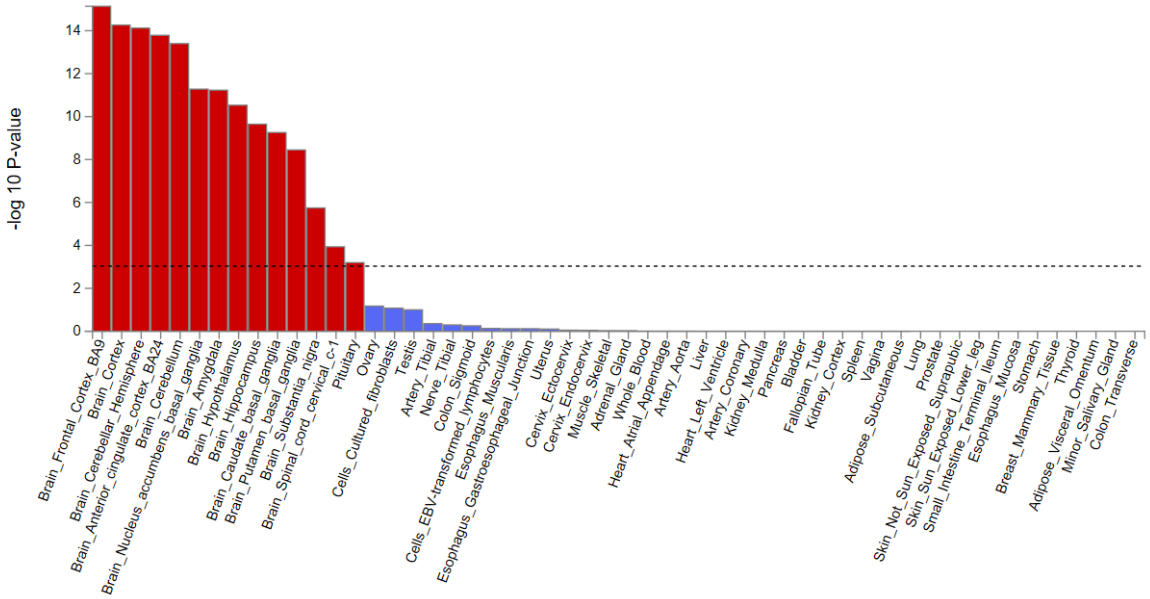
Supplementary Information

Figure S1. MAGMA Tissue Enrichment



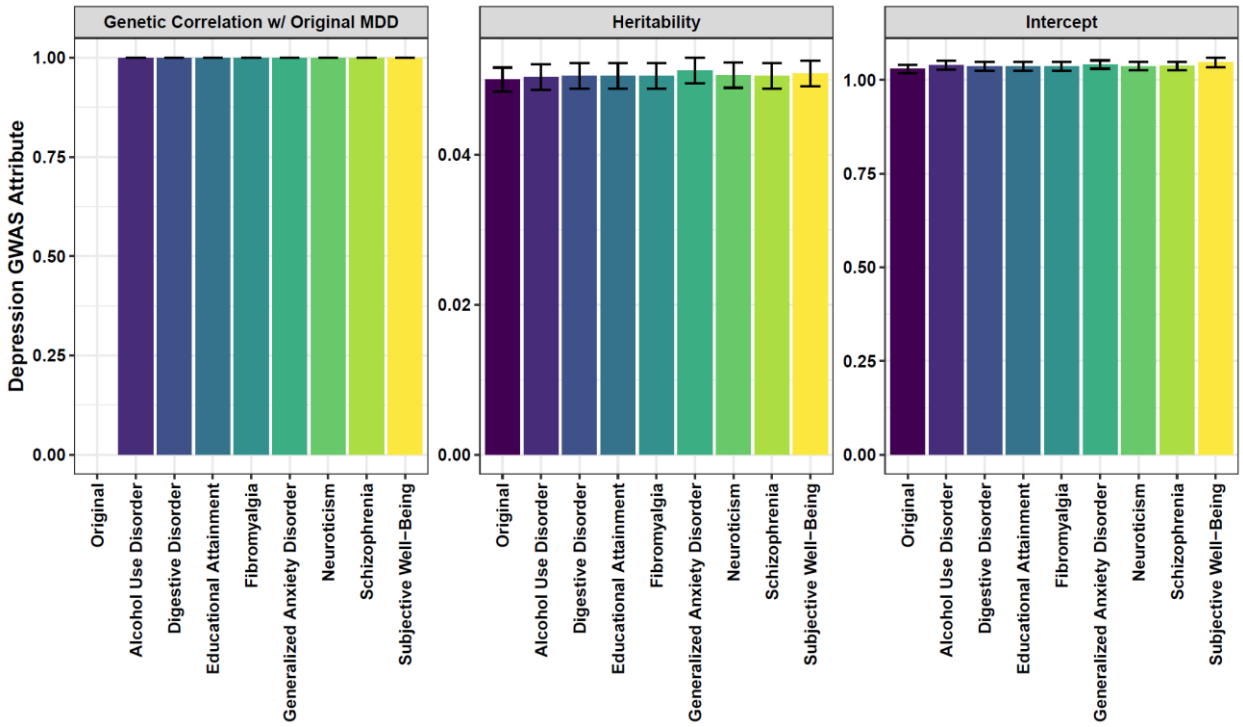
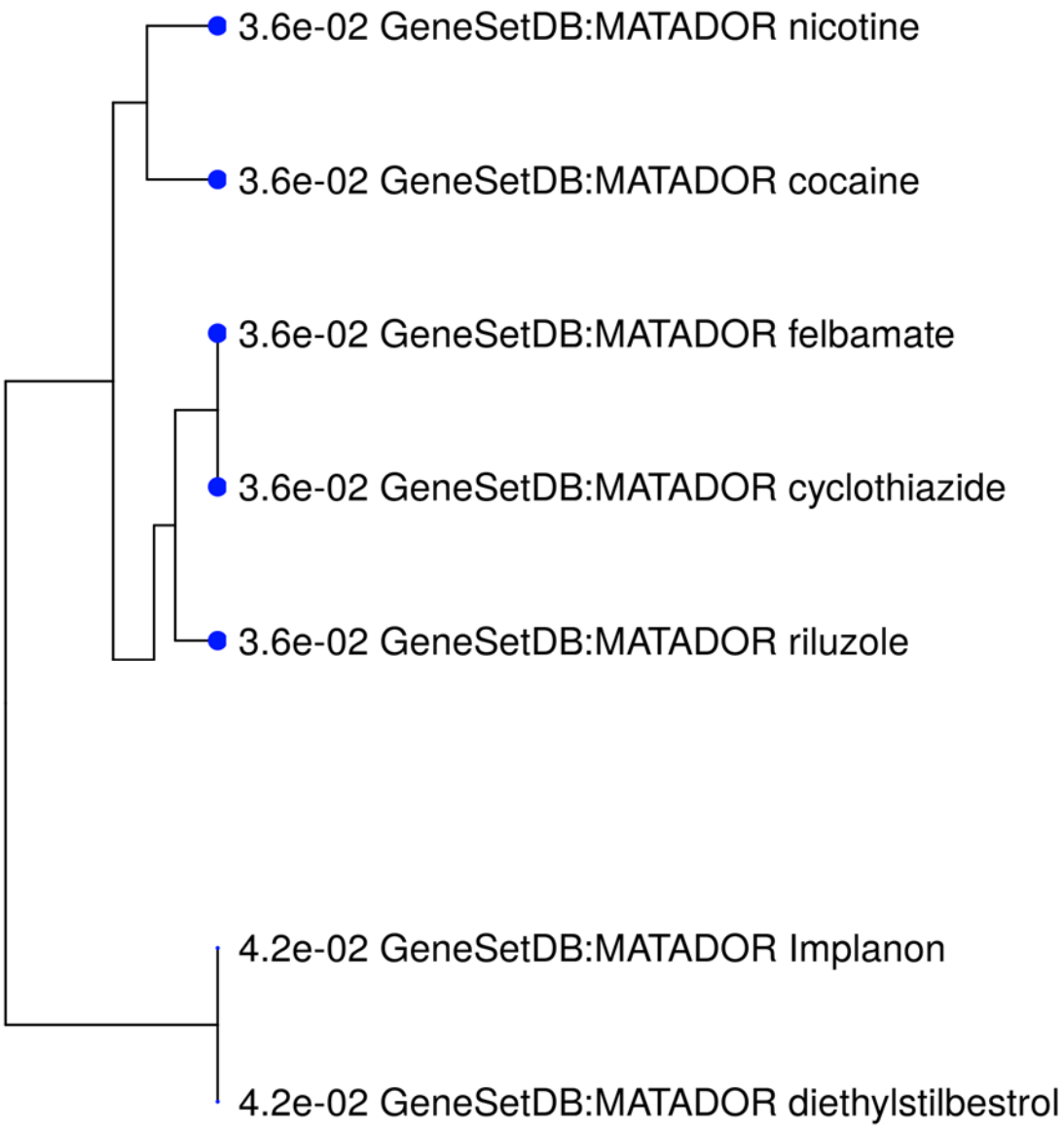


Figure S2: Depression conditioned with comorbid conditions. Genome-wide attributes of conditioned depression GWAS including heritability, linkage-disequilibrium (LD)-score intercept, genetic correlation between conditioned and unconditioned depression, and proportion of GWS SNPs retained after conditioning. Error bars represented standard errors surrounding each genetic correlation, heritability, and intercept point estimate. Sample size for each analysis is the same as the primary analysis, n=1,154,267.

