

Supplementary Material for Sbarra et al.

Loneliness and Depression: Bidirectional Mendelian Randomization Analyses Using Data from Three Large Genome-Wide Association Studies

Table S1. F Statistics for Mendelian Randomization Analyses from Loneliness to MDD and MDD to Loneliness

Exposure	Outcome	SNPs (n)	Mean F	Range F
Loneliness	Major Depression Disorder: Million Veterans Program	15	35.69	29.81-56.41
Loneliness	Major Depression Disorder: Psychiatric Genetic Consortium	15	35.81	29.81-56.41
Major Depression Disorder: Million Veterans Program	Loneliness	19	30.52	25.33-45.80
Major Depression Disorder: Psychiatric Genetic Consortium	Loneliness	11	28.86	25.75-37.37

Table S2. Cochran's heterogeneity statistic for Inverse Variance Weighted Mendelian Randomization analyses from Loneliness to MDD and MDD to Loneliness

Exposure	Outcome	SNPs (n)	Q Statistic	p
Loneliness	Major Depression Disorder: Million Veterans Program	15	29.87	0.007
Loneliness	Major Depression Disorder: Psychiatric Genetic Consortium	15	38.88	<0.001
Major Depression Disorder: Million Veterans Program	Loneliness	19	44.58	<0.001
Major Depression Disorder: Psychiatric Genetic Consortium	Loneliness	11	32.83	0.001

Table S3. I^2_{GX} statistic from Loneliness to MDD and MDD to Loneliness

Exposure	Outcome	SNPs (n)	I^2_{GX}
Loneliness	Major Depression Disorder: Million Veterans Program	15	0.318
Loneliness	Major Depression Disorder: Psychiatric Genetic Consortium	15	0.348
Major Depression Disorder: Million Veterans Program	Loneliness	19	0.528
Major Depression Disorder: Psychiatric Genetic Consortium	Loneliness	11	0.471

Table S4. Univariable Mendelian Randomization using Steiger filtering for Loneliness on MDD in the Psychiatric Genetic Consortium

Exposure	Outcome	Method	SNPs (n)	β	95%CI
Loneliness	MDD: PGC	Inverse Variance Weighted	13	0.576	0.232, 0.920
		Weighted Median	13	0.704	0.294, 1.115
		Weighted Mode	13	0.910	0.168, 1.652
		RAPS	13	0.599	0.315, 0.884
		MR-PRESSO	13	0.576	0.490, 0.662

Table S5. Bidirectional Outlier-corrected SNPs in MR-PRESSO Analyses

Exposure	Outcome	SNP	Outlier Test, <i>p</i>
Loneliness	MDD: MVP	rs773020	0.045
MDD: MVP	Loneliness	rs4779889	<0.019
MDD: MVP	Loneliness	rs9586	0.019

Table S6. Bidirectional MR-PRESSO Global and Distortion Analyses in the Million Veterans Program

Exposure	Outcome	Global Test, <i>p</i>	Distortion Test, <i>p</i>
Loneliness	MDD: MVP	0.017	0.533
MDD: MVP	Loneliness	0.003	0.924

Table S7. Association of genome-wide significant SNPs used as instruments for Loneliness to MDD

SNP	Chr	Pos	EA	OA	N	EAF	BETA	SE	<i>r</i> ²	<i>p</i>	N	EAF	BETA	SE	<i>r</i> ²	<i>p</i>
Exposure: Loneliness											Outcome: MDD - Million Veterans Program					
rs10456089	6	11959836	G	A	511000	0.933	0.036	0.006	6.26E-05	<0.001	250215	0.924	-0.009	0.018	3.70E-08	0.2537
rs11039265	11	47523214	C	A	511000	0.648	0.018	0.003	5.85E-05	<0.001	250215	0.642	0.005	0.01	1.99E-06	0.2069
rs11068917	12	118791120	C	A	511000	0.812	-0.022	0.004	6.26E-05	<0.001	250215	0.826	-0.016	0.012	6.46E-06	0.0014
rs11867618	17	65875587	G	A	511000	0.853	-0.024	0.004	8.81E-05	<0.001	250215	0.86	-0.013	0.013	3.03E-05	0.0237
rs13291079	9	96360650	T	C	511000	0.573	0.02	0.003	5.83E-05	<0.001	250215	0.572	0.011	0.009	9.67E-06	0.0036
rs159960	1	8476428	A	G	511000	0.441	0.017	0.003	6.70E-05	<0.001	250215	0.475	0.009	0.009	4.09E-06	0.019
rs171697	5	103956516	C	G	511000	0.664	-0.019	0.003	5.99E-05	<0.001	250215	0.677	-0.022	0.01	3.01E-05	<0.001
rs348258	20	47768988	C	T	511000	0.684	-0.018	0.003	6.40E-05	<0.001	250215	0.685	-0.005	0.01	9.00E-06	0.2148
rs4958586	5	152248567	G	A	511000	0.375	-0.02	0.003	8.03E-05	<0.001	250215	0.367	-0.001	0.009	9.40E-09	0.8574
rs599550	18	53252388	G	A	511000	0.171	-0.03	0.004	0.00011	<0.001	250215	0.145	-0.01	0.013	1.74E-05	0.0567
rs62347916	5	24239998	G	A	511000	0.511	0.017	0.003	6.05E-05	<0.001	250215	0.511	0.003	0.009	1.05E-05	0.3718
rs74338595	2	212749786	T	C	511000	0.701	0.02	0.003	7.00E-05	<0.001	250215	0.702	0.009	0.01	2.92E-06	0.0483
rs7626596	3	82000680	G	A	511000	0.434	0.018	0.003	6.87E-05	<0.001	250215	0.442	-0.002	0.009	2.55E-07	0.5946
rs773020	9	77768122	G	A	511000	0.1	-0.031	0.005	7.17E-05	<0.001	250215	0.094	0.004	0.017	6.75E-06	0.5461
rs7770860	6	131186393	T	C	511000	0.627	-0.018	0.003	6.49E-05	<0.001	250215	0.62	-0.008	0.009	1.20E-05	0.0546
Exposure: Loneliness											Outcome: MDD - Psychiatric Genetic Consortium					
rs10456089	6	11959836	G	A	511000	0.933	0.036	0.006	6.26E-05	<0.001	142646	0.924	-0.021	0.018	9.13E-06	0.2537
rs11039265	11	47523214	C	A	511000	0.648	0.018	0.003	5.85E-05	<0.001	142646	0.642	0.012	0.01	1.28E-05	0.2069
rs11068917	12	118791120	C	A	511000	0.812	-0.022	0.004	6.26E-05	<0.001	142646	0.826	-0.037	0.012	7.11E-05	0.0014
rs13291079	9	96360650	T	C	511000	0.573	0.02	0.003	6.54E-05	<0.001	142646	0.86	-0.029	0.013	3.59E-05	0.0237
rs159960	1	8476428	A	G	511000	0.441	0.017	0.003	8.81E-05	<0.001	142646	0.572	0.026	0.009	5.95E-05	0.0036
rs171697	5	103956516	C	G	511000	0.664	-0.019	0.003	5.83E-05	<0.001	142646	0.475	0.021	0.009	3.86E-05	0.019
rs2732650	17	44344988	C	G	511000	0.781	-0.021	0.004	6.70E-05	<0.001	142646	0.677	-0.051	0.01	0.000198	<0.001
rs348258	20	47768988	C	T	511000	0.684	-0.018	0.003	6.40E-05	<0.001	142646	0.685	-0.012	0.01	1.08E-05	0.2148
rs4958586	5	152248567	G	A	511000	0.375	-0.02	0.003	8.03E-05	<0.001	142646	0.367	-0.002	0.009	2.26E-07	0.8574

