Depression increases the genetic susceptibility to high body mass index: evidence from UK Biobank

Article

Supplemental Material

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Depression increases the genetic susceptibility to high body mass index: Evidence from UK Biobank

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Supplementary Methods

UK Biobank

UK biobank participants were aged 37 to 73 years when first recruited in one of the 22 assessment centres between years 2006 and 2010 (Allen et al., 2012). Participants' baseline information was collected using touchscreen questionnaires, verbal interview, physical examination, and biological samples, including blood, saliva and urine (Hewitt, Walters, Padmanabhan, & Dawson, 2016). Information on health status and hospital admissions is available through linkage to Hospital Episode Statistics (HES) (Biobank, 2013).

Genetic information is available for all UK Biobank individuals (Bycroft et al., 2018). Genotyping was performed using two closely related arrays – UK BiLEVE array (for 50 000 individuals) and UK Biobank Axiom array (for 450 500 individuals). Each array contains 800 000 markers with 95% similarity in content (Bycroft et al., 2018). UK Biobank imputes variants using reference panels from the Haplotype Reference Consortium and UK10K + 1000 genomes. Details of methodology for genotyping, imputation and quality control can be found elsewhere (Bycroft et al., 2018).

BMI and other anthropometric measures

Using a standard procedure, a trained nurse measured height, weight, waist circumference (WC) and other anthropometric measures of the participants during the baseline assessment (Biobank, 2014). Participant's height was measured to the nearest centimetre with a Seca 240 height measure, without shoes. Weight was measured to the nearest 0.1 kg using the Tanita BC-418 MA body composition analyser after removal of shoes and heavy clothes (Biobank, 2014). Measured weight (kg) and height (m) were used to derive BMI (kg/m^2). Individuals with a BMI greater than or equal to $30kg/m^2$ were grouped as those with obesity, and those below 30 kg/m^2 were grouped without obesity (WHO, 2016). Waist circumference was measured using Seca 200cm tape around the smallest part of the trunk when the individuals exhaled (Biobank, 2014). Bioimpedance data including body fat percentage (BFP) was obtained from a Tanita BC418MA body composition analyser (Biobank, 2014).

Socioeconomic and lifestyle covariates

In addition to age, sex and assessment center, we considered a range of lifestyle and socioeconomic factors as potential confounders (Sudlow et al., 2015). These variables were self-reported during the baseline assessment, with the exception of the Townsend deprivation index, which was obtained from the local National Health System Primary care trust registries ("UK Biobank "). Townsend deprivation index is an area-based score generated by including four census variables: no-car ownership,

overcrowding, no-house ownership, and unemployment (Phillimore, Beattie, & Townsend, 1994). Educational status was based on highest qualification and grouped as “none”, “A-levels and below” and “degree or professional”. Sedentary behaviour was based on a questions on daily time spent watching TV, using a computer, and driving, with information on these three questions combined to a single indicator and classified as ”less than five hours” vs. “five hours or more”. Participants were also asked about the number of days they had spent at least 10 minutes at a time walking, or undertaking moderate and vigorous activities, and each type of activity was grouped as “not at all”, “one to four days”, and “five to seven days”. To adjust for the quality of diet, we included the average daily consumption of fruit, vegetables and salad. Further adjustments included smoking (“never”, “previous”, and “current”), alcohol consumption (“never”, “previous”, and “current”), and general health status (“excellent”, “good”, “fair”, and “poor”). Information on antidepressant medication use (“yes” and “no) was based on self-reported regular use of prescription medications, and included selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA), monoamine oxidase inhibitors (MAOI) and others ("UK Biobank ").

