Box 1: Overview of Mendelian randomization (MR) assumptions and methods²

Main assumptions of MR

MR has three core assumptions:

- 1. Relevance assumption: The genetic variant(s) are strongly associated with the exposure of interest.
- 2. Independence assumption: There are no (unmeasured) confounders between the genetic variants and outcomes of interest.
- 3. Exclusion restriction criteria (no pleiotropy): There is no pathway between the genetic variant(s) and the outcome other than via the exposure of interest.

Additional, more nuanced assumptions apply to the interpretation of MR analyses. This includes that genetic variants act equally in all individuals (instrument homogeneity), and that genetic variants are truly randomly allocated across the population. This is not always true (e.g., due to ancestral clustering of genetic variants). Consideration should be given to core and advanced assumptions before making strong causal claims.

Common statistical approaches to MR

In the case of summary data MR with multiple genetic variants, typically the "main" MR effect will be estimated with a fixed or random-effects inverse variance weighted method. This combines Wald ratios for individual SNP-outcome effects, giving an overall MR estimate. This method is statistically powerful but can be biased in the presence of pleiotropy.

Pleiotropy robust methods: methods have been developed to account for pleiotropic SNPs, including MR-Egger, the weighted median and weighted mode estimators, MR-PRESSO and MR-RAPs. These make different assumptions about the pleiotropic effects of the genetic variants. A combination of these methods, each giving consistent estimates, allows the greatest confidence that results do not only reflect pleiotropy.

Multivariable MR: this allows the joint effects of two or more exposure to be estimated simultaneously. Multivariable MR can be used, for example, to account for a known pleiotropic pathway or to explore mediated effects.

MR is a rapidly evolving field, with new methodological approaches frequently becoming available. Since all have slightly different assumptions, data requirements, strengths and weaknesses, the most appropriate strategy is the application of multiple methods to test the robustness of findings to these differences.

A more extensive introduction to MR assumptions and methods can be found here.

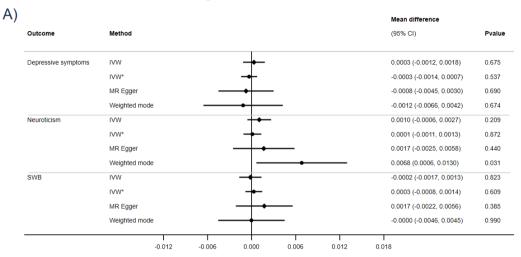
Supplementary Table 1: Number of SNPs and mean F statistics for each individual analysis for A) blood pressure traits as exposures and B) blood pressure traits as outcomes

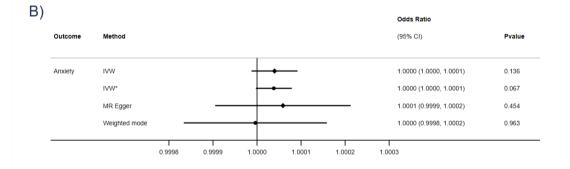
Supplementary ⁻	i adie 1a: Nui	TIDER OF SINF	rs and mean F s	austics for each	i individual analy	sis ior blood pres	sure traits as ex	cposures					
Exposure	Clumping threshold (<i>r</i> ²)	Outcome	Outcome										
		Anxiety		Depressive symptoms		Neuroticism		Subjective wellbeing					
		Number of SNPs used in analysis	Mean F statistic	Number of SNPs used in analysis	Mean F statistic	Number of SNPs used in analysis	Mean F statistic	Number of SNPs used in analysis	Mean F statistic				
Diastolic blood pressure	<0.05	631	63.61	1041	60.94	1041	60.94	751	61.66				
	<0.001	291	80.01	433	80.05	433	80.05	336	81.24				
Systolic blood pressure	<0.05	620	60.26	978	59.58	978	59.58	710	60.45				
	<0.001	293	74.38	431	75.16	431	75.16	326	76.66				
Pulse pressure	<0.05	533	59.82	975	59.70	975	59.67	748	60.41				
	<0.001	212	79.94	356	82.28	355	82.38	292	81.55				
Hypertension	<0.05	53	48.52	81	46.61	81	46.61	53	48.72				
	<0.001	48	49.93	66	48.66	66	48.66	48	50.77				
					1	1		1	1				

Supplementary Table 1b:	Number of S	NPs and mea	an F statistics	for each indi	vidual analysi	s for blood pressur	e traits as outcom	es
Exposure					Outcome			
	Diastoli pres		Systoli pres		Pulse	e pressure	Hyper	tension
	Number of SNPs used in analysis	Mean F statistic	Number of SNPs used in analysis	Mean F statistic	Number of SNPs used in analysis	Mean F statistic	Number of SNPs used in analysis	Mean F statistic
Anxiety	0	NA	0	NA	0	NA	0	NA
Depressive symptoms	1	38.45	1	38.45	1	38.45	1	38.45
Neuroticism	10	38.45	10	38.45	10	38.45	10	38.45
Subjective wellbeing	1	27.56	1	27.56	1	27.56	1	27.56

Supplementary Figure 1: The bidirectional association between systolic blood pressure (SBP) and anxiety, depressive symptoms, neuroticism and subjective wellbeing. Panel A presents results with SBP as the exposure for continuous outcomes, panel B presents results with SBP as the exposure for dichotomous outcomes, and panel C with SBP as the outcome.