Figure S3. Drug repurposing.



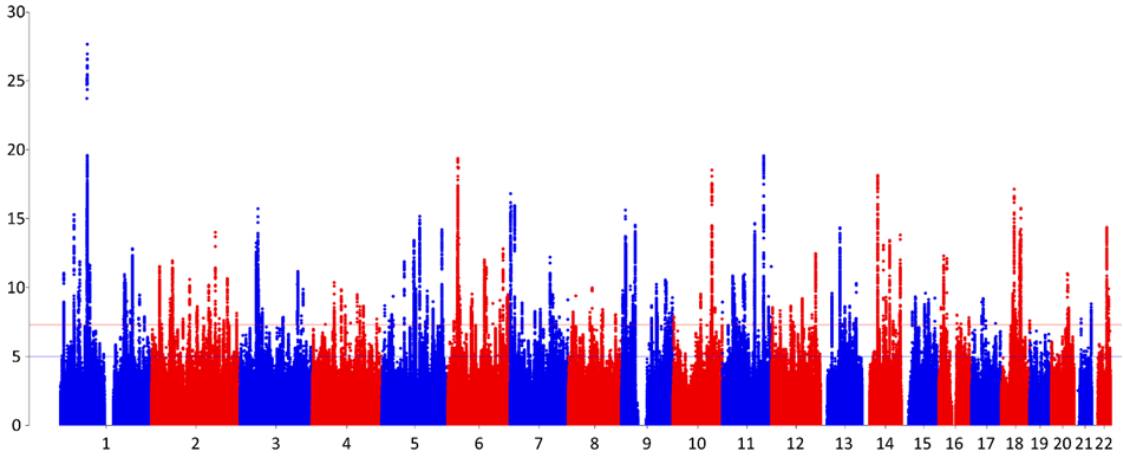


Figure S4. Transancestry meta-analysis. Manhattan plot for transancestry meta-analysis of MDD-META (n= 1,213,867).

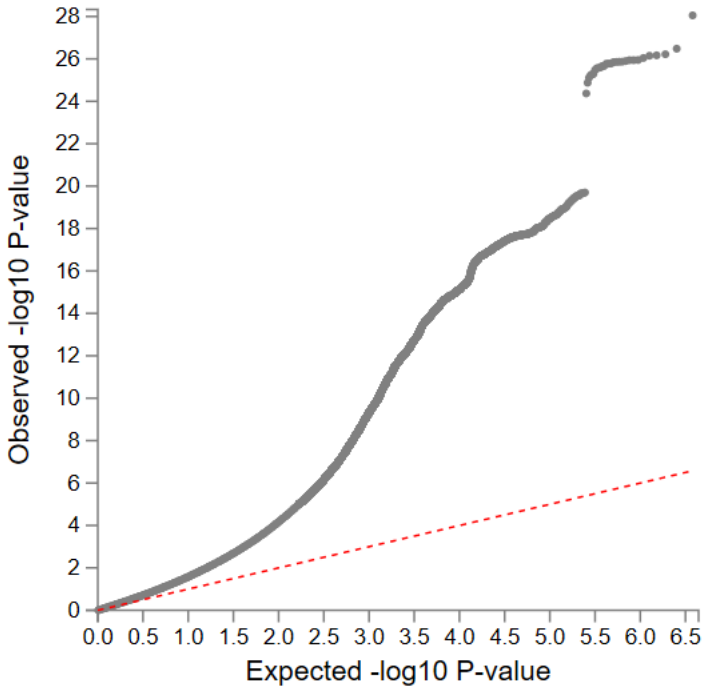


Figure S5. QQ-plot for the MDD-META analysis. Observed p-value is plotted on the y axis and expected p-value is plotted on the x axis. The red line represents a result with no inflation. LD-score regression showed that 97% of observed inflation is due to the high polygenicity of depression, with no evidence for inflation due to stratification or confounds indicated by the intercept (1.03, SE 0.011) or attenuation ratio (0.0297, SE 0.011).

