

Table S1. GWAS datasets included in the analyses

Trait	Sample size	Reference
BD	41,917 cases from 57 cohorts collected in Europe, North America and Australia and 371,549 controls of European origin	[5]
SCZ	53,386 cases and 77,258 controls of European origin	[6]
MDD	170,756 cases and 329,443 controls from PGC and the UK Biobank	[7]
ADHD	20,183 cases and 35,191 controls from 12 cohorts (including the iPSYCH population-based cohort from Denmark and 11 European, North American and Chinese cohorts aggregated by the PGC)	[23]
ASD	18,381 cases and 27,969 controls from the iPSYCH cohort and five family-based trio samples of European ancestry from the PGC	[24]
PTSD	23,212 cases and 151,447 controls of European origin	[25]
OCD	2,688 cases and 7,037 controls of European origin	[26]
TS	4,819 cases and 9,488 controls	[27]
AN	16,992 cases and 55,525 controls of European origin	[28]
BMI	806,834 individuals from the UK Biobank and the GIANT consortium	[29]
T2D	55,193 and 74,132 controls of European origin	[30]
CRP	575,531 individuals of European origin from the UK Biobank and the CHARGE Consortium	[32]
CAD	122,733 cases and 424,528 controls of European ancestry from the UK Biobank and CARDIoGRAMplusC4D	[31]
Chronotype	449,734 individuals from the UK Biobank	[34]
Insomnia	109,548 cases and 277,440 controls from the UK Biobank	[33]
Sleep duration	446,118 individuals from the UK Biobank	[35]

The table shows the phenotypes analyzed in this study, the original GWAS datasets from which summary statistics were obtained and relative references. In the case of studies including data from 23andMe, we used the publicly available version of genome-wide summary statistics that exclude data for 23andMe participants (as 23andMe policies only allow the publication of summary statistics including up to 10,000 variants).

Abbreviations: ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorders; BD, bipolar disorder; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; se, standard error; PTSD, post-traumatic stress disorder; T2D, type 2 diabetes.

Table S2. Complete table of genetic correlations between psychiatric and metabolic or sleep traits, significant after multiple testing adjustment based on the number of tests (n = 120)

Trait 1	Trait 2	r_g	se	Z	p	adj p
BD	SCZ	0.70	0.02	46.12	0.0e+00	0.0e+00
BD	MDD	0.45	0.02	20.64	1.2×10^{-94}	1.4×10^{-92}
BD	ADHD	0.22	0.03	6.63	3.3×10^{-11}	3.9×10^{-9}
BD	OCD	0.32	0.06	5.77	8.1×10^{-9}	9.7×10^{-7}
BD	PTSD	0.38	0.05	7.17	7.8×10^{-13}	9.3×10^{-11}
BD	ASD	0.22	0.04	5.43	5.7×10^{-8}	6.9×10^{-6}
BD	AN	0.22	0.03	7.71	1.2×10^{-14}	1.5×10^{-12}
BD	Insomnia	0.11	0.03	4.23	2.4×10^{-5}	0.0028
BD	Sleep duration	0.11	0.02	4.91	9.0×10^{-7}	0.0001
SCZ	MDD	0.34	0.02	16.85	1.1×10^{-63}	1.3×10^{-61}
SCZ	CRP	-0.06	0.02	-3.75	0.0002	0.0211
SCZ	BMI	-0.10	0.01	-7.07	1.6×10^{-12}	1.9×10^{-10}
SCZ	ADHD	0.18	0.03	5.98	2.3×10^{-9}	2.7×10^{-7}
SCZ	OCD	0.32	0.05	6.37	1.9×10^{-10}	2.3×10^{-8}
SCZ	PTSD	0.31	0.05	6.45	1.2×10^{-10}	1.4×10^{-8}
SCZ	ASD	0.26	0.03	7.48	7.5×10^{-14}	9.0×10^{-12}
SCZ	AN	0.23	0.03	8.59	9.0×10^{-18}	1.1×10^{-15}
SCZ	Chronotype	-0.10	0.02	-5.38	7.6×10^{-8}	9.1×10^{-6}
SCZ	Sleep duration	0.15	0.02	7.37	1.7×10^{-13}	2.1×10^{-11}
MDD	CRP	0.11	0.02	5.50	3.8×10^{-8}	4.6×10^{-6}
MDD	BMI	0.11	0.02	6.55	5.6×10^{-11}	6.8×10^{-9}
MDD	T2D	0.14	0.02	6.58	4.8×10^{-11}	5.8×10^{-9}
MDD	ADHD	0.46	0.03	15.66	2.9×10^{-55}	3.5×10^{-53}
MDD	OCD	0.24	0.05	4.78	1.8×10^{-6}	0.0002
MDD	PTSD	0.72	0.07	10.71	9.4×10^{-27}	1.1×10^{-24}
MDD	TS	0.23	0.04	5.48	4.3×10^{-8}	5.1×10^{-6}
MDD	ASD	0.37	0.03	12.66	9.3×10^{-37}	1.1×10^{-34}
MDD	AN	0.27	0.03	8.31	9.2×10^{-17}	1.1×10^{-14}
MDD	Insomnia	0.44	0.03	17.60	2.3×10^{-69}	2.8×10^{-67}
MDD	Sleep duration	-0.11	0.02	-4.43	9.4×10^{-6}	0.0011
MDD	CAD	0.21	0.02	10.33	5.1×10^{-25}	6.2×10^{-23}
CRP	BMI	0.52	0.04	14.28	3.1×10^{-46}	3.7×10^{-44}
CRP	T2D	0.40	0.04	10.73	7.7×10^{-27}	9.2×10^{-25}
CRP	ADHD	0.30	0.04	8.27	1.4×10^{-16}	1.6×10^{-14}
CRP	OCD	-0.22	0.04	-5.39	6.9×10^{-8}	8.3×10^{-6}
CRP	PTSD	0.21	0.04	4.98	6.5×10^{-7}	7.7×10^{-5}
CRP	AN	-0.28	0.03	-9.28	1.7×10^{-20}	2.1×10^{-18}
CRP	Insomnia	0.16	0.02	6.97	3.2×10^{-12}	3.8×10^{-10}
CRP	CAD	0.27	0.03	7.77	7.8×10^{-15}	9.3×10^{-13}
BMI	T2D	0.55	0.02	25.26	8.9×10^{-141}	1.1×10^{-138}
BMI	ADHD	0.35	0.02	14.65	1.4×10^{-48}	1.7×10^{-46}
BMI	OCD	-0.29	0.04	-6.97	3.2×10^{-12}	3.8×10^{-10}
BMI	PTSD	0.32	0.04	7.77	8.1×10^{-15}	9.7×10^{-13}
BMI	AN	-0.31	0.02	-13.52	1.3×10^{-41}	1.5×10^{-39}
BMI	Insomnia	0.19	0.02	8.98	2.8×10^{-19}	3.3×10^{-17}

