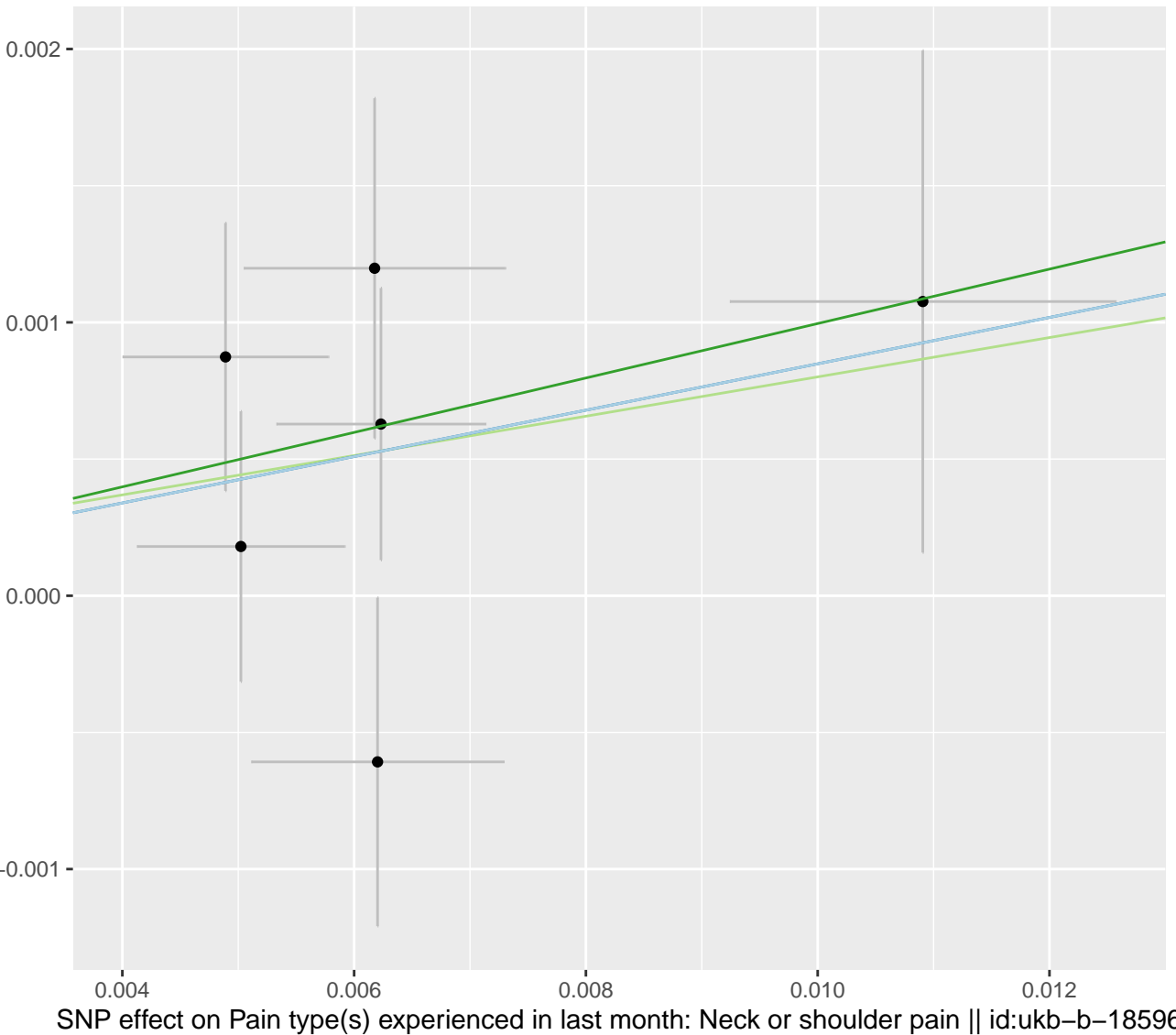
SNP effect on Pain type(s) experienced in last month: Neck or shoulder pain || id:ukb-b-18596

MR Test

Inverse variance weighted (fixed effects)  
Inverse variance weighted (multiplicative random effects)