Table S1. Replication of findings from the primary meta-analysis by an independent 23andMe cohort of 1,342,778 participants. 211 variants were available in the 23andMe cohort for testing. Of 211 variants tested, 209 (99%) had the same direction of effect, 192 showed at least nominal significance p<0.05 (91%), 144 remained significant after testing for multiple comparisons p<0.05/211=2.37E-04 (68%), and 81 were independently genome-wide significant p<5E-08 (38%). Only 2 SNPs were discordant, both with p>0.05 (0.9%). SNPs with only nominal significance are in italics, SNPs that survive multiple testing correction are in bold, and SNPs which were genome-wide significant in the independent cohort are bold and underlined. Tests were regressions with uncorrected 2-sided t-tests reported.

rsid	Ref Allele	MDD-META log(OR)	23andMe Effect	MDD-META p-value	23andMe p-value
rs11688767	**A**	**-0.0214**	**-0.0314**	**2.71E-13**	**5.63E-32**
rs11756123	**A**	**0.0227**	**0.0319**	**2.35E-13**	**1.56E-29**
rs61902811	**A**	**-0.0277**	**-0.0304**	**5.90E-20**	**7.42E-28**
rs7531118	**T**	**-0.0339**	**-0.0286**	**8.90E-29**	**1.96E-26**
rs827120	**A**	**0.0211**	**0.0288**	**8.21E-13**	**2.39E-26**
rs3756335	**A**	**-0.0178**	**-0.0281**	**1.59E-09**	**9.15E-25**
rs7523829	**A**	**0.027**	**0.0276**	**3.99E-20**	**2.06E-24**
rs72839477	**T**	**-0.0447**	**-0.0501**	**1.87E-16**	**3.92E-24**
rs7988498	**T**	**-0.0191**	**-0.0271**	**8.44E-11**	**5.01E-24**
rs55649128	**T**	**0.0239**	**0.0271**	**3.34E-15**	**2.62E-22**
rs67981811	**C**	**0.0498**	**0.0465**	**1.99E-20**	**5.38E-22**
rs16909922	**A**	**-0.0287**	**-0.0439**	**1.39E-08**	**6.21E-22**
rs13186288	**T**	**0.0176**	**0.0261**	**8.37E-09**	**1.51E-20**
rs301816	**A**	**-0.0201**	**-0.025**	**1.85E-11**	**3.78E-20**
rs4702	**A**	**-0.0183**	**-0.0241**	**5.82E-10**	**2.50E-19**
rs7030813	**T**	**0.0248**	**0.0243**	**5.10E-16**	**1.84E-18**
rs11135349	**A**	**-0.0231**	**-0.0234**	**3.12E-15**	**2.66E-18**
rs11772627	**C**	**-0.0307**	**-0.0291**	**2.45E-16**	**4.97E-18**
rs4632195	**T**	**0.0227**	**0.0231**	**8.27E-15**	**6.39E-18**
rs113188507	**A**	**0.0223**	**0.0263**	**5.55E-12**	**6.61E-18**
rs3814424	**T**	**0.0262**	**0.0308**	**3.63E-11**	**7.06E-18**
rs13204572	**C**	**-0.0383**	**-0.0443**	**7.67E-12**	**8.13E-18**
rs1806153	**T**	**0.0234**	**0.0276**	**3.08E-11**	**1.69E-17**

rs102275	T	-0.0196	-0.0236	1.44E-10	3.47E-17
rs10973303	T	0.0298	0.031	2.33E-13	6.73E-17
rs7023933	A	-0.0265	-0.0298	2.39E-11	8.07E-17
rs17186548	A	-0.0252	-0.027	3.86E-12	1.60E-16
rs45534736	C	0.0418	0.0503	3.16E-10	2.81E-16
rs73581580	A	0.0407	0.0427	1.61E-10	3.24E-16
rs60157091	T	0.0213	0.0212	3.40E-13	2.86E-15
rs12635614	A	0.0187	0.0214	1.32E-10	3.04E-15
rs7200826	T	0.0236	0.0238	1.85E-12	9.33E-15
rs9517313	C	0.0199	0.0214	3.48E-11	2.16E-14
rs2369818	T	0.0211	0.0218	3.55E-12	6.88E-14
rs12135327	T	0.0212	0.02	5.03E-13	8.34E-14
rs11674333	A	0.0207	0.0201	1.26E-12	8.36E-14
rs12967143	C	-0.0271	-0.0216	2.02E-17	1.12E-13
rs12517438	T	-0.0178	-0.0197	1.30E-09	1.75E-13
rs1267042	T	0.0192	0.0214	7.31E-09	2.11E-13
rs10061069	C	-0.0224	-0.0234	5.24E-10	4.70E-13
rs4728354	T	-0.0163	-0.0196	3.75E-08	5.69E-13
rs7809993	C	-0.019	-0.0193	2.48E-10	9.03E-13
rs4753209	A	-0.0241	-0.0193	2.71E-15	1.25E-12
rs9775587	T	0.0197	0.0197	5.54E-11	1.49E-12
rs2806933	A	0.0236	0.0193	5.48E-15	2.19E-12
rs1054169	A	0.0234	0.0187	1.58E-15	4.18E-12
rs4980365	T	-0.0193	-0.0212	1.77E-08	7.33E-12
rs7940164	T	-0.0205	-0.019	4.53E-11	1.46E-11
rs17105472	A	-0.0317	-0.03	4.27E-10	1.50E-11
rs35905305	T	-0.0202	-0.0181	5.46E-12	1.70E-11
rs7193263	A	-0.0193	-0.0192	8.65E-10	2.36E-11
rs6536630	A	-0.0177	-0.0179	1.41E-09	2.57E-11
rs74927570	T	-0.0225	-0.0233	3.25E-09	3.21E-11
rs4267411	T	-0.0215	-0.0226	1.04E-08	4.06E-11
rs7617480	A	0.0269	0.0204	9.42E-15	7.72E-11
rs3099439	T	-0.0225	-0.0177	3.08E-14	8.44E-11