rs599550	18	53252388	G	A	511000	0.171	-0.03	0.004	0.00011	<0.001	142646	0.145	-0.024	0.013	2.55E-05	0.0567
rs62347916	5	24239998	G	A	511000	0.511	0.017	0.003	6.05E-05	<0.001	142646	0.511	0.008	0.009	5.59E-06	0.3718
rs74338595	2	212749786	T	C	511000	0.701	0.02	0.003	7.00E-05	<0.001	142646	0.702	0.02	0.01	2.73E-05	0.0483
rs7626596	3	82000680	G	A	511000	0.434	0.018	0.003	6.87E-05	<0.001	142646	0.442	-0.005	0.009	1.99E-06	0.5946
rs773020	9	77768122	G	A	511000	0.1	-0.031	0.005	7.17E-05	<0.001	142646	0.094	0.01	0.017	2.55E-06	0.5461
rs7770860	6	131186393	T	C	511000	0.627	-0.018	0.003	6.49E-05	<0.001	142646	0.62	-0.018	0.009	2.59E-05	0.0546

Table S8. Association of genome-wide significant SNPs used as instruments for MDD to Loneliness

SNP	Chr	Pos	EA	OA	N	EA	BETA	SE	r ²	p	N	EA	BETA	SE	r ²	p
Exposure: MDD - Million Veterans Program																
rs11156432	6	105440616	A	C	448956	0.242	0.042	0.008	5.74E-05	<0.001	455364	0.197	0.001	0.001	2.17E-06	0.32
rs11533158	9	140262426	T	C	448956	0.685	-0.032	0.006	6.53E-05	<0.001	455364	0.693	-0.002	0.001	1.35E-05	0.013
rs11770148	7	1899447	A	G	448956	0.814	0.048	0.008	9.31E-05	<0.001	455364	0.826	0.002	0.001	5.94E-06	0.1
rs11877758	18	35138110	T	G	448956	0.684	-0.033	0.006	6.07E-05	<0.001	455364	0.688	-0.002	0.001	6.96E-06	0.075
rs147763467	17	47700587	T	C	448956	0.017	-0.123	0.024	5.83E-05	<0.001	455364	0.02	-0.001	0.003	3.04E-07	0.71
rs1553172	1	197818233	A	G	448956	0.49	0.033	0.006	6.93E-05	<0.001	455364	0.49	0.002	0.001	1.75E-05	0.0048
rs28712194	8	1778193	T	C	448956	0.238	0.036	0.006	6.68E-05	<0.001	455364	0.243	0.001	0.001	3.45E-10	0.99
rs4776729	15	66399197	A	G	448956	0.866	-0.045	0.009	6.00E-05	<0.001	455364	0.858	-0.001	0.001	3.61E-06	0.2
rs4779889	15	31814203	T	G	448956	0.215	-0.035	0.007	5.74E-05	<0.001	455364	0.22	0.002	0.001	1.06E-05	0.028
rs4972656	2	175240292	T	C	448956	0.564	0.038	0.006	0.000102	<0.001	455364	0.566	0.002	0.001	1.42E-05	0.011
rs6030257	20	41087450	A	C	448956	0.632	0.03	0.006	5.73E-05	<0.001	455364	0.629	-0.001	0.001	2.00E-06	0.34
rs612823	11	133834104	T	C	448956	0.609	0.033	0.006	6.86E-05	<0.001	455364	0.62	0.001	0.001	5.61E-06	0.11
rs61902811	11	113370758	A	G	448956	0.359	-0.035	0.006	8.09E-05	<0.001	455364	0.368	-0.003	0.001	2.59E-05	<0.001
rs7523829	1	73758117	A	G	448956	0.489	0.029	0.006	5.84E-05	<0.001	455364	0.467	0.001	0.001	3.16E-06	0.23
rs75452111	2	184480902	A	G	448956	0.384	0.032	0.006	6.23E-05	<0.001	455364	0.395	0.001	0.001	2.36E-06	0.3
rs7574611	2	51214993	A	C	448956	0.413	-0.031	0.006	6.26E-05	<0.001	455364	0.431	-0.002	0.001	1.65E-05	0.0061
rs7629352	3	16848835	A	G	448956	0.691	-0.034	0.006	6.99E-05	<0.001	455364	0.701	-0.003	0.001	1.99E-05	0.0026
rs76966748	2	148569240	A	G	448956	0.047	0.102	0.016	8.46E-05	<0.001	455364	0.065	0.001	0.002	1.31E-06	0.44
rs9586	3	49213637	T	C	448956	0.769	-0.034	0.007	5.91E-05	<0.001	455364	0.778	-0.004	0.001	4.06E-05	<0.001
Exposure: MDD - Psychiatric Genetic Consortium																
rs17499892	7	136692467	A	C	142646	0.624	-0.05	0.009	0.000204	<0.001	455364	0.61	-0.002	0.001	9.17E-06	0.041
rs1936365	6	28268452	C	G	142646	0.144	-0.069	0.013	0.000203	<0.001	455364	0.163	-0.002	0.001	9.36E-06	0.039
rs1950829	14	42097937	A	G	142646	0.487	0.054	0.009	0.000264	<0.001	455364	0.481	0.001	0.001	8.25E-07	0.54
rs2012697	1	72819612	T	C	142646	0.398	-0.048	0.009	0.000197	<0.001	455364	0.401	-0.001	0.001	4.78E-06	0.14
rs2060886	18	53167520	T	C	142646	0.426	-0.046	0.009	0.000181	<0.001	455364	0.422	-0.003	0.001	3.49E-05	<0.001
rs2451828	5	7448796	T	C	142646	0.024	0.159	0.031	0.000189	<0.001	455364	0.023	0.001	0.003	2.05E-07	0.76
rs34382743	2	145741849	T	C	142646	0.596	0.046	0.009	0.000183	<0.001	455364	0.598	0.001	0.001	7.16E-06	0.071
rs4811079	20	49157052	C	G	142646	0.625	0.049	0.009	2.00E-04	<0.001	455364	0.638	-0.001	0.001	5.31E-06	0.12
rs6689226	1	73806923	T	C	142646	0.407	0.05	0.009	0.000201	<0.001	455364	0.369	0.001	0.001	3.16E-06	0.23
rs6832890	4	42106538	C	G	142646	0.206	-0.06	0.011	0.000198	<0.001	455364	0.197	-0.002	0.001	1.12E-05	0.024
rs78676209	5	44212359	C	G	142646	0.948	-0.104	0.02	0.000183	<0.001	455364	0.954	0.001	0.002	2.23E-07	0.75