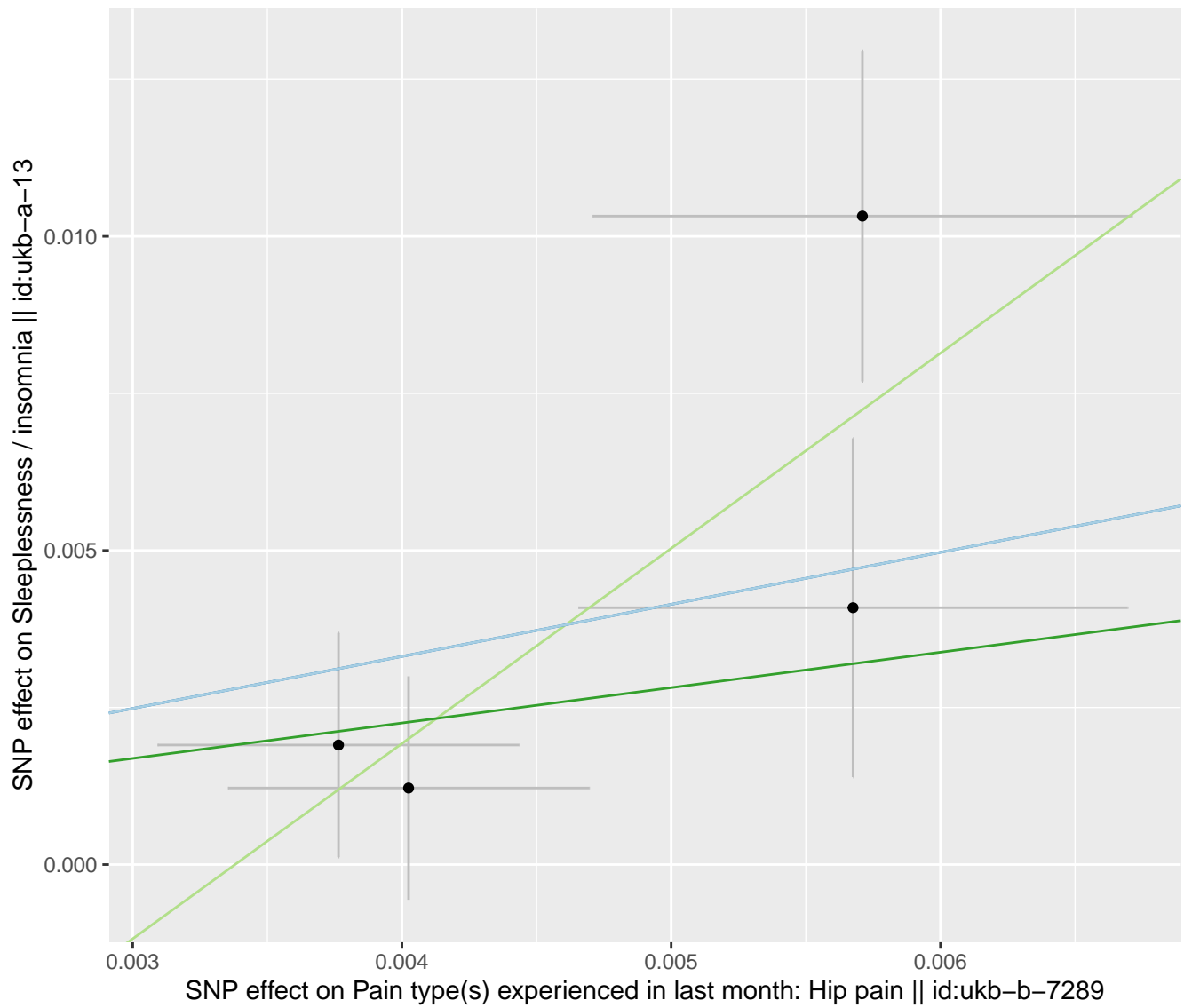
MR Egger  
Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064