Statistical analysis

Mendelian randomisation (MR): Since the genetic variants, that used as an instrument for the exposure (in our case:- depression), are randomly allocated during conception, and this allele segregation occurs before any of the factors affecting the exposure and outcome exist, the common limitations (confounding and reverse causation) of observational studies can be largely avoided (Zheng et al., 2017). Primarily MR used one-sample analysis within the UK Biobank and for sensitivity analysis, several two-sample MR approaches were performed. The one-sample MR analysis included a first stage logistic regression of depression against the GRS_{MDD}. Using the predicted probability values (converted to log odds) from the first regression, the second regression (linear) analysis was completed against BMI. Both stage analyses included adjustment for age, sex, assessment centre, genotyping array and 15 principal components. Coefficient derived from the second regression analysis indicates the causal estimates. A sensitivity analysis using three two-sample MR analysis approaches were performed. Firstly, inverse-variance weighted regression, which is regression of gene-outcome estimates on gene-exposure estimates with the intercept constrained at zero (Burgess, Butterworth, & Thompson, 2013). This analyses give a reliable estimates if there is no unbalanced horizontal pleiotropy. Second, MR-Egger which is the weighted regression of gene-outcome estimates on gene-exposure estimates with an intercept unconstrained at zero (Bowden, Davey Smith, & Burgess, 2015). MR-Egger is robust for directional pleiotropy but should fulfilled a weaker assumption called the InSIDE assumption (the correlation between gene-exposure estimates and the pleiotropic effect [the direct effect of genetic variants on outcome] is zero) (Bowden et al., 2015). Under the fulfilment of InSIDE assumption, the slope from the weighted regression of gene-outcome on gene-exposure provides the causal estimates while an intercept significantly different from zero indicates the presence of directional pleiotropy (Bowden et al., 2015). The third MR-analyses methods (weighted median-based MR) does not require the InSIDE assumption and give a reliable estimates if at least

half of the genetic variants are valid instruments (i.e. reliable event though half of the genetic variants are pleiotropic) (Bowden, Davey Smith, Haycock, & Burgess, 2016).

Supplementary table 1. Association with MDD for the 44-MDD variants used to construct the genetic risk score in the UK Biobank and the PGC consortium meta-analysis.