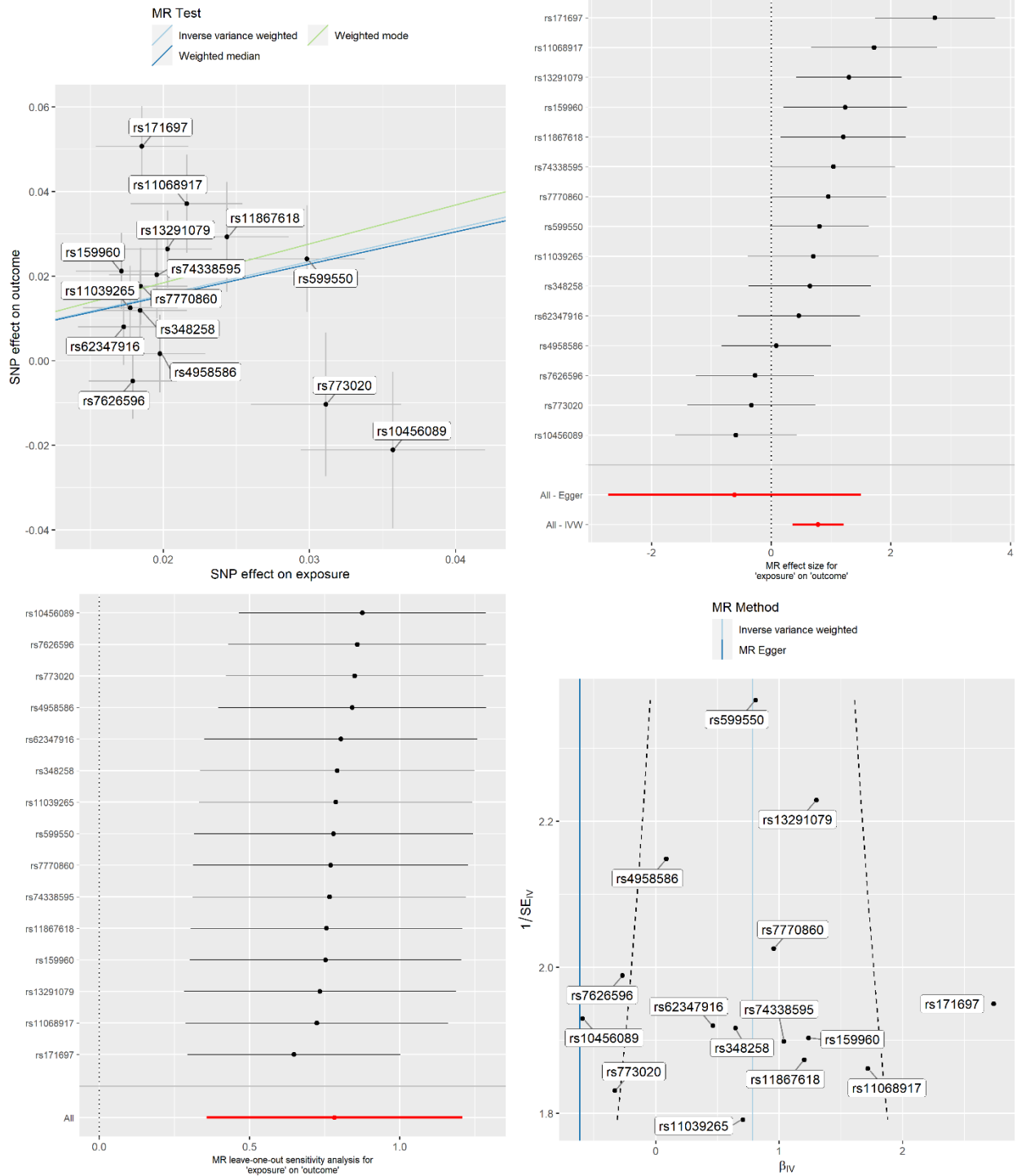


Figure S1. Sensitivity analyses of Loneliness Exposure on Major Depressive Disorder in the Psychiatric Genetic Consortium including Method Comparison (top left), Forest plot (top right), Leave-one-out (bottom left) and Funnel Plot (bottom right)