Footnote: IVW = inverse variance weighted method

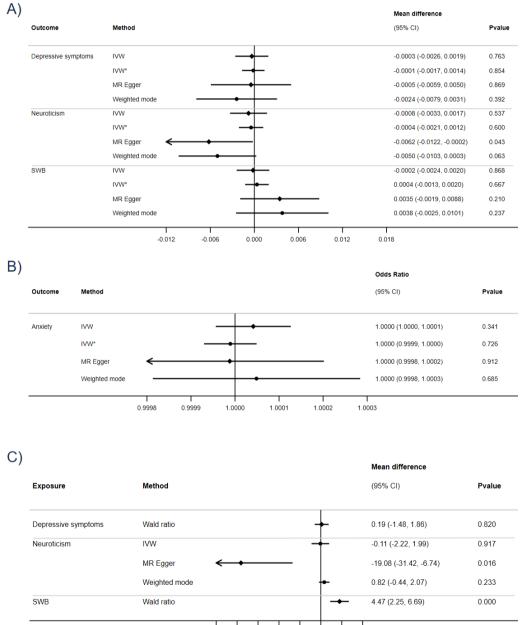




										Mean difference	
	Method									(95% CI)	Pval
symptoms	Wald ratio					+				-0.15 (-2.60, 2.30)	0.905
	IVW					+	_			-0.16 (-4.74, 4.42)	0.945
	MR Egger	<		_						-39.56 (-67.74, -11.39)	0.025
	Weighted mode					+	-			1.46 (-0.29, 3.21)	0.136
	Wald ratio							•		7.87 (4.61, 11.12)	0.000
						-			Т		
		-20	-15	-10	-5	0	5	10		15	1 15

Supplementary Figure 2: The bidirectional association between pulse pressure (PP) and anxiety, depressive symptoms, neuroticism and subjective wellbeing. Panel A presents results with PP as the exposure for continuous outcomes, panel B presents results with PP as the exposure for dichotomous outcomes, and panel C with PP as the outcome.

Footnote: IVW = inverse variance weighted method



-25.0 -20.0 -15.0 -10.0 -5.0 0.0 5.0 10.0

Supplementary Figure 3: The bidirectional association between hypertension and anxiety, depressive symptoms, neuroticism and subjective wellbeing. Panel A presents results with hypertension as the exposure for continuous outcomes, panel B presents results with hypertension as the exposure for dichotomous outcomes, and panel C with hypertension as the outcome.

Footnote: IVW = inverse variance weighted method

.)								Mean difference	
	Outcome	N	Method					(95% CI)	Pvalu
	Depressive sym	nptoms l'	vw					-0.0575 (-0.2676, 0.1525)	0.591
		Г	VW*					0.0165 (-0.1770, 0.2100)	0.867
		N	VR Egger					-0.1260 (-0.9386, 0.6865)	0.762
		v	Weighted mode					-0.0504 (-0.6188, 0.5180)	0.863
	Neuroticism	r	vw		+	_		0.1296 (-0.1351, 0.3943)	0.337
		r	VW*		-+			0.0871 (-0.1518, 0.3260)	0.475
		N	MR Egger		•			0.1783 (-0.8673, 1.2240)	0.739
		v	Weighted mode			•	_	0.5331 (-0.1123, 1.1786)	0.110
	SWB	r	vw					0.0295 (-0.2092, 0.2682)	0.809
		r	VW*		-			-0.0222 (-0.2424, 0.1980)	0.843
		N	MR Egger			•		0.5339 (-0.3991, 1.4669)	0.268
		v	Weighted mode		•	-		-0.1299 (-0.6481, 0.3882)	0.625
			-1.2	-0.6	0.0	I 0.6	1.2	l 1.8	
				0.0	0.0	0.0			
)									
)								Odds Ratio	
	Outcome								
	outcome	Method						(95% CI)	Pvalue
	Anxiety	IVW			+			1.0059 (0.9988, 1.0131)	0.103
					++				
		IVW				_		1.0059 (0.9988, 1.0131)	0.103
		IVW IVW*	ode					1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126)	0.103 0.104
		IVW IVW* MR Egger	ode 1 0.960		1.000			1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306)	0.103 0.104 0.723
		IVW IVW* MR Egger	1		1.000			1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306)	0.103 0.104 0.723
)		IVW IVW* MR Egger	1		1.000	1.020	1.04	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306)	0.103 0.104 0.723
)	Anxiety	IVW IVW* MR Egger	0.960		1.000		1.04 C	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306) 40	0.103 0.104 0.723 0.287
)		IVW IVW* MR Egger	1		1.000		1.04 C	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306)	0.103 0.104 0.723
)	Anxiety	IVW IVW* MR Egger Weighted m	0.960		1.000		1.04 C (§	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306) 40	0.103 0.104 0.723 0.287
)	Anxiety	IVW IVW* MR Egger Weighted m	0.960 Method		1.000		1.04 C (§	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306) 40 Ddds Ratio 95% Cl)	0.103 0.104 0.723 0.287 Pvalue
)	Anxiety Exposure Depressive st	IVW IVW* MR Egger Weighted m	I 0.960 Method Wald ratio		1.000	1.020	1.0- ((1 1	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306) 40 Adds Ratio 95% C1) .03 (0.97, 1.08)	0.103 0.104 0.723 0.287 Pvalue 0.317
)	Anxiety Exposure Depressive st	IVW IVW* MR Egger Weighted m	Method Wald ratio	0.980	1.000	 1.020	1.04 C ((1 1 0	1.0059 (0.9988, 1.0131) 1.0057 (0.9988, 1.0126) 1.0060 (0.9737, 1.0393) 1.0107 (0.9913, 1.0306) 40 A0 A0 A0 A0 A0 A0 A0 A0 A0 A	0.103 0.104 0.723 0.287 Pvalue 0.317 0.929

0.6 0.8 1.0 1.2 1.4