SNP	Gene	Chr·	Effect allele	Other allele	Missing (UKB)	P_HWE (UKB)	EAF (UKB)	Log (OR) in MDD per one risk allele higher (UKB)			EAF (PGC)	Log (OR) in MDD per one risk allele higher (PGC)		
								logOR	SE	P		logOR	SE	P
rs12129573	*LINC01360*	1	A	C	0.04	0.37	0.35	0.027	0.009	3.8E-03	0.37	0.034	0.005	4.0E-12
rs1432639	*NEGR1*	1	A	C	0.36	0.99	0.60	0.038	0.009	2.3E-05	0.63	0.039	0.005	4.6E-15
rs159963	*RERE, SLC45A1*	1	C	A	2.30	0.72	0.41	0.020	0.009	2.9E-02	0.44	0.026	0.005	3.2E-08
rs2389016		1	T	C	0.10	0.14	0.30	0.016	0.010	9.6E-02	0.28	0.031	0.005	1.0E-08
rs4261101		1	G	A	1.08	0.12	0.64	-0.004	0.009	6.3E-01	0.63	0.028	0.005	1.0E-08
rs9427672	*DENND1B*	1	G	A	1.52	0.06	0.76	0.027	0.010	1.2E-02	0.76	0.031	0.006	3.1E-08
rs11682175	*VRK2*	2	C	T	0.76	0.42	0.47	0.024	0.009	6.8E-03	0.48	0.027	0.005	4.7E-09
rs1226412	*LINC01876, NR4A2, GPD2*	2	T	C	0.46	0.85	0.80	0.032	0.011	4.5E-03	0.79	0.033	0.006	2.4E-08
rs7430565	*RSRC1, LOC1000996447, MLF1*	3	G	A	0.06	0.86	0.42	0.016	0.009	6.9E-02	0.42	0.028	0.005	2.9E-09
rs9862324†	*TOPAZ1, TCAIM, ZNF445*	3	C	T	0.13	0.08	0.32	0.027	0.009	4.0E-03	0.34	0.028	0.005	4.6E-08
rs34215985	*SLC30A9, LINC00682, DCAF4L1*	4	G	C	1.36	0.78	0.80	0.012	0.011	3.0E-01	0.76	0.036	0.006	3.1E-09
rs11135349		5	C	A	0.11	0.43	0.54	0.020	0.009	2.3E-02	0.52	0.029	0.005	1.1E-09
rs2018142†		5	C	A	0.11	0.52	0.48	0.034	0.009	1.4E-04	0.48	0.033	0.005	7.5E-12
rs277325	*LINC00461, MEF2C*	5	A	G	3.10	0.66	0.40	0.014	0.009	1.4E-01	0.42	0.031	0.005	7.9E-11
rs34660260‡	*LOC101927421*	5	C	T	2.30	0.85	0.60	0.027	0.009	3.7E-03	0.62	0.028	0.005	7.0E-09
rs4869056	*TENM2*	5	G	A	0.42	0.12	0.38	0.026	0.009	3.9E-03	0.37	0.028	0.005	6.8E-09
rs3095337‡	*extended MHC*	6	G	C	0.12	0.96	0.79	0.043	0.011	9.6E-05	0.82	0.040	0.006	3.3E-11
rs9402472	*C6orf168, FBXL4*	6	A	G	2.91	0.13	0.24	0.006	0.010	5.8E-01	0.24	0.033	0.006	2.8E-08
rs12666117		7	A	G	2.76	0.46	0.46	0.016	0.009	7.7E-02	0.47	0.027	0.005	1.4E-08
rs6460902†	*TMEM106B, VWDE*	7	A	G	0.38	0.16	0.42	0.039	0.009	1.7E-05	0.41	0.027	0.005	2.6E-08
rs1354115	*PUM3, LINC01231*	9	A	C	0.16	0.94	0.63	0.019	0.009	4.3E-02	0.62	0.028	0.005	2.4E-08
rs7029033	*DENND1A, LHX2*	9	T	C	0.07	0.63	0.07	0.015	0.018	3.8E-01	0.07	0.052	0.009	2.7E-08
rs7856424	*ASTN2*	9	C	T	0.22	0.25	0.72	0.023	0.010	2.2E-02	0.71	0.030	0.005	8.5E-09
rs958538†		9	T	C	0.78	0.86	0.75	0.020	0.010	5.8E-02	0.76	0.033	0.006	5.1E-09
rs61867293	*SORCS3*	10	C	T	1.06	0.55	0.81	0.019	0.011	9.5E-02	0.80	0.036	0.006	7.0E-10
rs1806153	*DKFZp686K1684, PAUPAR, ELP4*	11	T	G	0.30	0.75	0.23	0.006	0.011	5.8E-01	0.22	0.036	0.006	1.2E-09
rs4074723	*SOX5*	12	C	A	0.65	0.73	0.59	0.011	0.009	2.3E-01	0.59	0.026	0.005	3.1E-08
rs12552	*OLFM4, LINC01065*	13	A	G	0.81	0.17	0.44	0.017	0.009	5.7E-02	0.44	0.043	0.005	6.1E-19
rs4143229	*ENOX1, LACC1, CCDC122*	13	C	A	0.14	0.43	0.07	0.013	0.017	4.6E-01	0.08	0.048	0.009	2.5E-08
rs10149470	*BAG5, APOPT1*	14	G	A	0.09	0.21	0.52	0.025	0.009	4.6E-03	0.51	0.028	0.005	3.1E-09
rs3742786†	*DLST, PROX2, RPS6KL1*	14	A	G	0.05	0.06	0.46	0.026	0.009	3.1E-03	0.49	0.029	0.005	3.8E-09
rs4904738	*LRFN5*	14	C	T	1.77	0.38	0.43	0.029	0.009	1.5E-03	0.43	0.028	0.005	2.6E-09
rs915057	*SYNE2, MIR548H1, ESR2*	14	G	A	2.07	0.29	0.57	0.007	0.009	4.1E-01	0.58	0.029	0.005	7.6E-10
rs8025231		15	C	A	0.42	0.50	0.45	0.033	0.009	2.2E-04	0.43	0.033	0.005	2.4E-12
rs11643192	*PMFBP1, DHX38*	16	A	C	0.76	0.81	0.38	0.020	0.009	3.0E-02	0.41	0.027	0.005	3.4E-08
rs7198928	*RBFOX1*	16	T	C	3.05	0.36	0.62	0.015	0.009	1.0E-01	0.62	0.028	0.005	1.0E-08
rs7200826	*SHISA9, CPPED1*	16	T	C	0.46	0.94	0.26	0.023	0.010	2.3E-02	0.25	0.031	0.005	2.4E-08
rs8063603	*RBFOX1*	16	G	A	3.33	0.95	0.32	0.018	0.010	6.5E-02	0.35	0.030	0.005	6.9E-09
rs17727765	*CRYBA1, MYO18A, NUFIP2*	17	C	T	2.19	2.1E-05	0.08	0.007	0.017	6.9E-01	0.08	0.048	0.008	8.5E-09
rs11663393	*DCC, MIR4528*	18	A	G	0.14	0.29	0.46	0.033	0.009	2.1E-04	0.45	0.028	0.005	1.7E-08
rs12958048	*TCF4, MIR4529*	18	A	G	0.31	0.88	0.33	0.021	0.009	2.5E-02	0.33	0.034	0.005	3.6E-11
rs1833288	*RAB27B, CCDC68*	18	A	G	3.57	0.48	0.72	0.022	0.010	2.8E-02	0.72	0.030	0.005	2.6E-08
rs62099069	*MIR924HG*	18	T	A	0.13	0.66	0.58	0.023	0.009	1.0E-02	0.58	0.027	0.005	1.3E-08
rs5758265	*L3MBTL2, EP300-AS1, CHADL*	22	A	G	0.55	0.60	0.29	0.033	0.010	8.0E-04	0.28	0.031	0.005	7.6E-09