rs61691222	T	0.0205	0.0202	2.95E-09	1.50E-10
rs835303	T	-0.0235	-0.0211	5.96E-11	1.53E-10
rs6066242	A	0.0202	0.0183	1.36E-10	1.53E-10
rs67455183	T	-0.024	-0.0248	2.08E-08	1.57E-10
rs2322702	A	-0.0184	-0.0174	8.05E-10	1.58E-10
rs1933802	C	-0.0206	-0.017	2.48E-12	2.55E-10
rs1484145	T	0.0196	0.0169	1.99E-11	3.46E-10
rs3980104	A	-0.0172	-0.0174	1.05E-08	4.77E-10
rs8138989	T	-0.0192	-0.0181	2.90E-09	7.27E-10
rs12525684	A	-0.0188	-0.0163	1.43E-10	1.26E-09
rs7432943	T	-0.0183	-0.0165	2.13E-09	1.28E-09
rs4478545	A	-0.0197	-0.0181	2.31E-09	1.31E-09
rs7152906	T	-0.0229	-0.0253	5.85E-15	1.48E-09
rs10441718	T	0.0195	0.0164	6.22E-11	1.60E-09
rs372519	A	0.017	0.0162	2.64E-08	2.03E-09
rs2509805	T	0.0217	0.0172	4.59E-12	2.48E-09
rs2274793	T	-0.0219	-0.0171	1.97E-12	2.89E-09
rs2585399	A	0.0169	0.0164	3.53E-08	3.52E-09
rs12003380	C	-0.0171	-0.016	3.96E-08	4.60E-09
rs11614007	A	0.0221	0.019	2.12E-09	8.87E-09
rs1452787	A	-0.0228	-0.0169	1.78E-12	9.21E-09
rs6012575	C	0.0179	0.0157	1.20E-08	1.11E-08
rs2876520	C	-0.0191	-0.0153	1.46E-10	1.50E-08
rs56059718	A	0.0227	0.0189	9.15E-10	2.08E-08
rs913930	A	-0.0177	-0.0238	1.22E-08	4.52E-08
rs1021363	A	0.0279	0.0151	1.16E-19	5.53E-08
rs779	A	-0.0261	-0.0223	1.44E-08	5.97E-08
rs12967855	A	0.0267	0.0155	3.49E-17	6.45E-08
rs55650481	T	-0.0259	-0.0229	4.05E-08	6.87E-08
rs1848393	A	-0.0192	-0.0147	4.23E-10	8.31E-08
rs17737641	A	-0.0582	-0.0396	2.49E-12	9.62E-08
rs75581564	A	0.0283	0.0224	6.85E-10	1.14E-07
rs10805794	A	-0.0166	-0.0141	2.20E-08	1.49E-07