BMI	Sleep duration	-0.09	0.02	-4.43	9.4×10^{-6}	0.0011
BMI	CAD	0.31	0.02	15.00	6.9×10^{-51}	8.3×10^{-49}
T2D	ADHD	0.32	0.03	12.16	5.0×10^{-34}	6.0×10^{-32}
T2D	OCD	-0.17	0.04	-3.81	0.0001	0.0164
T2D	PTSD	0.25	0.05	5.21	1.9×10^{-7}	2.2×10^{-5}
T2D	AN	-0.20	0.03	-7.37	1.8×10^{-13}	2.1×10^{-11}
T2D	Insomnia	0.21	0.03	8.09	5.9×10^{-16}	7.0×10^{-14}
T2D	Chronotype	0.07	0.02	3.71	0.0002	0.0248
T2D	CAD	0.41	0.02	18.69	6.3×10^{-78}	7.6×10^{-76}
ADHD	PTSD	0.66	0.09	7.47	8.1×10^{-14}	9.7×10^{-12}
ADHD	TS	0.22	0.06	3.99	6.5×10^{-5}	0.0078
ADHD	ASD	0.37	0.05	7.86	3.9×10^{-15}	4.7×10^{-13}
ADHD	Insomnia	0.37	0.03	10.67	1.4×10^{-26}	1.7×10^{-24}
ADHD	CAD	0.27	0.03	9.86	5.9×10^{-23}	7.1×10^{-21}
OCD	TS	0.51	0.09	5.53	3.1×10^{-8}	3.8×10^{-6}
OCD	AN	0.45	0.08	5.82	5.8×10^{-9}	6.9×10^{-7}
PTSD	ASD	0.35	0.08	4.46	8.3×10^{-6}	0.0010
PTSD	Insomnia	0.48	0.07	7.33	2.3×10^{-13}	2.7×10^{-11}
PTSD	Sleep duration	-0.23	0.06	-3.86	0.0001	0.0133
PTSD	CAD	0.30	0.05	6.06	1.4×10^{-9}	1.7×10^{-7}
ASD	AN	0.19	0.05	3.74	0.0002	0.0219
ASD	Chronotype	-0.18	0.03	-5.45	5.1×10^{-8}	6.1×10^{-6}
AN	Sleep duration	-0.12	0.03	-3.83	0.0001	0.0152
Insomnia	Sleep duration	-0.47	0.02	-20.45	6.3×10^{-93}	7.5×10^{-91}
Insomnia	CAD	0.26	0.03	10.11	4.8×10^{-24}	5.8×10^{-22}
Sleep duration	CAD	-0.09	0.02	-3.88	0.0001	0.0127

Abbreviations: ADHD, attention deficit/hyperactivity disorder; AN, anorexia nervosa; ASD, autism spectrum disorders; BD, bipolar disorder; BMI, body mass index; CAD, coronary artery disease; CRP, C-reactive protein; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; SCZ, schizophrenia; se, standard error; PTSD, post-traumatic stress disorder; T2D, type 2 diabetes. The adj p column reports p-values adjusted according to Bonferroni based on the number of conducted tests (n = 120).