SNP: Single nucleotide polymorphism. Chr.: Chromosome. † Imputation quality was poor for all the six variants (info score ≤0.89 and MAF≤0.01), hence we replaced them with a proxy variant. ‡ These indicate SNPs with two alternative rs-numbers: rs116755193 for rs34660260, and rs115507122 for rs3095337. UKB: UK Biobank; PGC: Psychiatric genetic Consortium; EAF: Effect allele frequency; and P_HWE: P-value for Hardy-Weinberg Equilibrium test.

Supplementary table 2. Association with BMI for the 73 BMI variants used to construct the genetic risk score in the UK Biobank and the GIANT consortium meta-analysis.

								Change† in BMI per one risk allele higher (UKB)					Change † in BMI per one risk allele higher (GIANT)		
SNP	**Gene**	**Chr·**	**Effect allele**	**Other allele**	**Missing (UKB)**	**P_HWE (UKB)**	**EAF (UKB)**	**Beta**	**SE**	**P**	**r^2**	**EAF (GIANT)**	**Beta**	**SE**	**P**
rs11165643	PTBP2	1	T	C	0·33	4·3E-01	0·59	0·019	0·002	1·3E-14	0.0015	0·58	0·022	0·003	2·1E-12
rs11583200	ELAVL4	1	C	T	1·12	3·4E-01	0·39	0·016	0·002	8·1E-11	0.0015	0·40	0·018	0·003	1·5E-08
rs12401738	FUBP1	1	A	G	0·77	1·1E-02	0·38	0·014	0·002	3·3E-08	0.0013	0·35	0·021	0·003	1·1E-10
rs12566985	FPGT-TNNI3K	1	G	A	0·23	2·9E-01	0·44	0·017	0·002	2·6E-12	0.0014	0·45	0·024	0·003	3·3E-15
rs17024393	GNAT2	1	C	T	0·20	4·0E-01	0·03	0·065	0·008	1·8E-17	0.0015	0·04	0·066	0·009	7·0E-14
rs2820292	NAV1	1	C	A	0·00	4·8E-01	0·57	0·021	0·002	1·5E-17	0.0015	0·56	0·020	0·003	1·8E-10
rs3101336	NEGR1	1	C	T	0·00	3·8E-01	0·60	0·022	0·002	3·6E-19	0.0015	0·61	0·033	0·003	2·7E-26
rs543874	SEC16B	1	G	A	0·00	2·4E-01	0·21	0·047	0·003	0·0E+00	0.0019	0·19	0·048	0·004	2·6E-35
rs657452	AGBL4	1	A	G	1·54	5·2E-02	0·39	0·018	0·002	1·8E-13	0.0014	0·39	0·023	0·003	5·5E-13
rs1016287	LINC01122	2	T	C	0·25	2·2E-01	0·30	0·019	0·003	2·3E-13	0.0014	0·29	0·023	0·003	2·3E-11
rs10182181	ADCY3	2	G	A	0·67	1·2E-01	0·49	0·036	0·002	0·0E+00	0.0019	0·46	0·031	0·003	8·8E-24
rs11126666	KCNK3	2	A	G	0·52	3·4E-01	0·25	0·003	0·003	3·0E-01	0.0013	0·28	0·021	0·003	1·3E-09
rs11688816	EHBP1	2	G	A	1·24	4·6E-01	0·54	0·013	0·002	4·3E-08	0.0011	0·52	0·017	0·003	1·9E-08
rs13021737	TMEM18	2	G	A	0·01	7·3E-01	0·83	0·050	0·003	0·0E+00	0.002	0·83	0·060	0·004	1·1E-50
rs2121279	LRP1B	2	T	C	0·66	7·2E-01	0·12	0·009	0·004	1·0E-02	0.0012	0·15	0·025	0·004	2·3E-08
rs7599312	ERBB4	2	G	A	3·01	5·8E-01	0·73	0·019	0·003	1·2E-11	0.0014	0·72	0·022	0·003	1·2E-10
rs13078960	CADM2	3	G	T	0·78	2·4E-01	0·20	0·022	0·003	2·9E-13	0.0012	0·20	0·030	0·004	1·7E-14
rs1516725	ETV5	3	C	T	0·42	5·8E-01	0·86	0·033	0·004	2·2E-21	0.0014	0·87	0·045	0·005	1·9E-22