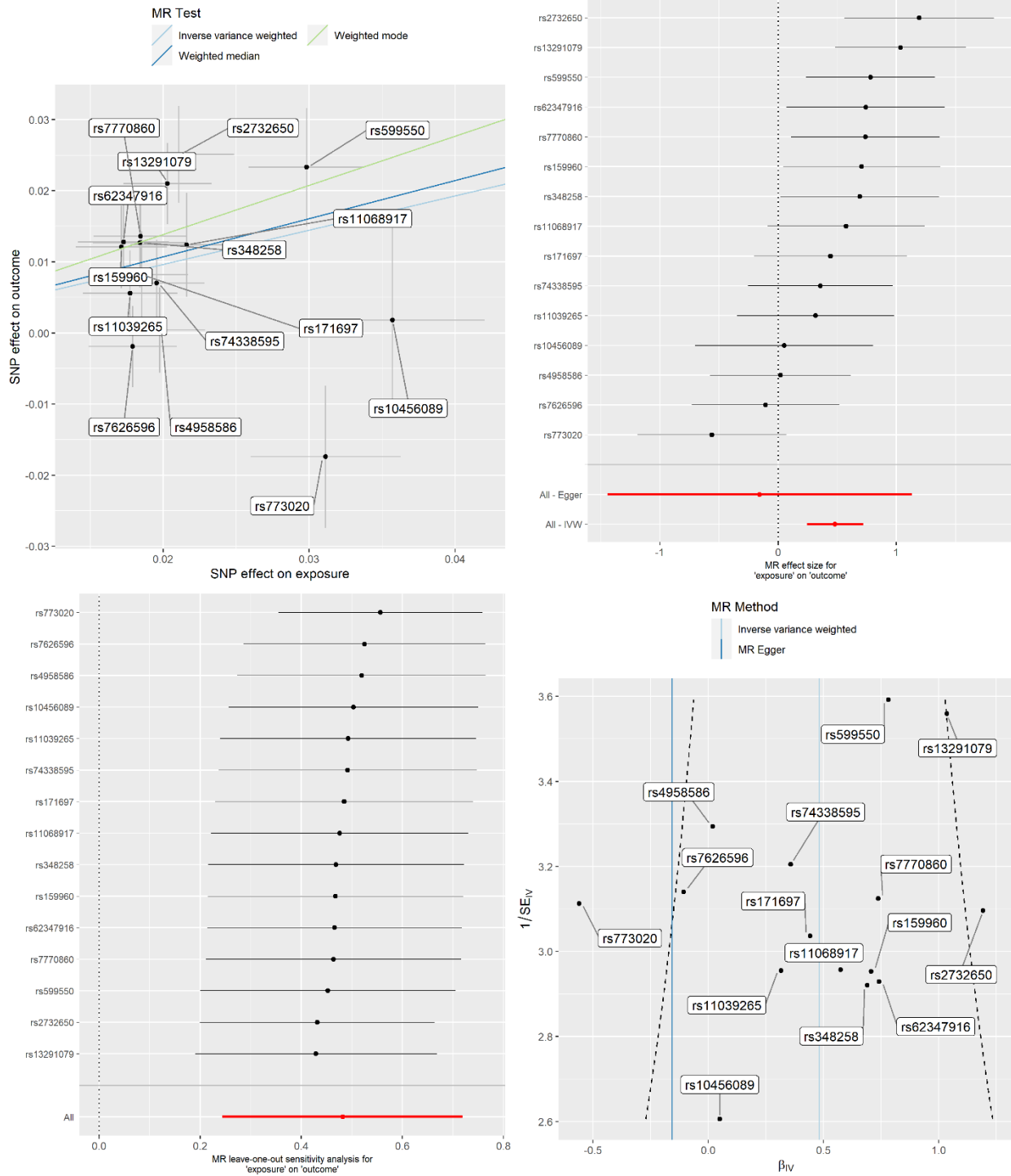


Figure S2. Sensitivity analyses of Loneliness Exposure on Major Depressive Disorder in the Million Veterans Program including Method Comparison (top left), Forest plot (top right), Leave-one-out (bottom left) and Funnel Plot (bottom right)

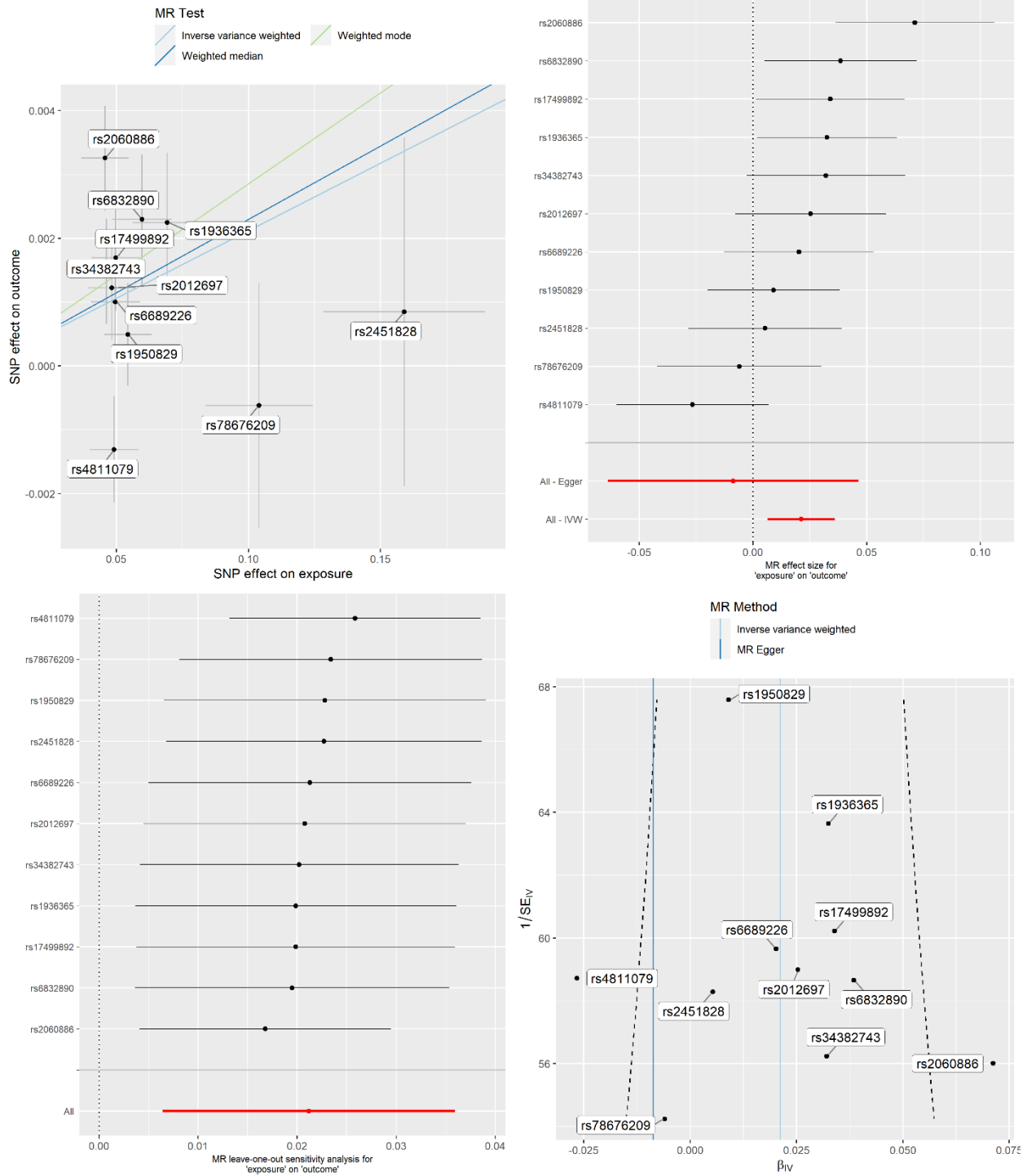


Figure S3. Sensitivity analyses of Major Depressive Disorder in the Psychiatric Genetic Consortium on Loneliness including Method Comparison (top left), Forest plot (top right), Leave-one-out (bottom left) and Funnel Plot (bottom right)