Table S3. Selection of insomnia and MDD instrumental variables

	Number of potential IVs to estimate the causal effects of MDD on insomnia	Number of potential IVs to estimate the causal effects of insomnia on MDD
Number of SNPs included in the publicly available summary statistics	8,483,301 [7]	12,663,596 [33]
Number of SNPs significant at a genome-wide threshold ($p < 5 \times 10^{-8}$)	4,625	528
Number of SNPs after clumping done with the TwoSampleMR package	50	13
Number of SNPs after removal of palindromic SNPs with intermediate allele frequencies during data harmonization conducted with the TwoSampleMR package	39	12

The table shows the number of SNPs available in the original datasets, together with relative references, and the process of selection of candidate instrumental variables (IV). For both studies, we used the publicly available version of genome-wide summary statistics that exclude data for 23andMe participants.

First, variants associated with MDD (left column) or insomnia (right column) at a genome-wide significant threshold ($p < 5 \times 10^{-8}$) were selected. Next, to select independent SNPs, clumping was conducted with the TwoSampleMR package, using European data from the IEU GWAS database as reference, with default parameters ($r^2 > 0.001$ in the range of 10,000 Mb). At this step, the SNP with the lowest p-value was retained. Finally, data harmonization procedures implemented in the TwoSample MR package included removal of palindromic SNPs with intermediate allele frequencies. After these steps, 39 IVs for MDD and 12 for insomnia were retained.

Table S4. Mendelian randomization analysis between insomnia and ADHD, ASD or PTSD

Outcome	Exposure	Method	beta	se	p
ADHD	Insomnia	MR Egger	-0.81	0.75	0.30
ADHD	Insomnia	Weighted median	0.11	0.18	0.54
ADHD	Insomnia	Inverse variance weighted	0.26	0.22	0.24
ADHD	Insomnia	Simple mode	0.20	0.27	0.48
ADHD	Insomnia	MR-PRESSO raw	0.29	0.21	0.18
ADHD	Insomnia	MR-PRESSO outlier corrected	0.23	0.13	0.10
Insomnia	ADHD	MR Egger	-0.17	0.24	0.49
Insomnia	ADHD	Weighted median	0.02	0.04	0.56
Insomnia	ADHD	Inverse variance weighted	0.03	0.05	0.54
Insomnia	ADHD	Simple mode	-0.01	0.07	0.94
Insomnia	ADHD	MR-PRESSO raw	0.03	0.05	0.54
Insomnia	ADHD	MR-PRESSO outlier corrected	0.03	0.03	0.38
PTSD	Insomnia	MR Egger	-0.41	0.43	0.35
PTSD	Insomnia	Weighted median	0.30	0.19	0.11
PTSD	Insomnia	Inverse variance weighted	0.41	0.15	0.008
PTSD	Insomnia	Simple mode	0.35	0.39	0.11
PTSD	Insomnia	MR-PRESSO raw	0.44	0.15	0.01
PTSD	Insomnia	MR-PRESSO outlier corrected	NA	NA	NA

Abbreviations: ADHD, attention deficit/hyperactivity disorder; NA, not available; PTSD, post-traumatic stress disorder; se, standard error. Significant results are reported in bold.

Table S5. Mendelian randomization analyses between MDD (exposure) and insomnia (outcome) using 70 IVs

Outcome	Exposure	Method	beta	se	<i>p</i>
Insomnia	MDD	MR Egger	0.20	0.25	0.42
Insomnia	MDD	Weighted median	0.26	0.04	6.2×10^{-9}
Insomnia	MDD	Inverse variance weighted	0.31	0.04	3.7×10^{-12}
Insomnia	MDD	Simple mode	0.20	0.09	0.03
Insomnia	MDD	MR-PRESSO raw	0.32	0.04	3.2×10^{-10}
Insomnia	MDD	MR-PRESSO outlier corrected	0.29	0.04	3.5×10^{-11}

This table shows results of the MR analysis between MDD (exposure) and insomnia (outcome). In this analysis, 70 IVs were selected using the top 10,000 variants reported by the MDD GWAS (including data from 23andMe participants) as exposure [7]. No significant horizontal pleiotropy was detected based on the MR Egger intercept ($p = 0.67$). Significant results are reported in bold. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error

Table S6. Results of mendelian randomization single-SNP tests between MDD (exposure) and insomnia (outcome) using 70 IVs

SNP	beta	se	<i>p</i>
rs1343605	1.07	0.17	2.9×10^{-10}
rs30266	1.09	0.18	7.1×10^{-10}
rs3099439	0.79	0.19	2.6×10^{-5}
rs5995992	0.85	0.21	5.3×10^{-5}
rs56314503	0.93	0.23	5.5×10^{-5}
rs2509805	0.94	0.25	0.0001
rs113188507	0.94	0.25	0.0002
rs61990288	0.72	0.20	0.0002
rs10913112	-0.71	0.20	0.0003
rs58104186	0.75	0.22	0.0006
rs3823624	0.81	0.24	0.0009
rs8037355	0.68	0.22	0.0019
rs60157091	0.79	0.25	0.0020
rs62188629	0.67	0.23	0.0039
rs6783233	0.73	0.26	0.0052
rs45510091	0.69	0.25	0.0060
rs3213572	0.64	0.23	0.0063
rs35553410	0.65	0.24	0.0064
rs301799	0.56	0.21	0.0071
rs1002656	0.45	0.21	0.0340
rs33431	-0.55	0.27	0.0393
rs2568958	0.28	0.14	0.0424
rs7685686	0.50	0.26	0.0492
rs725616	0.49	0.26	0.0603
rs61902811	0.38	0.21	0.0645
rs1890946	0.39	0.22	0.0747
rs9592461	0.41	0.24	0.0785
rs1568452	0.36	0.21	0.0879
rs57344483	0.42	0.25	0.0985
rs7932640	0.28	0.18	0.1249
rs7200826	0.32	0.21	0.1252
rs78337797	0.39	0.26	0.1327
rs1409379	0.35	0.24	0.1497
rs1448938	0.33	0.24	0.1757
rs997934	0.35	0.26	0.1836
rs1095626	-0.26	0.20	0.1859
rs7030813	0.28	0.21	0.1882
rs1021363	0.23	0.18	0.1910
rs4346585	0.30	0.23	0.2044
rs10789214	0.31	0.27	0.2444
rs9545360	0.27	0.25	0.2773
rs7241572	0.25	0.23	0.2795
rs1226412	0.23	0.25	0.3580
rs12967855	0.19	0.21	0.3604
rs7837935	0.21	0.24	0.3733
rs7585722	0.22	0.26	0.3966