rs16851483	RASA2	3	T	G	0·04	3·6E-01	0·07	0·031	0·005	9·9E-11	0.0014	0·07	0·048	0·008	3·5E-10
rs2365389	FHIT	3	C	T	0·96	6·5E-01	0·59	0·015	0·002	2·3E-09	0.0013	0·58	0·020	0·003	1·6E-10
rs3849570	GBE1	3	A	C	0·04	8·8E-01	0·35	0·010	0·003	3·6E-05	0.0013	0·36	0·019	0·003	2·6E-08
rs6804842	RARB	3	G	A	1·22	4·2E-01	0·57	0·013	0·002	1·9E-07	0.0014	0·57	0·019	0·003	2·5E-09
rs10938397	GNPDA2	4	G	A	0·00	7·6E-04	0·43	0·029	0·002	6·9E-32	0.0016	0·43	0·040	0·003	3·2E-38
rs11727676	HHIP	4	T	C	0·00	4·8E-01	0·90	0·007	0·004	1·0E-01	0.0013	0·91	0·036	0·006	2·6E-08
rs13107325	SLC39A8	4	T	C	0·00	1·1E-01	0·07	0·051	0·005	2·2E-29	0.0014	0·07	0·048	0·007	1·8E-12
rs17001654	SCARB2	4	G	C	2·33	3·0E-01	0·14	0·014	0·003	3·9E-05	0.0014	0·15	0·031	0·005	7·8E-09
rs2112347	POC5	5	T	G	0·00	5·1E-04	0·64	0·028	0·003	2·4E-29	0.0016	0·63	0·026	0·003	6·2E-17
rs13191362	PARK2	6	A	G	0·38	2·1E-01	0·88	0·020	0·004	6·4E-08	0.0015	0·88	0·028	0·005	7·3E-09
rs2033529	TDRG1	6	G	A	0·72	6·1E-01	0·29	0·023	0·003	3·8E-18	0.0014	0·29	0·019	0·003	1·4E-08
rs205262	C6orf106	6	G	A	0·16	2·6E-01	0·27	0·030	0·003	1·5E-27	0.0015	0·27	0·022	0·004	1·8E-10
rs2207139	TFAP2B	6	G	A	0·02	8·7E-01	0·17	0·039	0·003	2·5E-34	0.0017	0·18	0·045	0·004	4·1E-29
rs9400239	FOXO3	6	C	T	0·69	5·6E-02	0·71	0·016	0·003	2·3E-09	0.0013	0·69	0·019	0·003	1·6E-08
rs1167827	HIP1	7	G	A	0·00	5·8E-02	0·56	0·022	0·002	6·2E-20	0.0015	0·55	0·020	0·003	6·3E-10
rs2245368	PMS2L11	7	C	T	0·00	2·9E-01	0·17	0·025	0·003	2·0E-14	0.0014	0·18	0·032	0·006	3·2E-08
rs17405819	HNF4G	8	T	C	0·02	1·8E-01	0·70	0·021	0·003	6·0E-16	0.0014	0·70	0·022	0·003	2·1E-11
rs2033732	RALYL	8	C	T	0·00	1·3E-01	0·74	0·011	0·003	6·0E-05	0.0013	0·75	0·019	0·004	4·9E-08
rs10733682	LMX1B	9	A	G	6·48	7·9E-02	0·47	0·014	0·002	4·9E-08	0.0017	0·48	0·017	0·003	1·8E-08
rs10968576	LINGO2	9	G	A	0·00	2·1E-02	0·32	0·024	0·003	4·9E-20	0.0015	0·32	0·025	0·003	6·6E-14
rs1928295	TLR4	9	T	C	0·01	9·0E-01	0·57	0·011	0·002	6·3E-06	0.0013	0·55	0·019	0·003	7·9E-10
rs4740619	C9orf93	9	T	C	0·18	5·1E-01	0·55	0·020	0·002	4·9E-17	0.0014	0·54	0·018	0·003	4·6E-09
rs6477694	EPB41L4B	9	C	T	1·36	4·4E-01	0·35	0·013	0·003	1·8E-07	0.0012	0·37	0·017	0·003	2·7E-08
rs11191560	NT5C2	10	C	T	0·02	2·3E-02	0·08	0·024	0·005	1·1E-07	0.0013	0·09	0·031	0·005	8·4E-09
rs17094222	HIF1AN	10	C	T	0·76	9·6E-01	0·21	0·013	0·003	6·0E-06	0.0013	0·21	0·025	0·004	5·9E-11
rs7899106	GRID1	10	G	A	0·35	4·7E-01	0·05	0·029	0·006	2·1E-07	0.0014	0·05	0·040	0·007	3·0E-08
rs12286929	CADM1	11	G	A	0·19	8·4E-01	0·53	0·014	0·002	2·2E-09	0.0013	0·52	0·022	0·003	1·3E-12
rs2176598	HSD17B12	11	T	C	0·00	5·6E-01	0·25	0·022	0·003	3·2E-15	0.0014	0·25	0·020	0·004	3·0E-08