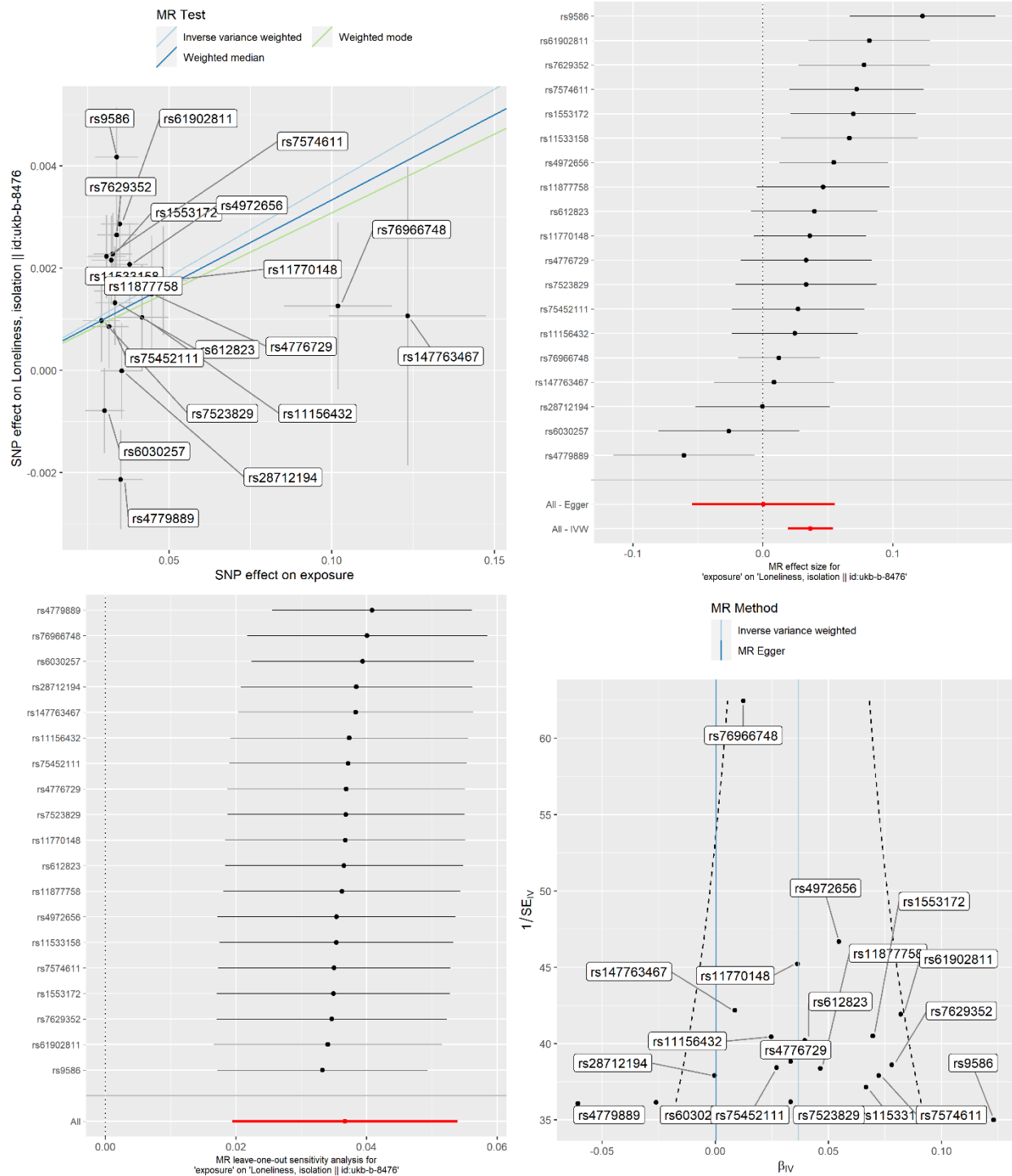


Figure S4. Sensitivity analyses of Major Depressive Disorder in the Million Veterans Program on Loneliness including Method Comparison (top left), Forest plot (top right), Leave-one-out (bottom left) and Funnel Plot (bottom right)