rs34488670	0.20	0.25	0.4247
rs10817969	0.14	0.22	0.5128
rs1466887	-0.16	0.26	0.5495
rs1982277	-0.11	0.22	0.6191
rs75581564	-0.13	0.26	0.6266
rs3793577	0.11	0.23	0.6313
rs17641524	0.09	0.20	0.6547
rs1045430	0.08	0.20	0.6791
rs7659414	-0.10	0.26	0.6835
rs1152578	-0.09	0.24	0.6979
rs2043539	0.07	0.19	0.6986
rs200949	0.07	0.19	0.7018
rs59283172	0.09	0.25	0.7169
rs34937911	0.10	0.27	0.7199
rs141954845	-0.07	0.23	0.7579
rs143186028	0.07	0.24	0.7655
rs4772087	-0.06	0.23	0.7908
rs11135349	-0.03	0.17	0.8445
rs56887639	0.04	0.21	0.8625
rs10774600	-0.04	0.26	0.8852
rs79924686	0.03	0.26	0.8985
rs198457	0.02	0.23	0.9395
rs11579246	0.01	0.24	0.9557
rs10149470	0.00	0.19	1.0000

This table shows results of the MR single-SNP tests between MDD (exposure) and insomnia (outcome). In this analysis, 70 IVs were selected using the top 10,000 variants reported by the MDD GWAS (including data from 23andMe participants) as exposure [7]. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error; SNP, single nucleotide polymorphisms

Table S7. Mendelian randomization analyses between MDD (exposure) and insomnia (outcome) using 69 IVs

Outcome	Exposure	Method	beta	se	p
Insomnia	MDD	MR Egger	0.25	0.27	0.36
Insomnia	MDD	Weighted median	0.26	0.05	9.7×10^{-9}
Insomnia	MDD	Inverse variance weighted	0.31	0.05	3.8×10^{-12}
Insomnia	MDD	Simple mode	0.22	0.09	0.02
Insomnia	MDD	MR-PRESSO raw	0.32	0.04	3.5×10^{-10}
Insomnia	MDD	MR-PRESSO outlier corrected	0.29	0.04	3.8×10^{-11}

This table shows results of the MR analysis between MDD (exposure) and insomnia (outcome). In this analysis, IVs were selected using the 102 significant and independent genetic variants reported by the MDD GWAS (including data from 23andMe participants) as exposure [7]. No significant horizontal pleiotropy was detected based on the MR Egger intercept ($p = 0.81$). Significant results are reported in bold. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error

Table S8. Results of mendelian randomization single-SNP tests between MDD (exposure) and insomnia (outcome) using 69 IVs

SNP	beta	se	<i>p</i>
rs1343605	1.07	0.17	2.9×10^{-10}
rs30266	1.09	0.18	7.1×10^{-10}
rs3099439	0.79	0.19	2.6×10^{-5}
rs5995992	0.85	0.21	5.3×10^{-5}
rs56314503	0.93	0.23	5.5×10^{-5}
rs2509805	0.94	0.25	0.0001
rs113188507	0.94	0.25	0.0002
rs61990288	0.72	0.20	0.0002
rs10913112	-0.71	0.20	0.0003
rs58104186	0.75	0.22	0.0006
rs3823624	0.81	0.24	0.0009
rs8037355	0.68	0.22	0.0019
rs60157091	0.79	0.25	0.0020
rs62188629	0.67	0.23	0.0039
rs6783233	0.73	0.26	0.0052
rs45510091	0.69	0.25	0.0060
rs3213572	0.64	0.23	0.0063
rs35553410	0.65	0.24	0.0064
rs301799	0.56	0.21	0.0071
rs1002656	0.45	0.21	0.0340
rs33431	-0.55	0.27	0.0393
rs2568958	0.28	0.14	0.0424
rs7685686	0.50	0.26	0.0492
rs725616	0.49	0.26	0.0603
rs61902811	0.38	0.21	0.0645
rs1890946	0.39	0.22	0.0747
rs9592461	0.41	0.24	0.0785
rs1568452	0.36	0.21	0.0879
rs57344483	0.42	0.25	0.0985
rs7932640	0.28	0.18	0.1249
rs7200826	0.32	0.21	0.1252
rs78337797	0.39	0.26	0.1327
rs1409379	0.35	0.24	0.1497
rs1448938	0.33	0.24	0.1757
rs997934	0.35	0.26	0.1836
rs1095626	-0.26	0.20	0.1859
rs7030813	0.28	0.21	0.1882
rs1021363	0.23	0.18	0.1910
rs4346585	0.30	0.23	0.2044
rs10789214	0.31	0.27	0.2444
rs9545360	0.27	0.25	0.2773
rs7241572	0.25	0.23	0.2795
rs1226412	0.23	0.25	0.3580
rs12967855	0.19	0.21	0.3604
rs7837935	0.21	0.24	0.3733
rs7585722	0.22	0.26	0.3966