rs11681373	A	0.0168	0.0144	1.65E-08	1.50E-07
rs12705593	T	-0.0209	-0.0143	4.66E-12	1.62E-07
rs150027890	A	0.0424	0.0341	4.75E-09	1.73E-07
rs34727251	A	-0.018	-0.0153	2.24E-08	2.19E-07
rs1950829	A	0.0239	0.0215	2.91E-16	2.76E-07
rs11686891	A	-0.0214	-0.0138	4.92E-13	2.93E-07
rs148466862	T	0.0507	0.0339	4.94E-12	3.76E-07
rs56211578	A	-0.0235	-0.0184	1.17E-08	5.09E-07
rs61127279	A	0.0192	0.014	8.95E-10	6.02E-07
rs58243949	T	-0.0245	-0.0164	4.13E-12	6.89E-07
rs13296641	A	-0.0204	-0.0143	8.65E-11	7.64E-07
rs2592105	C	-0.0168	-0.0138	4.51E-08	1.11E-06
rs145678014	T	-0.0471	-0.0328	2.71E-10	1.42E-06
rs16841842	A	-0.0265	-0.0244	1.03E-13	1.66E-06
rs146791497	T	0.0389	0.0303	1.64E-08	1.67E-06
rs10987507	A	-0.0185	-0.0144	3.10E-08	2.00E-06
rs387627	T	0.0198	0.0142	2.31E-09	2.15E-06
rs10026036	A	0.0177	0.0131	4.44E-09	2.39E-06
rs1038093	T	0.0184	0.0131	1.37E-09	2.54E-06
rs66511648	T	-0.0189	-0.014	9.50E-09	2.73E-06
rs111471551	A	-0.0342	-0.0234	8.19E-10	2.93E-06
rs118109745	A	-0.0811	-0.0593	6.76E-10	3.14E-06
rs4131791	T	-0.0226	-0.0125	3.04E-14	4.57E-06
rs7589705	T	0.0386	0.0273	2.76E-08	4.58E-06
rs3088142	T	0.019	0.0193	1.36E-10	4.78E-06
rs7837935	T	-0.0274	-0.0174	2.13E-11	5.23E-06
rs61935769	A	-0.0173	-0.0128	1.13E-08	5.60E-06
rs7534271	C	0.0165	0.0123	3.42E-08	7.32E-06
rs34165207	A	0.0194	0.0118	1.01E-10	1.19E-05
rs12102100	A	0.0198	0.0184	5.04E-11	1.60E-05
rs1837713	A	0.0232	0.0133	8.68E-12	2.10E-05
rs35023999	A	0.0196	0.0113	2.16E-11	2.33E-05
rs2060337	T	0.0166	0.0114	3.05E-08	2.73E-05

rs667138	**A**	**-0.0256**	**-0.0155**	**2.48E-09**	**3.14E-05**
rs1414592	**C**	**-0.0164**	**-0.011**	**2.04E-08**	**3.74E-05**
rs2062479	**C**	**0.0167**	**0.0111**	**3.00E-08**	**4.47E-05**
rs3793577	**A**	**-0.0195**	**-0.0171**	**2.43E-11**	**4.76E-05**
rs13319803	**A**	**-0.0217**	**-0.0174**	**4.17E-13**	**4.99E-05**
rs57389877	**A**	**0.0167**	**0.0109**	**2.05E-08**	**5.28E-05**
rs11644513	**T**	**-0.0172**	**-0.0114**	**3.60E-08**	**5.42E-05**
rs2418449	**T**	**0.0223**	**0.0119**	**5.55E-12**	**5.67E-05**
rs4971586	**A**	**-0.0178**	**-0.0106**	**1.20E-09**	**7.77E-05**
rs4846898	**A**	**-0.0165**	**-0.0108**	**2.95E-08**	**8.11E-05**
rs75122126	**T**	**0.0629**	**0.0367**	**3.03E-09**	**0.000103029**
rs61903989	**T**	**-0.0447**	**-0.0272**	**6.24E-09**	**0.000103084**
rs1437336	**T**	**-0.0272**	**-0.0169**	**2.25E-08**	**0.000104391**
rs169235	**A**	**-0.02**	**-0.012**	**6.50E-09**	**0.000104872**
rs422907	**A**	**-0.0175**	**-0.0107**	**1.06E-08**	**0.000114402**
rs7017108	**T**	**0.0177**	**0.0104**	**2.48E-09**	**0.000123837**
rs2408225	**T**	**0.0186**	**0.0104**	**2.48E-10**	**0.000132009**
rs4785307	**A**	**0.0169**	**0.0104**	**3.76E-08**	**0.00015257**
rs1152578	**T**	**-0.0183**	**-0.0101**	**4.61E-10**	**0.000176494**
rs728017	**A**	**-0.0185**	**-0.0161**	**5.87E-10**	**0.000191811**
rs151286028	**A**	**0.0251**	**0.0125**	**9.46E-09**	**0.000213961**
rs57344483	*A*	*-0.0334*	*-0.0188*	*5.86E-09*	*0.00023436*
rs12959940	*A*	*0.0268*	*0.0156*	*6.55E-09*	*0.00024793*
rs78337797	*T*	*0.027*	*0.0191*	*4.65E-09*	*0.00033103*
rs72704544	*A*	*-0.0215*	*-0.0119*	*7.26E-09*	*0.00036516*
rs7564151	*C*	*-0.0183*	*-0.0096*	*1.87E-09*	*0.00045879*
rs993885	*A*	*0.0174*	*0.0151*	*2.36E-08*	*0.00046576*
rs9458641	*A*	*-0.0219*	*-0.0114*	*7.89E-10*	*0.00047774*
rs17822102	*A*	*0.0171*	*0.0098*	*2.77E-08*	*0.00051586*
rs12926421	*A*	*0.022*	*0.0144*	*8.96E-10*	*0.00052757*
rs4776729	*A*	*-0.0278*	*-0.0135*	*1.54E-10*	*0.00053664*
rs612823	*T*	*0.0217*	*0.0096*	*2.09E-12*	*0.00056238*
rs1006737	*A*	*0.0175*	*0.0097*	*1.17E-08*	*0.00058167*