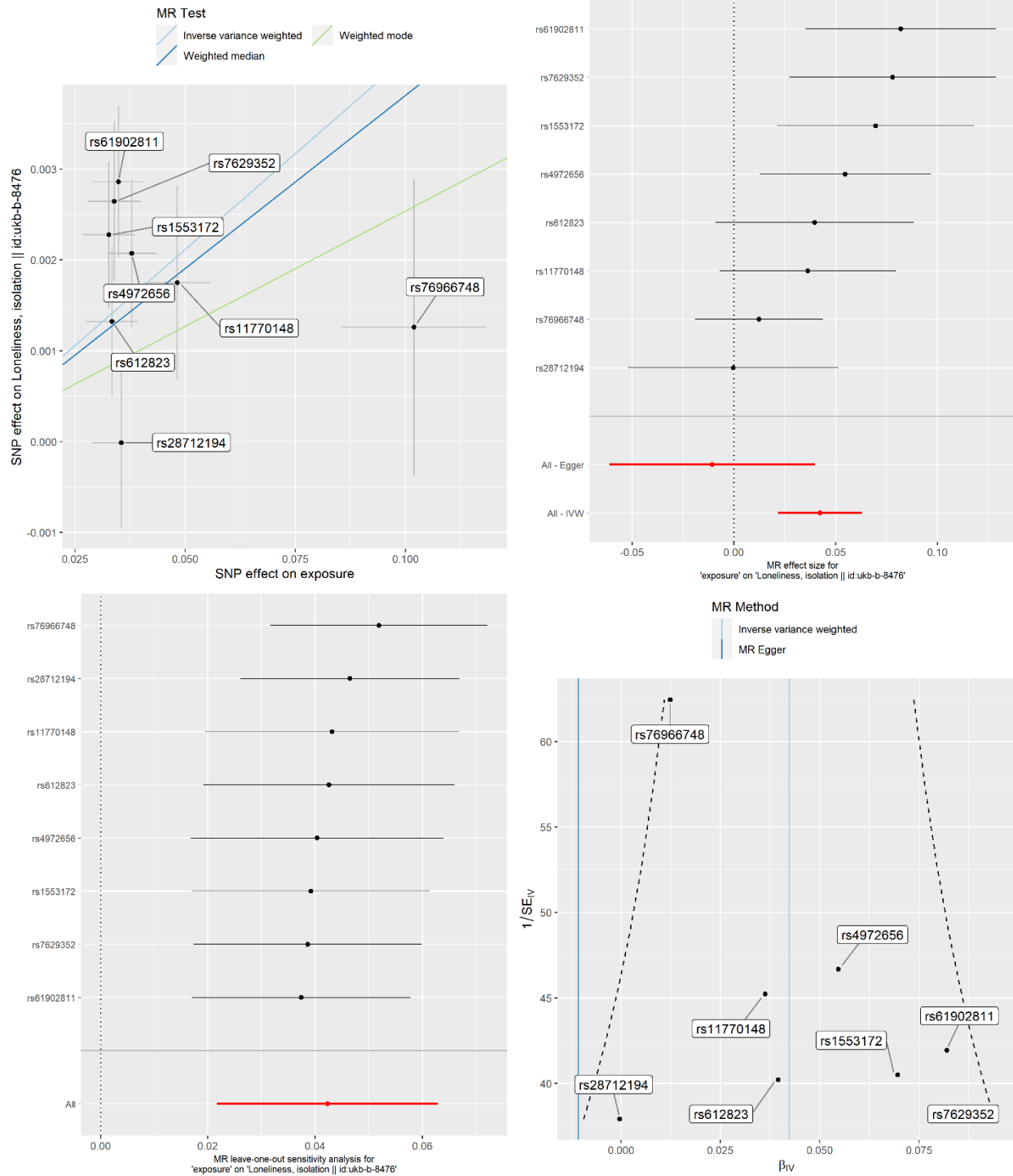


Figure S5. Sensitivity Analysis using 10^{-8} Significant Threshold for MDD in the Million Veterans Program and Loneliness including Method Comparison (top left), Forest plot (top right), Leave-one-out (bottom left) and Funnel Plot (bottom right)

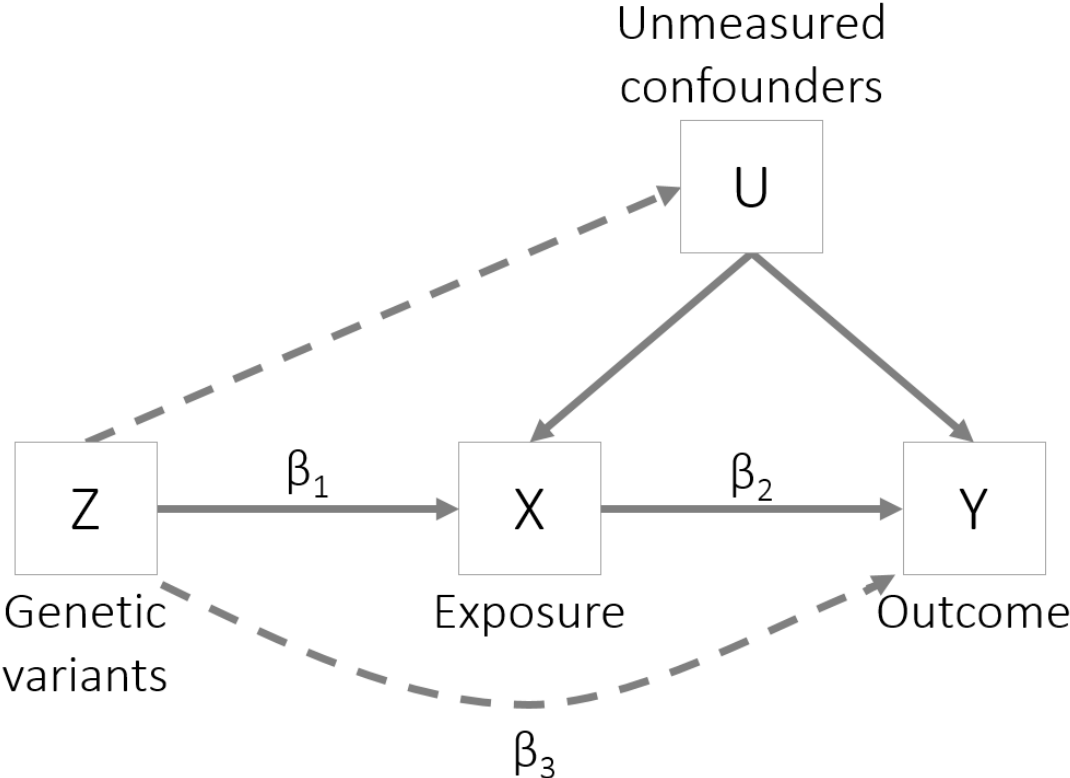


Figure S6. Mendelian Randomization Model

Table S9. Univariable Mendelian Randomization Sensitivity Analyses for Loneliness and Major Depressive Disorder using Loneliness phenotype from Elsworth et al.

Exposure	Outcome	Method	SNPs (n)	β	95%CI
Loneliness	MDD: MVP	Inverse Variance Weighted	16	1.790	0.905, 2.675
		Weighted Median	16	1.732	0.856, 2.608
		Weighted Mode	16	2.108	0.36, 3.855
		RAPS	16	1.890	1.271, 2.509
		MR-PRESSO	16	1.779	0.599, 2.96
Loneliness	MDD: PGC	Inverse Variance Weighted	16	2.777	1.253, 4.302
		Weighted Median	16	2.744	1.279, 4.209
		Weighted Mode	16	4.105	1.38, 6.83
		RAPS	16	2.966	2.002, 3.93
		MR-PRESSO	16	2.310	1.99, 2.631

Table S10. F Statistics for Mendelian Randomization Sensitivity Analyses from Loneliness to MDD and MDD to Loneliness using Loneliness phenotype from Elsworth et al.

Exposure	Outcome	SNPs (n)	Mean F	Range F
Loneliness	MDD: MVP	16	35.9	30.14-57.45
Loneliness	MDD: PGC	16	35.9	30.14-57.45

Table S11. Cochran's heterogeneity statistic for Inverse Variance Weighted Mendelian Randomization Sensitivity analyses from Loneliness to MDD and MDD to Loneliness using Loneliness phenotype from Elsworth et al.

Exposure	Outcome	SNPs (n)	Q Statistic	p
Loneliness	MDD: MVP	16	33.67	0.004
Loneliness	MDD: PGC	16	40.78	<0.001

Table S12. I^2_{GX} statistics for Sensitivity Analyses from Loneliness to MDD and MDD to Loneliness using Loneliness phenotype from Elsworth et al.

Exposure	Outcome	SNPs (n)	I^2_{GX}
Loneliness	MDD: MVP	16	0.405
Loneliness	MDD: PGC	16	0.405

Table S13. Outlier-corrected SNPs in MR-PRESSO Sensitivity Analyses in the Million Veterans Program using Loneliness phenotype from Elsworth et al.

Exposure	Outcome	SNP	Outlier Test, p
Loneliness	MDD: MVP	rs62085660	0.032
Loneliness	MDD: MVP	rs773020	0.048
Loneliness	MDD: PGC	rs30266	0.032

Table S14. MR-PRESSO Global and Distortion Sensitivity Analyses in the Million Veterans Program using Loneliness phenotype from Elsworth et al.