rs34488670	0.20	0.25	0.4247
rs10817969	0.14	0.22	0.5128
rs1466887	-0.16	0.26	0.5495
rs1982277	-0.11	0.22	0.6191
rs75581564	-0.13	0.26	0.6266
rs3793577	0.11	0.23	0.6313
rs17641524	0.09	0.20	0.6547
rs1045430	0.08	0.20	0.6791
rs7659414	-0.10	0.26	0.6835
rs1152578	-0.09	0.24	0.6979
rs2043539	0.07	0.19	0.6986
rs200949	0.07	0.19	0.7018
rs59283172	0.09	0.25	0.7169
rs34937911	0.10	0.27	0.7199
rs141954845	-0.07	0.23	0.7579
rs143186028	0.07	0.24	0.7655
rs4772087	-0.06	0.23	0.7908
rs11135349	-0.03	0.17	0.8445
rs56887639	0.04	0.21	0.8625
rs10774600	-0.04	0.26	0.8852
rs198457	0.02	0.23	0.9395
rs11579246	0.01	0.24	0.9557
rs10149470	0.00	0.19	1.0000

This table shows results of the MR single-SNP tests between MDD (exposure) and insomnia (outcome). In this analysis, 69 IVs were selected using the 102 significant and independent genetic variants reported by the MDD GWAS (including data from 23andMe participants) as exposure [7]. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error; SNP, single nucleotide polymorphisms

Table S9. Mendelian randomization analyses between insomnia (exposure) and MDD (outcome) using 81 IVs

Outcome	Exposure	Method	beta	se	p
MDD	Insomnia	MR Egger	0.13	0.15	0.42
MDD	Insomnia	Weighted median	0.46	0.04	2.0×10^{-32}
MDD	Insomnia	Inverse variance weighted	0.48	0.04	3.8×10^{-34}
MDD	Insomnia	Simple mode	0.49	0.09	1.6×10^{-6}
MDD	Insomnia	MR-PRESSO raw	0.51	0.04	1.1×10^{-24}
MDD	Insomnia	MR-PRESSO outlier corrected	0.49	0.03	4.7×10^{-29}

This table shows results of the MR analysis between MDD (exposure) and insomnia (outcome). In this analysis, 81 IVs were selected using the top 10,000 variants reported by the insomnia GWAS (including data from 23andMe participants) as exposure [33]. During this analysis, significant horizontal pleiotropy was detected based on the MR Egger intercept ($p = 0.02$). However, the association was confirmed to be significant when using the MR-PRESSO outlier corrected method (which applies a correction for horizontal pleiotropy via outlier removal). Consistently, the MR-PRESSO distortion test was not significant ($p = 0.44$) suggesting no significant difference in the causal estimates before and after correction for outliers. Significant results are reported in bold. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error

Table S10. Results of MR single-SNP tests between insomnia (exposure) and MDD (outcome) using 81 IVs

SNP	beta	se	<i>p</i>
rs2568960	1.20	0.14	4.8×10^{-18}
rs2431108	1.45	0.19	8.4×10^{-15}
rs9787523	1.30	0.21	8.4×10^{-10}
rs2894699	1.06	0.21	2.8×10^{-7}
rs4955420	1.18	0.25	2.4×10^{-6}
rs7162423	0.91	0.20	3.3×10^{-6}
rs1789695	1.09	0.24	5.0×10^{-6}
rs10896647	1.09	0.24	6.1×10^{-6}
rs4595203	0.75	0.17	7.5×10^{-6}
rs11663217	0.92	0.21	1.1×10^{-5}
rs4304930	0.50	0.12	1.2×10^{-5}
rs11729015	1.06	0.25	1.7×10^{-5}
rs1358393	0.64	0.16	3.9×10^{-5}
rs9317586	0.81	0.20	5.2×10^{-5}
rs4702	0.59	0.15	5.2×10^{-5}
rs8076183	0.85	0.22	0.0001
rs39654	0.79	0.21	0.0002
rs10761231	0.73	0.20	0.0003
rs34501189	0.83	0.23	0.0003
rs55728265	0.72	0.21	0.0005
rs3814883	0.80	0.24	0.0007
rs57001955	0.63	0.19	0.0009
rs2122194	0.77	0.23	0.0011
rs12821431	0.61	0.19	0.0011
rs2503185	0.73	0.23	0.0016
rs3732730	0.56	0.18	0.0018
rs10930502	0.70	0.24	0.0036
rs13107325	0.55	0.19	0.0040
rs13037010	0.49	0.18	0.0056
rs4674625	0.64	0.24	0.0065
rs75218827	0.58	0.22	0.0072
rs34877766	0.56	0.21	0.0078
rs12272545	0.52	0.20	0.0083
rs6982265	0.63	0.24	0.0090
rs56182580	0.56	0.22	0.0104
rs4981170	0.57	0.22	0.0109
rs7184998	0.47	0.19	0.0137
rs4664299	0.58	0.24	0.0142
rs10801874	0.58	0.24	0.0148
rs72808262	0.52	0.23	0.0238
rs62530187	0.45	0.20	0.0285
rs1795922	0.43	0.20	0.0345
rs1411751	0.47	0.22	0.0361
rs4383496	0.40	0.19	0.0385
rs34227359	0.48	0.23	0.0393
rs1935884	0.30	0.15	0.0432
rs73034109	0.50	0.25	0.0455