rs3817334	MTCH2	11	T	C	0·00	6·5E-02	0·41	0·026	0·002	2·8E-26	0.0015	0·41	0·026	0·003	5·1E-17
rs4256980	TRIM66	11	G	C	0·60	7·7E-01	0·66	0·020	0·002	4·9E-17	0.0014	0·65	0·021	0·003	2·9E-11
rs11057405	CLIP1	12	G	A	0·00	6·1E-01	0·89	0·031	0·004	3·9E-15	0.0014	0·90	0·031	0·006	2·0E-08
rs7138803	BCDIN3D	12	A	G	0·00	7·9E-01	0·37	0·028	0·002	7·7E-29	0.0016	0·38	0·032	0·003	8·2E-24
rs12429545	OLFM4	13	A	G	1·62	4·7E-01	0·13	0·025	0·004	2·8E-12	0.0015	0·13	0·033	0·005	1·1E-12
rs4771122	MTIF3	13	T	C	0·00	1·5E-01	0·20	0·009	0·003	9·8E-04	0.0013	0·20	0·030	0·005	2·3E-10
rs10132280	STXBP6	14	C	A	1·90	8·6E-01	0·70	0·021	0·003	1·3E-15	0.0015	0·68	0·023	0·003	1·1E-11
rs11847697	PRKD1	14	T	C	0·00	6·4E-01	0·04	0·025	0·006	2·7E-05	0.0013	0·04	0·049	0·008	4·0E-09
rs12885454	PRKD1	14	C	A	0·27	2·7E-01	0·64	0·014	0·003	7·9E-09	0.0013	0·64	0·021	0·003	1·9E-10
rs7141420	NRXN3	14	T	C	2·53	5·5E-02	0·52	0·021	0·002	8·0E-18	0.0015	0·53	0·024	0·003	1·2E-14
rs16951275	MAP2K5	15	T	C	0·02	4·4E-02	0·77	0·028	0·003	3·1E-23	0.0015	0·78	0·031	0·004	1·9E-17
rs3736485	DMXL2	15	A	G	0·98	1·2E-02	0·46	0·010	0·002	4·9E-05	0.0012	0·45	0·018	0·003	7·4E-09
rs12446632	GPRC5B	16	G	A	0·04	6·7E-01	0·86	0·028	0·003	1·0E-15	0.0014	0·87	0·040	0·005	1·5E-18
rs1558902	FTO	16	A	T	0·05	8·3E-01	0·40	0·073	0·002	0·0E+00	0.0039	0·42	0·082	0·003	7·5E-153
rs2650492	SBK1	16	A	G	1·99	1·1E-01	0·30	0·017	0·003	9·7E-11	0.0014	0·30	0·021	0·004	1·9E-09
rs758747	NLRC3	16	T	C	2·79	3·5E-01	0·27	0·016	0·003	1·5E-08	0.0016	0·27	0·023	0·004	7·5E-10
rs9925964	KAT8	16	A	G	0·32	5·9E-01	0·64	0·025	0·003	1·2E-22	0.0015	0·62	0·019	0·003	8·1E-10
rs1000940	RABEP1	17	G	A	0·16	3·4E-02	0·30	0·016	0·003	2·1E-09	0.0014	0·32	0·019	0·003	1·3E-08
rs12940622	RPTOR	17	G	A	0·18	2·7E-01	0·56	0·018	0·002	9·2E-14	0.0014	0·57	0·018	0·003	2·5E-09
rs1808579	C18orf8	18	C	T	0·27	8·1E-01	0·51	0·018	0·002	7·2E-14	0.0014	0·53	0·017	0·003	4·2E-08
rs6567160	MC4R	18	C	T	0·08	3·4E-01	0·23	0·052	0·003	6.1E-78	0.0023	0·24	0·056	0·004	3·9E-53
rs7243357	GRP	18	T	G	0·86	6·4E-01	0·83	0·017	0·003	8·3E-08	0.0014	0·81	0·022	0·004	3·9E-08
rs17724992	PGPEP1	19	A	G	1·09	7·5E-03	0·73	0·018	0·003	2·4E-11	0.0014	0·75	0·019	0·004	3·4E-08
rs2075650	TOMM40	19	A	G	0·00	3·9E-01	0·85	0·022	0·003	1·9E-10	0.0013	0·85	0·026	0·005	1·2E-08
rs2287019	QPCTL	19	C	T	1·74	1·5E-02	0·82	0·031	0·003	1·2E-22	0.0018	0·80	0·036	0·004	4·6E-18
rs29941	KCTD15	19	G	A	0·00	2·9E-04	0·67	0·013	0·003	1·6E-07	0.0013	0·67	0·018	0·003	2·4E-08
rs3810291	ZC3H4	19	A	G	0·00	6·5E-01	0·68	0·030	0·003	1·3E-30	0.0016	0·67	0·028	0·004	4·8E-15