rs28406450	*A*	*-0.0172*	*-0.0092*	*9.21E-09*	*0.00075174*
rs35553410	*T*	*-0.0206*	*-0.0104*	*2.39E-09*	*0.00081353*
rs9671376	*T*	*0.0203*	*0.0137*	*6.16E-09*	*0.00088614*
rs61914045	*A*	*0.0212*	*0.011*	*6.52E-09*	*0.00089441*
rs6472981	*T*	*-0.0243*	*-0.0155*	*4.14E-08*	*0.00100325*
rs68170059	*T*	*-0.02*	*-0.01*	*7.26E-09*	*0.00126251*
rs2582897	*T*	*0.0209*	*0.0087*	*8.15E-12*	*0.0015667*
rs4937872	*A*	*-0.018*	*-0.0087*	*2.62E-09*	*0.00174179*
rs193085025	*T*	*0.0186*	*0.0087*	*4.87E-09*	*0.00191826*
rs1597076	*A*	*0.0172*	*0.0087*	*4.85E-08*	*0.00213804*
rs2881971	*C*	*0.0194*	*0.009*	*1.43E-09*	*0.00227707*
rs2576241	*A*	*-0.0182*	*-0.0127*	*6.52E-10*	*0.00235118*
rs972189	*T*	*0.0206*	*0.0083*	*1.82E-11*	*0.00257341*
rs62170849	*T*	*0.0196*	*0.0089*	*1.45E-09*	*0.00262104*
rs79104582	*A*	*-0.0293*	*-0.0133*	*3.71E-08*	*0.00276618*
rs4943314	*T*	*-0.0233*	*-0.01*	*1.65E-10*	*0.00291422*
rs8180817	*C*	*-0.019*	*-0.008*	*1.77E-10*	*0.00316619*
rs7561603	*A*	*0.0166*	*0.0079*	*2.22E-08*	*0.00317539*
rs7101595	*T*	*0.0163*	*0.0077*	*2.86E-08*	*0.00404599*
rs13031157	*T*	*0.0172*	*0.0077*	*6.56E-09*	*0.00429667*
rs10149470	*A*	*-0.0231*	*-0.0097*	*1.21E-14*	*0.00485789*
rs72710803	*A*	*-0.0354*	*-0.0136*	*2.18E-11*	*0.00502361*
rs11686677	*T*	*0.0211*	*0.0146*	*1.09E-08*	*0.00568261*
rs997934	*T*	*0.018*	*0.0118*	*1.58E-09*	*0.00619321*
rs72925321	*A*	*-0.0365*	*-0.0161*	*1.32E-08*	*0.00625947*
rs13295668	*C*	*-0.024*	*-0.0093*	*3.56E-08*	*0.00770432*
rs1466887	*T*	*-0.0169*	*-0.0072*	*1.59E-08*	*0.00779882*
rs4628229	*T*	*-0.0202*	*-0.0077*	*6.36E-10*	*0.00905882*
rs1637736	*T*	*-0.0178*	*-0.0072*	*1.00E-08*	*0.00973912*
rs487385	*T*	*-0.02*	*-0.0084*	*2.04E-08*	*0.01107473*
rs28562465	*T*	*0.0161*	*0.0067*	*4.58E-08*	*0.01180372*
rs6695276	*T*	*0.0315*	*0.0122*	*2.65E-08*	*0.01771946*
rs112181005	*A*	*-0.025*	*-0.0091*	*2.77E-08*	*0.02189729*