rs75742406	0.45	0.23	0.0525
rs4977893	0.45	0.23	0.0535
rs10947428	0.36	0.19	0.0618
rs1883638	-0.43	0.24	0.0758
rs56410336	0.40	0.23	0.0871
rs10494048	0.36	0.21	0.0883
rs12713388	0.37	0.23	0.1066
rs293567	0.26	0.17	0.1125
rs13095140	-0.31	0.20	0.1193
rs2344121	0.35	0.23	0.1278
rs1533305	0.34	0.23	0.1363
rs7072776	0.36	0.25	0.1447
rs11897824	0.27	0.20	0.1686
rs10877022	0.32	0.24	0.1848
rs4297935	0.26	0.21	0.2172
rs4799681	0.26	0.22	0.2404
rs7915425	0.29	0.25	0.2458
rs2286729	0.24	0.20	0.2486
rs77176363	0.25	0.22	0.2520
rs9938120	0.25	0.22	0.2521
rs35681248	0.24	0.21	0.2558
rs1064213	0.20	0.21	0.3287
rs9889282	0.19	0.21	0.3754
rs463245	0.20	0.25	0.4133
rs2664299	-0.19	0.24	0.4263
rs1349490	-0.18	0.23	0.4291
rs118166957	0.15	0.19	0.4456
rs12684080	0.14	0.19	0.4665
rs1823125	0.09	0.15	0.5383
rs1846644	0.12	0.20	0.5546
rs62144054	-0.07	0.13	0.5664
rs12927162	0.08	0.18	0.6388
rs2718777	0.06	0.23	0.8069
rs72807818	-0.01	0.21	0.9620

This table shows results of the MR single-SNP tests between MDD (exposure) and insomnia (outcome). In this analysis, 81 IVs were selected using the top 10,000 variants reported by the insomnia GWAS (including data from 23andMe participants) as exposure [33]. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error; SNP, single nucleotide polymorphisms

Table S11. Mendelian randomization analyses between insomnia (exposure) and MDD (outcome) using 223 IVs

Outcome	Exposure	Method	beta	se	<i>p</i>
MDD	Insomnia	MR Egger	0.74	0.24	0.002
MDD	Insomnia	Weighted median	1.17	0.07	4.2×10^{-57}
MDD	Insomnia	Inverse variance weighted	1.24	0.07	2.5×10^{-71}
MDD	Insomnia	Simple mode	1.12	0.21	4.6×10^{-7}
MDD	Insomnia	MR-PRESSO raw	1.28	0.07	5.5×10^{-52}
MDD	Insomnia	MR-PRESSO outlier corrected	1.25	0.06	1.1×10^{-55}

This table shows results of the MR analysis between MDD (exposure) and insomnia (outcome). In this analysis, 223 IVs were selected using the top 554 independent genetic variants reported by the insomnia GWAS (including data from 23andMe participants) as exposure [33]. During this analysis, significant horizontal pleiotropy was detected based on the MR Egger intercept ($p = 0.03$). However, the association was confirmed to be significant when using the MR-PRESSO outlier corrected method (which applies a correction for horizontal pleiotropy via outlier removal). Consistently, the MR-PRESSO distortion test was not significant ($p = 0.60$), suggesting no significant difference in the causal estimates before and after correction for outliers. Significant results are reported in bold. Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error

Table S12. Results of MR single-SNP tests between insomnia (exposure) and MDD (outcome) using 223 IVs