Single nucleotide polymorphism (SNP) in **bold** are neuronal otherwise non-neuronal SNP

UKB: UK Biobank; GIANT: **G**enetic **I**nvestigation of **AN**thropometric **T**raits; EAF: Effect allele frequency; and P_HWE: P-value for Hardy-Weinberg Equilibrium test

SNPs have been selected based on genome-wide association analyses on BMI in the GIANT consortium (Locke et al, 2015) not including the UK Biobank.

† Estimates in UKB from models adjusted for age, age square, sex, assessment centre, type of genotyping array, and 15 principal components; GIANT estimates adjusted for age, age square, and study-specific covariates (for example, genotype-derived principal components).

Supplementary table 3. Association between BMI genetic risk score (or rs6567160 variant near *MC4R* gene) and different anthropometric measures among individuals with and without depression

		Depression case				Control				
		Beta	**SE**	**P**	**r^2**	**Beta**	**SE**	**P**	**r^2**	**P-interaction†**
Waist Circumference	Total GRS‡	0.179	0.009	0.00E+00	0.0086	0.150	0.003	0.00E+00	0.0068	0.0009
	Neuronal GRS‡	0.186	0.011	0.00E+00	0.0064	0.154	0.004	0.00E+00	0.0049	0.0021
	non-neuronal GRS‡	0.170	0.017	1.70E-23	0.0024	0.149	0.006	0.00E+00	0.0021	0.1908
	rs6567160	0.058	0.008	7.80E-12	0.0013	0.038	0.003	4.40E-37	0.0006	0.0118
Body fat percentage	Total GRS‡	0.139	0.008	0.00E+00	0.0054	0.117	0.003	0.00E+00	0.0042	0.0041
	Neuronal GRS‡	0.137	0.009	0.00E+00	0.0036	0.118	0.003	0.00E+00	0.0029	0.0355
	non-neuronal GRS‡	0.147	0.014	5.70E-25	0.0018	0.119	0.005	0.00E+00	0.0013	0.0487
	rs6567160	0.034	0.007	2.20E-06	0.0004	0.017	0.003	2.70E-11	0.0001	0.0195
		OR	**SE**	**P**	**Pseudo-r^2**	**OR**	**SE**	**P**	**Pseudo-r^2**	**P-interaction**
Obesity (BMI≥30kg/m2)	Total GRS‡	1.564	0.026	0.00E+00	0.0095	1.550	0.011	0.00E+00	0.0089	0.83
	Neuronal GRS‡	1.573	0.031	0.00E+00	0.0069	1.568	0.013	0.00E+00	0.0066	0.99
	non-neuronal GRS‡	1.560	0.046	2.50E-22	0.0034	1.528	0.019	0.00E+00	0.003	0.74
	rs6567160	1.127	0.023	1.30E-07	0.0017	1.110	0.009	2.30E-28	0.0013	0.54