MR Test

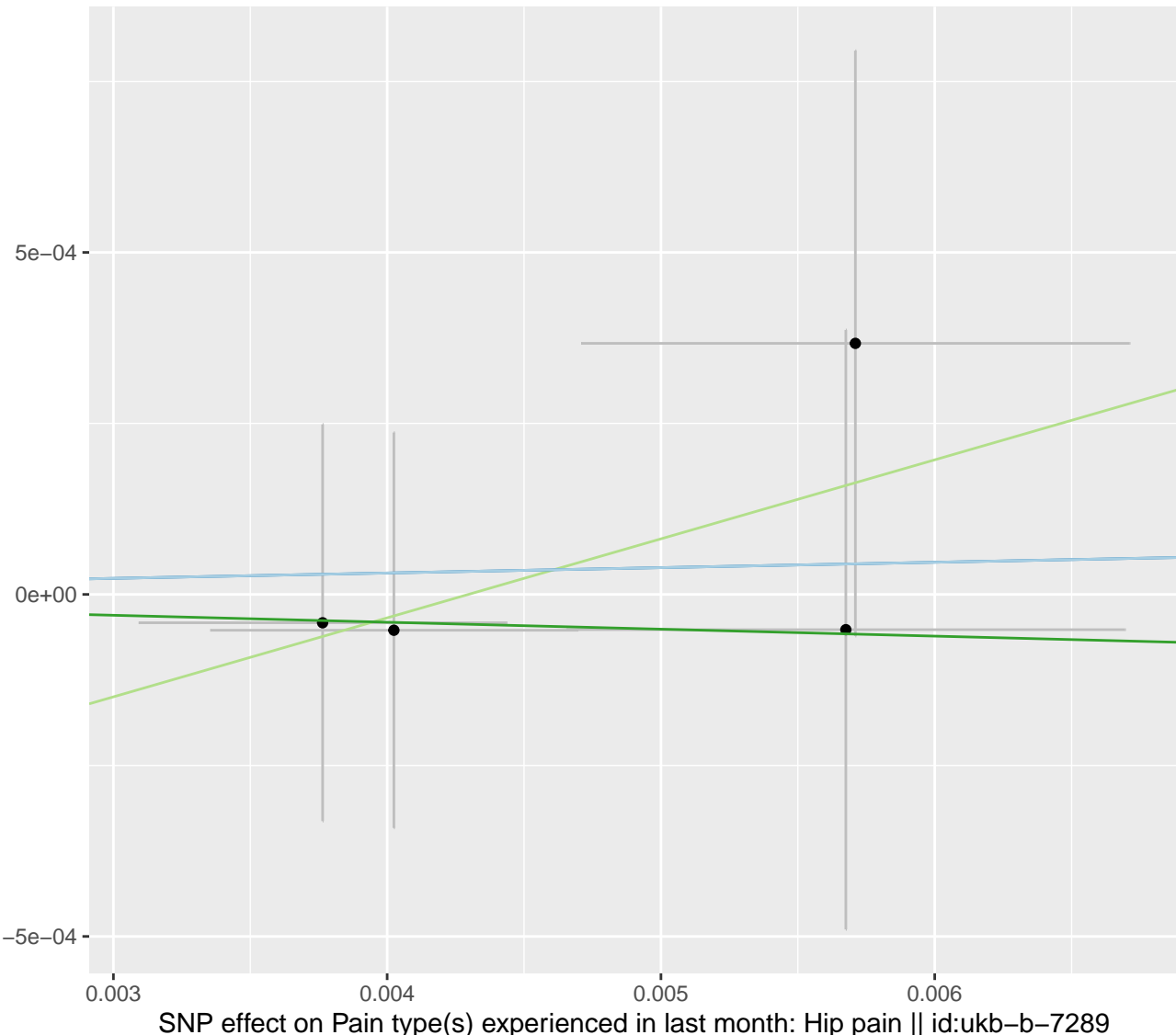
- Inverse variance weighted (fixed effects)
- Inverse variance weighted (multiplicative random effects)
- MR Egger
- Weighted median



SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82

### MR Test

- Inverse variance weighted (fixed effects)
- Inverse variance weighted (multiplicative random effects)
- MR Egger
- Weighted median