SNP	beta	se	<i>p</i>
rs2568960	3.18	0.37	4.8×10^{-18}
rs2431108	3.25	0.42	8.4×10^{-15}
rs9787523	3.38	0.55	8.4×10^{-10}
rs12790660	2.91	0.58	4.1×10^{-7}
rs516890	3.65	0.73	6.4×10^{-7}
rs218985	3.27	0.67	1.1×10^{-6}
rs7162423	2.22	0.48	3.3×10^{-6}
rs10842059	4.16	0.90	3.8×10^{-6}
rs1789695	2.63	0.58	5.0×10^{-6}
rs4595203	2.04	0.45	7.5×10^{-6}
rs4831647	3.78	0.86	1.1×10^{-5}
rs9543859	3.22	0.73	1.1×10^{-5}
rs4304930	1.25	0.29	1.2×10^{-5}
rs1820514	3.72	0.86	1.5×10^{-5}
rs11729015	3.15	0.73	1.7×10^{-5}
rs8766	2.08	0.49	2.1×10^{-5}
rs314281	2.26	0.54	2.6×10^{-5}
rs6786798	3.20	0.77	3.0×10^{-5}
rs1358393	1.77	0.43	3.9×10^{-5}
rs8084405	3.76	0.92	4.4×10^{-5}
rs9317586	2.18	0.54	5.2×10^{-5}
rs4702	1.62	0.40	5.2×10^{-5}
rs12617557	2.69	0.67	6.3×10^{-5}
rs7619638	2.64	0.67	7.4×10^{-5}
rs2003273	3.03	0.77	7.6×10^{-5}
rs240110	2.41	0.61	8.5×10^{-5}
rs10035289	2.10	0.54	9.3×10^{-5}
rs12580149	2.63	0.68	0.0001
rs8076183	2.43	0.63	0.0001
rs790316	2.75	0.72	0.0001
rs10104523	2.30	0.61	0.0002
rs694786	2.01	0.54	0.0002
rs11765062	3.20	0.86	0.0002
rs10992756	1.82	0.50	0.0003
rs12605642	1.94	0.54	0.0003
rs10927078	2.56	0.71	0.0003
rs4906347	2.06	0.58	0.0003
rs6661750	2.20	0.61	0.0003
rs76924513	2.50	0.70	0.0004
rs1552514	2.81	0.80	0.0004
rs45510091	2.55	0.73	0.0005
rs12598089	2.98	0.86	0.0005
rs2123641	2.68	0.78	0.0006
rs910187	1.89	0.55	0.0006
rs9815484	1.60	0.47	0.0006
rs3814883	2.07	0.61	0.0007
rs2581458	2.64	0.80	0.0010

rs11954162	1.93	0.59	0.0011
rs1806152	2.28	0.70	0.0012
rs61979497	2.98	0.92	0.0012
rs4409363	2.84	0.88	0.0012
rs3733421	2.72	0.88	0.0020
rs7173565	1.68	0.54	0.0021
rs776935	1.88	0.61	0.0021
rs67588220	1.56	0.52	0.0027
rs4858241	2.22	0.75	0.0031
rs2616192	2.25	0.77	0.0033
rs10930502	1.96	0.67	0.0036
rs13107325	1.42	0.49	0.0040
rs7133378	1.87	0.66	0.0044
rs12618343	2.03	0.71	0.0045
rs579448	2.02	0.72	0.0049
rs62178707	1.73	0.61	0.0049
rs12311881	2.46	0.88	0.0052
rs13037010	1.41	0.51	0.0056
rs11984380	1.97	0.72	0.0061
rs1864896	1.98	0.73	0.0068
rs75218827	1.65	0.61	0.0072
rs12137221	2.32	0.87	0.0075
rs3755831	1.46	0.55	0.0078
rs12272545	1.32	0.50	0.0083
rs4912844	-1.94	0.74	0.0089
rs76901635	1.98	0.76	0.0096
rs11165657	1.70	0.66	0.0103
rs56182580	1.37	0.53	0.0104
rs4981170	1.40	0.55	0.0109
rs11724690	2.03	0.80	0.0110
rs503460	1.49	0.59	0.0113
rs7184998	1.18	0.48	0.0137
rs585522	1.16	0.47	0.0138
rs13001483	1.68	0.70	0.0167
rs8110135	1.95	0.82	0.0170
rs10837042	1.49	0.63	0.0181
rs8036386	1.44	0.63	0.0217
rs7551881	1.70	0.75	0.0234
rs10400508	1.98	0.88	0.0244
rs6533604	1.87	0.85	0.0281
rs62530187	1.27	0.58	0.0285
rs9509284	1.37	0.63	0.0291
rs12023901	1.77	0.81	0.0294
rs2884836	1.67	0.77	0.0297
rs4455151	1.70	0.78	0.0300
rs11903069	1.62	0.77	0.0350
rs1411751	1.21	0.58	0.0361
rs2158414	1.57	0.75	0.0367
rs10517119	1.92	0.92	0.0369

rs4383496	0.99	0.48	0.0385
rs7708900	1.48	0.72	0.0385
rs797091	1.67	0.81	0.0401
rs1549577	1.28	0.63	0.0414
rs4681358	1.45	0.72	0.0430
rs7844069	1.48	0.73	0.0431
rs2356265	1.44	0.71	0.0434
rs73034109	1.16	0.58	0.0455
rs2418884	0.80	0.41	0.0505
rs11807834	1.39	0.71	0.0524
rs75742406	1.19	0.61	0.0525
rs2016475	1.33	0.69	0.0527
rs10947428	0.83	0.44	0.0618
rs11077334	1.64	0.88	0.0624
rs10148610	1.32	0.73	0.0726
rs9325358	0.88	0.49	0.0726
rs6812227	1.24	0.70	0.0758
rs9936879	1.01	0.58	0.0783
rs17836224	-1.28	0.73	0.0801
rs6878050	-1.40	0.80	0.0801
rs62429521	-1.33	0.76	0.0823
rs12983032	-1.10	0.64	0.0871
rs6864168	1.46	0.86	0.0896
rs2232839	1.30	0.77	0.0920
rs10368	1.42	0.85	0.0956
rs62396748	1.01	0.61	0.0987
rs145664840	1.19	0.72	0.0997
rs17416209	1.19	0.74	0.1074
rs293567	0.66	0.42	0.1125
rs75869405	1.19	0.75	0.1126
rs2544211	1.13	0.72	0.1138
rs566903	1.18	0.75	0.1146
rs13095140	-0.81	0.52	0.1193
rs13269117	1.17	0.75	0.1198
rs2344121	0.96	0.63	0.1278
rs593839	1.12	0.73	0.1278
rs11173201	1.04	0.70	0.1363
rs9943753	0.96	0.64	0.1365
rs111296206	1.18	0.79	0.1374
rs834233	1.10	0.75	0.1425
rs8069356	1.17	0.80	0.1447
rs12677105	1.12	0.77	0.1452
rs8076005	1.10	0.77	0.1539
rs669245	-1.24	0.88	0.1588
rs11897824	0.82	0.59	0.1686
rs8063871	1.10	0.80	0.1691
rs6965799	-0.98	0.72	0.1700
rs879483	1.18	0.86	0.1700
rs1416901	0.79	0.58	0.1708