Exposure	Outcome	Global Test, <i>p</i>	Distortion Test, <i>p</i>
Loneliness: Elsworth et al.	MDD: MVP	0.006	0.978
Loneliness: Elsworth et al.	MDD: PGC	0.002	0.331

Table S15. Association of genome-wide significant SNPs from Sensitivity Analyses for Loneliness to MDD using Loneliness phenotype from Elsworth et al.

SNP	Chr	Pos	EA	OA	N	EAF	BETA	SE	r ²	p	N	EAF	BETA	SE	r ²	p
Exposure: Loneliness Outcome: MDD - Million Veterans Program																
rs1022688	20	47648856	A	G	455364	0.33	0.005	0.001	7.04E-05	<0.001	448956	0.343	0.011	0.006	6.35E-06	0.0914
rs10456089	6	11959836	A	G	455364	0.079	-0.01	0.002	8.86E-05	<0.001	448956	0.069	-0.002	0.014	3.70E-08	0.8975
rs10950394	7	12263587	T	C	455364	0.419	0.005	0.001	6.88E-05	<0.001	448956	0.424	0.012	0.006	9.72E-06	0.0367
rs13291079	9	96360650	C	T	455364	0.423	-0.005	0.001	9.83E-05	<0.001	448956	0.419	-0.021	0.006	3.03E-05	<0.001
rs159960	1	8476428	G	A	455364	0.556	-0.004	0.001	6.62E-05	<0.001	448956	0.533	-0.012	0.006	9.67E-06	0.0372
rs2149351	9	120501644	G	T	455364	0.757	-0.005	0.001	6.79E-05	<0.001	448956	0.763	-0.001	0.007	8.01E-08	0.8496
rs30266	5	103972357	A	G	455364	0.328	0.005	0.001	7.38E-05	<0.001	448956	0.319	0.008	0.006	4.31E-06	0.1644
rs599550	18	53252388	A	G	455364	0.848	0.009	0.001	0.000126	<0.001	448956	0.864	0.023	0.008	1.74E-05	0.0051
rs62085660	17	66097739	G	C	455364	0.742	-0.005	0.001	7.44E-05	<0.001	448956	0.716	-0.03	0.007	4.63E-05	<0.001
rs6430286	2	148834364	A	G	455364	0.425	-0.005	0.001	7.10E-05	<0.001	448956	0.433	-0.007	0.006	3.18E-06	0.2319
rs67988891	5	152204741	G	C	455364	0.319	-0.006	0.001	9.14E-05	<0.001	448956	0.313	-0.002	0.006	3.18E-07	0.7055
rs7107356	11	47676170	G	A	455364	0.507	0.004	0.001	6.70E-05	<0.001	448956	0.504	0.008	0.006	4.42E-06	0.1589
rs74338595	2	212749786	C	T	455364	0.291	-0.005	0.001	7.54E-05	<0.001	448956	0.294	-0.007	0.006	2.92E-06	0.252
rs7626596	3	82000680	A	G	455364	0.567	-0.005	0.001	7.49E-05	<0.001	448956	0.554	0.002	0.006	2.55E-07	0.7351
rs773020	9	77768122	A	G	455364	0.9	0.008	0.001	7.26E-05	<0.001	448956	0.901	-0.017	0.01	6.75E-06	0.0817
rs7770860	6	131186393	C	T	455364	0.373	0.005	0.001	7.33E-05	<0.001	448956	0.37	0.014	0.006	1.20E-05	0.0203
Exposure: Loneliness Outcome: MDD - Psychiatric Genetic Consortium																
rs1022688	20	47648856	A	G	455364	0.33	0.005	0.001	7.04E-05	<0.001	142646	0.334	0.011	0.009	8.87E-06	0.2606
rs10456089	6	11959836	A	G	455364	0.079	-0.01	0.002	8.86E-05	<0.001	142646	0.076	0.021	0.018	9.13E-06	0.2537
rs10950394	7	12263587	T	C	455364	0.419	0.005	0.001	6.88E-05	<0.001	142646	0.415	0.022	0.009	4.30E-05	0.0133
rs13291079	9	96360650	C	T	455364	0.423	-0.005	0.001	9.83E-05	<0.001	142646	0.428	-0.026	0.009	5.95E-05	0.0036
rs159960	1	8476428	G	A	455364	0.556	-0.004	0.001	6.62E-05	<0.001	142646	0.525	-0.021	0.009	3.86E-05	0.019
rs2149351	9	120501644	G	T	455364	0.757	-0.005	0.001	6.79E-05	<0.001	142646	0.764	-0.027	0.01	4.69E-05	0.0097
rs30266	5	103972357	A	G	455364	0.328	0.005	0.001	7.38E-05	<0.001	142646	0.323	0.05	0.01	0.000195	<0.001
rs599550	18	53252388	A	G	455364	0.848	0.009	0.001	0.000126	<0.001	142646	0.855	0.024	0.013	2.55E-05	0.0567
rs62085660	17	66097739	G	C	455364	0.742	-0.005	0.001	7.44E-05	<0.001	135581	0.733	-0.01	0.011	6.21E-06	0.3589
rs6430286	2	148834364	A	G	455364	0.425	-0.005	0.001	7.10E-05	<0.001	142646	0.425	-0.001	0.009	1.24E-07	0.894
rs67988891	5	152204741	G	C	455364	0.319	-0.006	0.001	9.14E-05	<0.001	135581	0.322	0.002	0.01	3.01E-07	0.8399
rs7107356	11	47676170	G	A	455364	0.507	0.004	0.001	6.70E-05	<0.001	142646	0.497	0.021	0.009	4.03E-05	0.0165
rs74338595	2	212749786	C	T	455364	0.291	-0.005	0.001	7.54E-05	<0.001	142646	0.298	-0.02	0.01	2.73E-05	0.0483
rs7626596	3	82000680	A	G	455364	0.567	-0.005	0.001	7.49E-05	<0.001	142646	0.558	0.005	0.009	1.99E-06	0.5946
rs773020	9	77768122	A	G	455364	0.9	0.008	0.001	7.26E-05	<0.001	142646	0.906	-0.01	0.017	2.55E-06	0.5461

rs7770860 6 131186393 C T 455364 0.373 0.005 0.001 7.33E-05 <0.001 142646 0.38 0.018 0.009 2.59E-05 0.0546

Table S16. Univariable Mendelian Randomization Estimates using 10^{-8} Significant Threshold for MDD in the Million Veterans Program on Loneliness

Exposure	Outcome	Method	SNPs (n)	β	95%CI
MDD: MVP	Loneliness	Inverse Variance Weighted	8	0.042	0.022, 0.063
		Weighted Median	8	0.038	0.014, 0.062
		Weighted Mode	8	0.025	-0.014, 0.065
		RAPS	8	0.045	0.027, 0.062
		MR-PRESSO	8	0.064	0.055, 0.072