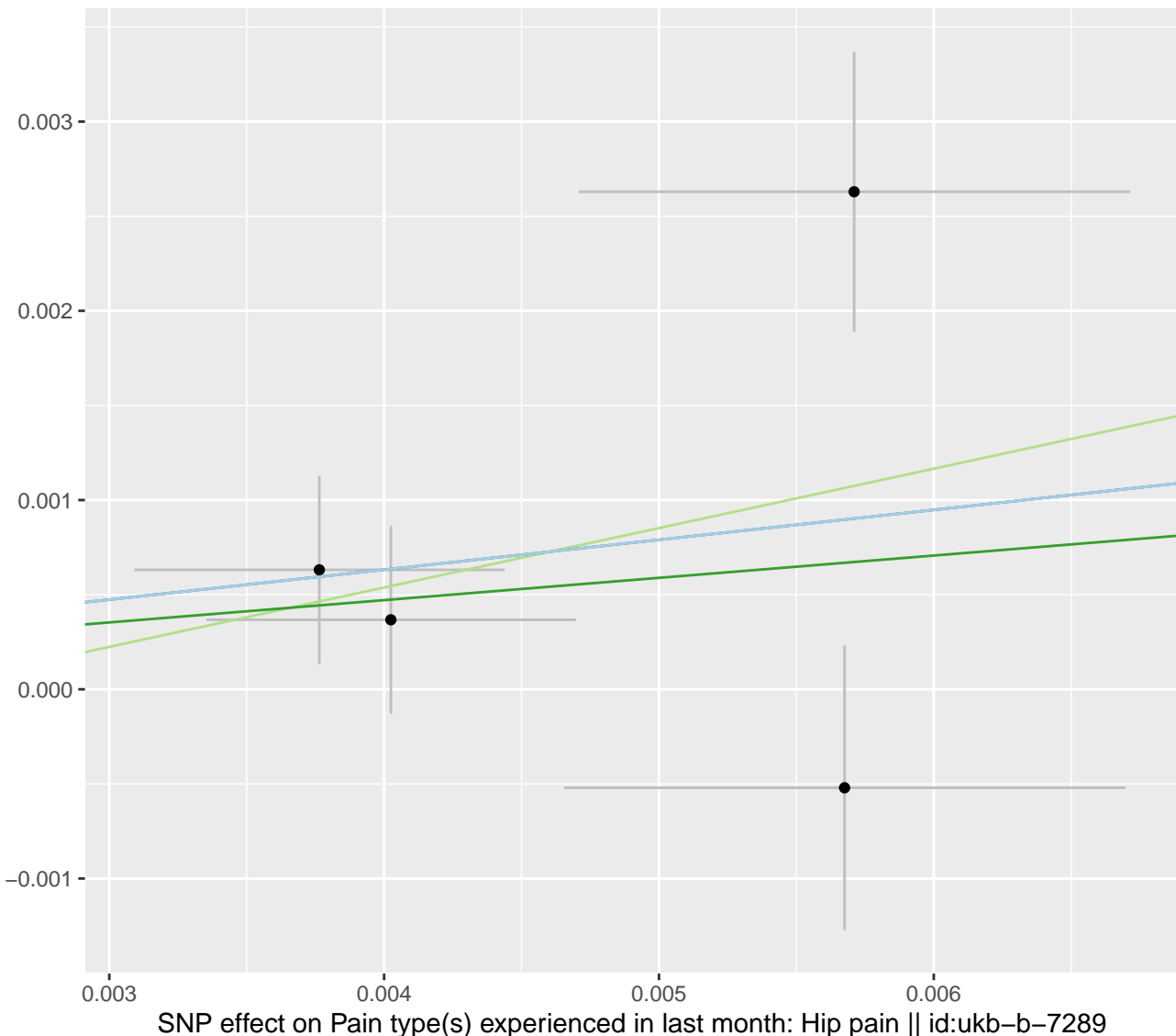


### MR Test

Inverse variance weighted (fixed effects)  
Inverse variance weighted (multiplicative random effects)