rs62442231	1.20	0.90	0.1824
rs4454035	0.97	0.73	0.1874
rs2271731	-1.02	0.78	0.1943
rs8054082	0.67	0.53	0.2041
rs3815156	0.86	0.71	0.2261
rs1007841	1.06	0.90	0.2389
rs6504568	1.02	0.87	0.2408
rs7915425	0.81	0.70	0.2458
rs2286729	0.64	0.56	0.2486
rs62472321	0.76	0.66	0.2500
rs77176363	0.70	0.61	0.2520
rs61788417	0.88	0.77	0.2522
rs35681248	0.58	0.51	0.2558
rs1383890	0.96	0.86	0.2643
rs9315688	0.80	0.73	0.2753
rs6019663	0.73	0.67	0.2779
rs11135493	0.73	0.70	0.2948
rs2184796	-0.92	0.88	0.2958
rs7853585	-0.72	0.69	0.2967
rs1064213	0.53	0.54	0.3287
rs112358407	0.84	0.88	0.3383
rs16895508	0.64	0.68	0.3417
rs12647020	0.88	0.94	0.3492
rs11980428	0.67	0.74	0.3705
rs57314044	0.59	0.66	0.3752
rs136310	0.78	0.88	0.3754
rs2615252	0.65	0.73	0.3754
rs9889282	0.49	0.55	0.3754
rs9971199	0.70	0.80	0.3816
rs35659126	-0.67	0.77	0.3841
rs1331156	0.66	0.76	0.3854
rs17727688	0.65	0.75	0.3861
rs12973258	0.67	0.79	0.3928
rs1397844	0.67	0.79	0.3928
rs79637296	0.71	0.84	0.3967
rs2861752	0.51	0.61	0.4025
rs463245	0.60	0.73	0.4133
rs10110224	0.70	0.86	0.4157
rs2664299	-0.50	0.63	0.4263
rs703848	0.46	0.59	0.4311
rs72899452	0.56	0.73	0.4412
rs118166957	0.38	0.49	0.4456
rs56324203	0.68	0.92	0.4598
rs9607581	0.49	0.68	0.4702
rs13093657	-0.57	0.82	0.4878
rs615526	0.52	0.77	0.5004
rs10906391	-0.52	0.82	0.5270
rs34971686	-0.48	0.78	0.5390
rs4653743	0.50	0.82	0.5404

rs12684650	0.35	0.59	0.5513
rs6471065	0.46	0.77	0.5535
rs62158170	0.22	0.38	0.5586
rs4402784	0.37	0.68	0.5916
rs62144053	-0.16	0.30	0.5938
rs78154941	0.37	0.70	0.6004
rs2065677	0.45	0.87	0.6036
rs1536053	0.40	0.78	0.6096
rs77276698	-0.28	0.56	0.6171
rs78531597	-0.44	0.89	0.6220
rs2236202	0.34	0.71	0.6312
rs12927162	0.23	0.49	0.6388
rs823248	0.30	0.72	0.6755
rs7657954	0.32	0.80	0.6922
rs12814145	0.28	0.75	0.7056
rs4803217	0.28	0.78	0.7176
rs62383290	0.27	0.84	0.7522
rs11956866	0.22	0.72	0.7624
rs10927840	0.23	0.83	0.7795
rs528964	-0.22	0.85	0.7988
rs58475265	-0.17	0.66	0.7993
rs34772727	-0.16	0.76	0.8346
rs62444044	0.17	0.86	0.8415
rs11871043	-0.10	0.55	0.8557
rs6872919	0.10	0.72	0.8890
rs34517439	-0.08	0.61	0.8931
rs429358	0.06	0.69	0.9357
rs72807818	-0.03	0.53	0.9620
rs7805564	0.03	0.83	0.9758

This table shows results of the MR single-SNP tests between MDD (exposure) and insomnia (outcome). In this analysis, 223 IVs were selected using the top 554 independent genetic variants reported by the insomnia GWAS (including data from 23andMe participants) as exposure [33]

Abbreviations: IV, instrumental variable; MDD, major depressive disorder; se, standard error; SNP, single nucleotide polymorphisms