Table S17. Univariable Mendelian Randomization Sensitivity Analyses for Major Depressive Disorder using full Million Veteran's Program GWAS and Loneliness

Exposure	Outcome	Method	SNPs (n)	β	95%CI
MDD: MVP (Full GWAS)	Loneliness	Inverse Variance Weighted	137	0.075	0.065, 0.085
		Weighted Median	137	0.072	0.060, 0.083
		Weighted Mode	137	0.079	0.036, 0.123
		RAPS	137	0.078	0.070, 0.086
		MR-PRESSO	137	0.075	0.072, 0.077

Table S18. F Statistic for Mendelian Randomization Sensitivity Analyses for MDD using full Million Veteran's Program GWAS data and Loneliness

Exposure	Outcome	SNPs (n)	Mean F	Range F
MDD: MVP (Full GWAS)	Loneliness	137	43.26	29.52 - 127.69

Table S19. Cochran's heterogeneity statistic for Inverse Variance Weighted Mendelian Randomization Sensitivity analyses for MDD using full Million Veteran's Program GWAS data and Loneliness

Exposure	Outcome	SNPs (n)	Q Statistic	p
MDD: MVP (Full GWAS)	Loneliness	137	218.75	<0.001

Table 20. I^2_{GX} statistic for Sensitivity Analyses for MDD using full Million Veteran's Program GWAS data and Loneliness

Exposure	Outcome	SNPs (n)	I^2_{GX}
MDD: MVP (Full GWAS)	Loneliness	137	0.318

Table S21. Outlier-corrected SNPs in MR-PRESSO Sensitivity Analyses for MDD using full Million Veteran's Program GWAS data and Loneliness

Exposure	Outcome	SNP	Outlier Test, p
MDD: MVP (Full GWAS)	Loneliness	rs1054169	<0.119
		rs2214123	<0.119

Table S22. Outlier-corrected SNPs in MR-PRESSO Sensitivity Analyses for MDD using full Million Veteran's Program GWAS data and Loneliness

Exposure	Outcome	Global Test, <i>p</i>	Distortion Test, <i>p</i>
MDD: MVP (Full GWAS)	Loneliness	<0.001	0.983

Table S23. Univariable Mendelian Randomization Sensitivity Analyses of Major Depressive Disorder without UKB sample using SNPs from full Million Veteran's Program GWAS and Loneliness

Exposure	Outcome	Method	SNPs (n)	β	95%CI
MDD: MVP (Full GWAS SNPs)	Loneliness	Inverse Variance Weighted	92	0.056	0.047, 0.065
		Weighted Median	92	0.051	0.039, 0.064
		Weighted Mode	92	0.051	0.024, 0.078
		RAPS	92	0.061	0.052, 0.070
		MR-PRESSO	92	0.056	0.055, 0.056

Table S24. F Statistic for Mendelian Randomization Sensitivity Analyses of Major Depressive Disorder without UKB sample using SNPs from full Million Veteran's Program GWAS and Loneliness

Exposure	Outcome	SNPs (n)	Mean F	Range F
MDD: MVP (Full GWAS SNPs)	Loneliness	92	13.35	1.21 - 36.82

Table S25. Cochran's heterogeneity statistic for Inverse Variance Weighted Mendelian Randomization Sensitivity analyses of Major Depressive Disorder without UKB sample using SNPs from full Million Veteran's Program GWAS and Loneliness

Exposure	Outcome	SNPs (n)	Q Statistic	<i>p</i>
MDD: MVP (Full GWAS SNPs)	Loneliness	92	117.64	0.031

Table 26. I^2_{GX} statistic for Sensitivity Analyses of Major Depressive Disorder without UKB sample using SNPs from full Million Veteran's Program GWAS and Loneliness

Exposure	Outcome	SNPs (n)	I^2_{GX}
MDD: MVP (Full GWAS SNPs)	Loneliness	92	0.326

Table S27. Univariable Mendelian Randomization Sensitivity Analyses for MDD meta-analysis from Wray et al. and Loneliness

Exposure	Outcome	Method	SNPs (n)	β	95%CI
MDD (Wray et al.)	Loneliness	Inverse Variance Weighted	35	0.049	0.037, 0.062
		Weighted Median	35	0.038	0.024, 0.053
		Weighted Mode	35	0.030	0.004, 0.055
		RAPS	35	0.052	0.042, 0.061
		MR-PRESSO	35	0.049	0.048, 0.05

Table S28. F Statistic for Mendelian Randomization Sensitivity Analyses for MDD meta-analysis from Wray et al. and Loneliness

Exposure	Outcome	SNPs (n)	Mean F	Range F
MDD (Wray et al.)	Loneliness	35	37.79	25.09 - 66.76

Table S29. Cochran's heterogeneity statistic for Inverse Variance Weighted Mendelian Randomization Sensitivity analyses for MDD meta-analysis from Wray et al. and Loneliness

Exposure	Outcome	SNPs (n)	Q Statistic	p
MDD (Wray et al.)	Loneliness	35	63.05	0.002

Table S30. I^2_{GX} statistic for Sensitivity Analyses for MDD meta-analysis from Wray et al. and Loneliness

Exposure	Outcome	SNPs (n)	I^2_{GX}
MDD (Wray et al.)	Loneliness	35	0.0

Table S31. Univariable Mendelian Randomization Sensitivity Analyses for Loneliness and Major Depressive Disorder using the PHQ-2 GWAS

Exposure	Outcome	Method	SNPs (n)	β	95%CI
Loneliness	MDD (PHQ-2)	Inverse Variance Weighted	14	0.700	0.417, 0.984
		Weighted Median	14	0.450	0.17, 0.748
		Weighted Mode	14	0.374	-0.14, 0.889
		RAPS	14	0.743	0.551, 0.936
		MR-PRESSO	14	0.617	0.551, 0.683

Table S32. F Statistic for Mendelian Randomization Sensitivity Analyses for Loneliness and Major Depressive Disorder using the PHQ-2 GWAS

Exposure	Outcome	SNPs (n)	Mean F	Range F
Loneliness	MDD (PHQ-2)	14	35.72	29.81 56.41

Table S33. Cochran's heterogeneity statistic for Inverse Variance Weighted Mendelian Randomization Sensitivity analyses for Loneliness and Major Depressive Disorder using the PHQ-2 GWAS

Exposure	Outcome	SNPs (n)	Q Statistic	p
Loneliness	MDD (PHQ-2)	14	32.82	0.002

Table S34. I^2_{GX} statistic for Sensitivity Analyses for Loneliness and Major Depressive Disorder using the PHQ-2 GWAS

Exposure	Outcome	SNPs (n)	I^2_{GX}
Loneliness	MDD (PHQ-2)	14	0.0