MR Egger  
Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064



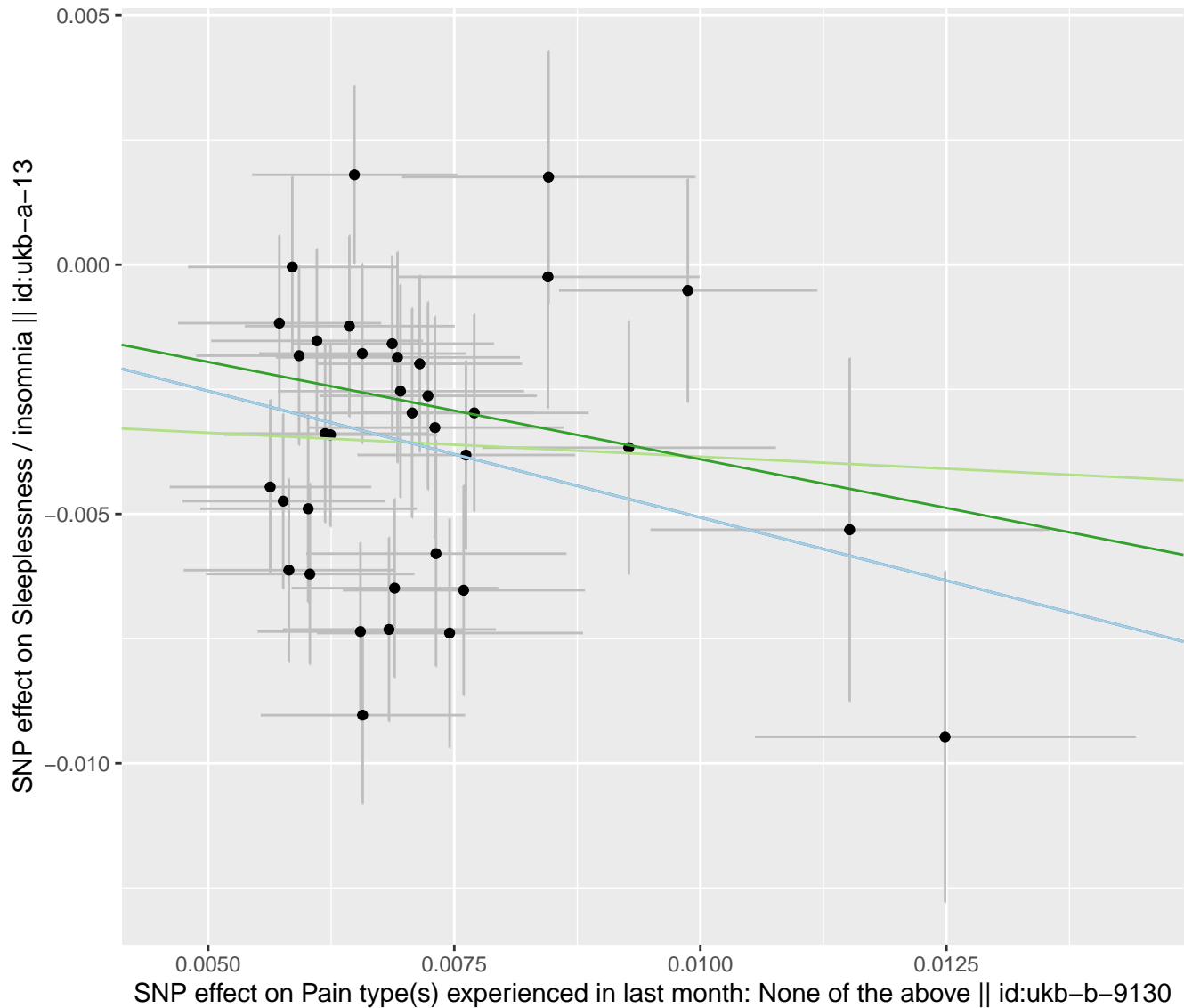
MR Test

Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

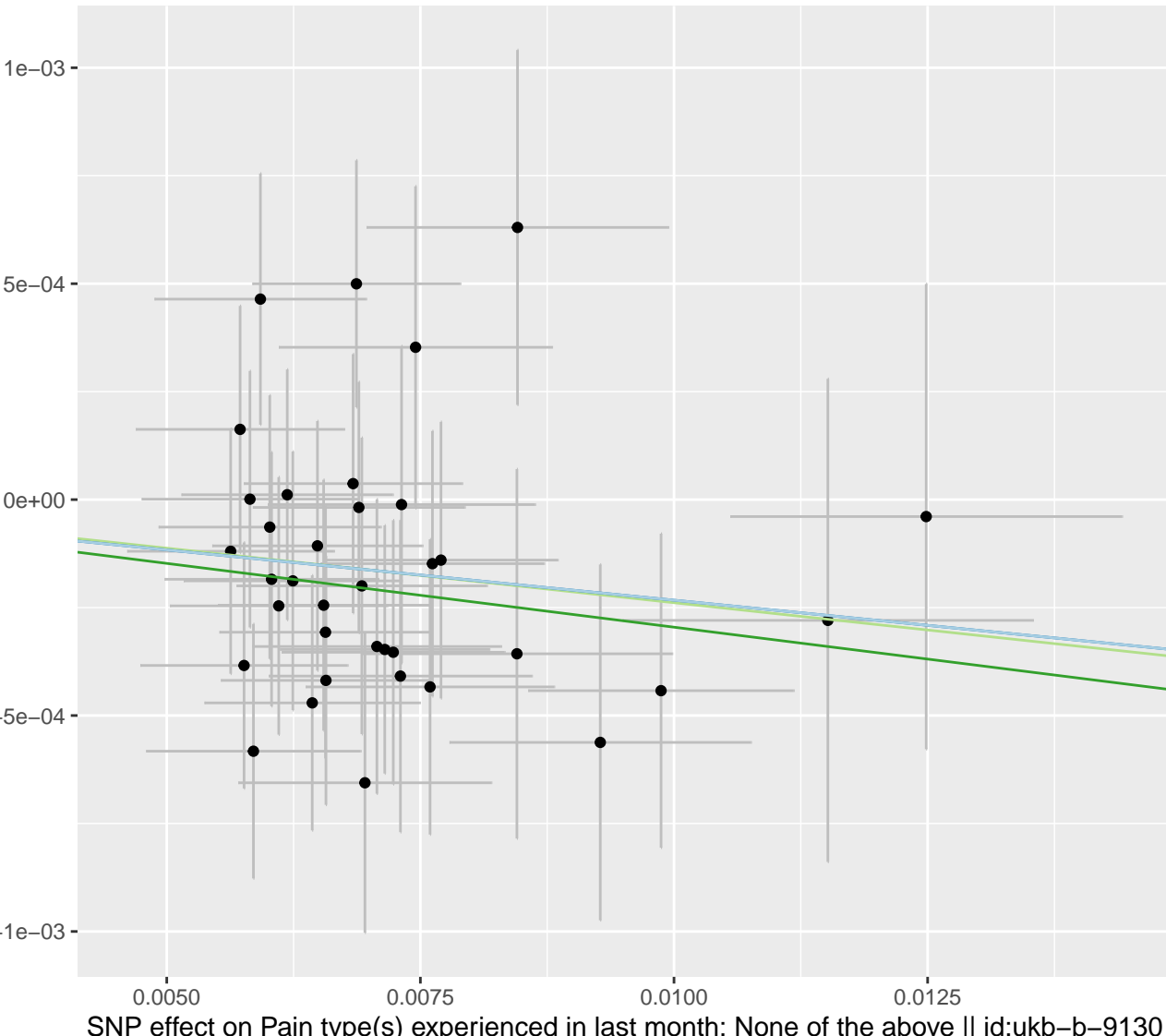


SNP effect on Non-cancer illness code self-reported: anxiety/panic attacks || id:ukb-a-82

MR Test

Inverse variance weighted (fixed effects)  
Inverse variance weighted (multiplicative random effects)