rs8030745	*T*	*0.0271*	*0.0978*	*2.70E-09*	*0.02257566*
rs2214123	*A*	*0.0198*	*0.0064*	*1.72E-10*	*0.02330805*
rs17115122	*A*	*0.0258*	*0.0139*	*9.06E-07*	*0.03617811*
rs11191499	*T*	*0.032*	*0.0096*	*2.12E-08*	*0.04276637*
rs6471757	A	-0.0183	-0.0069	2.47E-09	0.051124463
rs2298969	A	0.0169	0.0078	2.21E-08	0.062179627
rs6551772	A	-0.0177	-0.0047	2.18E-09	0.078383056
rs324300	A	0.0176	0.0049	4.23E-09	0.079289754
rs10786815	A	0.0201	0.0058	3.13E-08	0.082518484
rs1246683	A	0.0434	0.0107	6.32E-09	0.101070391
rs10858298	A	-0.0194	-0.0049	4.03E-09	0.104068736
rs72696282	A	-0.0425	-0.0132	9.02E-10	0.109714725
rs11065505	T	-0.0249	-0.0058	8.09E-09	0.116135206
rs114851235	A	-0.0462	-0.0098	1.07E-10	0.124234514
rs1261070	A	-0.0362	-0.0099	8.93E-11	0.192013886
rs57022387	T	-0.0285	-0.0054	2.96E-09	0.212347737
rs9074	A	0.0229	-0.0766	3.73E-12	0.286605715
rs6512258	T	0.0187	0.0023	3.28E-08	0.463239632
rs73225543	T	0.0374	0.004	4.63E-08	0.505736388
rs2888018	T	-0.0183	-0.0025	4.38E-09	0.570999767
rs150924233	T	-0.1016	-0.0073	3.99E-08	0.599990254
rs35975963	A	0.0348	-0.0012	1.69E-08	0.822933364
rs3904715	A	0.0315	0.0009	2.53E-08	0.862748031
rs1931388	A	0.0242	NA	9.19E-16	NA
rs5995992	T	-0.0257	NA	4.37E-15	NA
rs1002656	T	-0.0252	NA	4.59E-15	NA
rs12530388	A	0.0204	NA	2.81E-12	NA
rs10913112	T	-0.0221	NA	3.20E-12	NA
rs11579246	A	0.0328	NA	9.51E-11	NA
rs1415118	T	-0.0183	NA	5.23E-10	NA
rs11911	A	0.0175	NA	4.66E-09	NA
rs2466367	T	0.0173	NA	2.71E-08	NA
rs7026627	T	0.0171	NA	3.29E-08	NA

Table S2. Top Eight Gene Ontology Biological Processes. 219 Biological processes had an FDR < 0.05. The top eight processes with FDR < $1x10^{-4}$ are included here, the rest of the processes are reported in the supplemental data. False discovery rate was used to account for multiple comparisons.

Enrichment FDR	Genes in list	Total genes	Functional Category
$1.20x10^{-10}$	96	2474	Nervous system development
$9.75x10^{-9}$	21	182	Synapse assembly
$9.75x10^{-9}$	32	434	Synapse organization
$2.74x10^{-8}$	25	282	Cell-cell adhesion via plasma-membrane adhesion molecules
$1.22x10^{-7}$	19	172	Homophilic cell adhesion via plasma membrane adhesion molecules
$1.15x10^{-5}$	55	1412	Neuron differentiation
$6.51x10^{-5}$	57	1575	Generation of neurons
$8.89x10^{-5}$	35	762	Synaptic signaling

Table S3. ICD codes for MVP case status. Classification as a case required at least one inpatient code or two or more outpatient codes for Major Depressive Disorder (MDD). Classification as a control required no record of inpatient or outpatient codes for MDD. Subjects with only one outpatient codes for MDD were excluded from all analyses.

ICD9	ICD10	description
2962		Major depressive disorder, single episode
2963		Major depressive disorder, recurrent episode
29620	F32.9	Major depressive disorder, single episode, unspecified
29621	F32.0	Major depressive disorder, single episode, mild
29622	F32.1	Major depressive disorder, single episode, moderate
29623	F32.2	Major depressive disorder, single episode, severe without psychotic features
29624	F32.3	Major depressive disorder, single episode, severe with psychotic features
29625	F32.4	Major depressive disorder, single episode, in partial remission
29626	F32.5	Major depressive disorder, single episode, in full remission
29630	F33.9	Major depressive disorder, recurrent, unspecified
29630	F33.40	Major depressive disorder, recurrent, in remission, unspecified
29631	F33.0	Major depressive disorder, recurrent, mild
29632	F33.1	Major depressive disorder, recurrent, moderate
29635	F33.41	Major depressive disorder, recurrent, in partial remission
29636	F33.42	Major depressive disorder, recurrent, in full remission
311	F32.9	Major depressive disorder, single episode, unspecified
29633	F33.2	Major depressive disorder, recurrent severe without psychotic features
29634	F33.3	Major depressive disorder, recurrent, severe with psychotic symptoms

Table S4. PHQ-2 Phenotype, adapted from the MVP Baseline Survey

31. Over the PAST 2 WEEKS, have you been bothered by any of these problems?

	Not at all	Several days	More days than not	Nearly every day
Feeling down, depressed, or hopeless	☐	☐	☐	☐
Little interest or pleasure in doing things	☐	☐	☐	☐

Table S5. Progress and History of Depression GWAS

Study	Cases	GWS loci
PGC MDD1	9,240	0
Howard Broad Depression	127,552	14
Hyde 23andMe	75,607	15
PGC MDD2	135,458	44
PGC Hyde Howard Meta	246,363	101
FinnGen Mood Disorders	10,418	0
MVP MDD	**83,810**	**10**
MVP African ancestry MDD	**25,843**	**0**
Current Meta (MDD-META)	**340,591**	**178**