MR Egger  
Weighted median





### MR Test

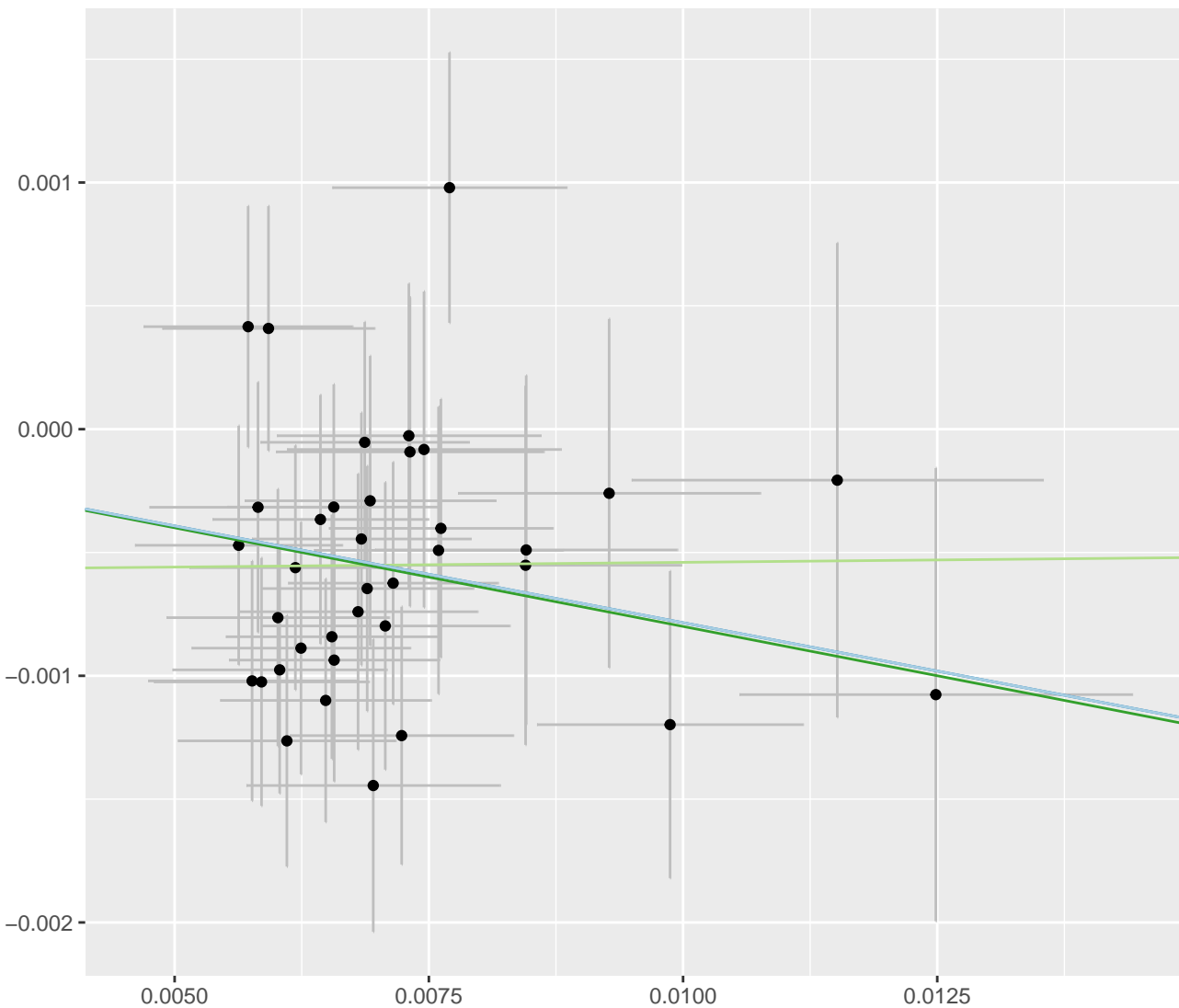
Inverse variance weighted (fixed effects)

Inverse variance weighted (multiplicative random effects)

MR Egger

Weighted median

SNP effect on Non-cancer illness code, self-reported: depression || id:ukb-b-12064



SNP effect on Pain type(s) experienced in last month: None of the above || id:ukb-b-9130

### MR Test

- Inverse variance weighted (fixed effects)
- Inverse variance weighted (multiplicative random effects)
- MR Egger
- Weighted median