† Two-way interaction between genetic variant and depression on BMI.

‡ Per 10 allele higher. For rs6567160 is per an allele higher.

Supplementary table 4. Association between genetic variants and BMI among individuals with and without depression (Variants are selected based on P<0.05 before multiple testing correction)

SNP (gene)	No of BMI increasing allele	Depression case			Control			P-interaction	p†
		Beta	SE	P	Beta	SE	P		
rs6567160 (MC4R)	0	Ref	Ref	Ref	Ref	Ref	Ref	2.3E-03	0.17
	1	0.070	0.013	2.00E-08	0.044	0.004	3.90E-24		
	2	0.166	0.026	2.00E-10	0.100	0.009	1.00E-27		
rs2287019 (QPCTL)	0	Ref	Ref	Ref	Ref	Ref	Ref	1.2E-02	0.88
	1	0.052	0.034	1.30E-01	0.042	0.012	5.20E-04		
	2	0.109	0.034	1.20E-03	0.069	0.012	4.60E-09		
rs1167827 (HIP1)	0	Ref	Ref	Ref	Ref	Ref	Ref	2.5E-02	1.83
	1	0.044	0.016	5.70E-03	0.019	0.006	7.40E-04		
	2	0.077	0.017	6.80E-06	0.037	0.006	4.20E-10		
rs12401738 (FUBP1)	0	Ref	Ref	Ref	Ref	Ref	Ref	2.9E-02	2.12
	1	-0.008	0.013	5.40E-01	0.009	0.004	3.60E-02		
	2	-0.009	0.018	6.20E-01	0.027	0.006	1.50E-05		
rs2121279 (LRP1B)	0	Ref	Ref	Ref	Ref	Ref	Ref	1.7E-02	1.24
	1	0.043	0.014	2.50E-03	0.006	0.005	2.10E-01		
	2	0.051	0.047	2.80E-01	0.042	0.016	1.10E-02		
rs1516725 (ETV5)	0	Ref	Ref	Ref	Ref	Ref	Ref	1.3E-02	0.95
	1	0.035	0.046	4.50E-01	0.037	0.016	2.00E-02		
	2	0.096	0.045	3.40E-02	0.066	0.016	2.10E-05		
rs2287019 (QPCTL)	0	Ref	Ref	Ref	Ref	Ref	Ref	1.2E-02	0.88
	1	0.052	0.034	1.30E-01	0.042	0.012	5.20E-04		
	2	0.109	0.034	1.20E-03	0.069	0.012	4.60E-09		

† Multiple testing corrected P-values.

Supplementary table 5. Association between BMI genetic risk score (or rs6567160 variant near *MC4R* gene) and BMI among individuals with and without hospital diagnosed depression (data from HES)

		Depression case				Control				P-interaction†	P-interaction‡
		Beta	SE	r^2	P	Beta	SE	r^2	P		
Total GRS§	All	0.27	0.019	0.0169	2.4E-35	0.21	0.003	0.0132	0.0E+00	6.8E-04	7.0E-04
	Women	0.28	0.031	0.0166	4.9E-22	0.22	0.005	0.0125	0.0E+00	8.0E-03	7.1E-03
	Men	0.24	0.031	0.0170	1.0E-14	0.20	0.005	0.0151	0.0E+00	7.7E-02	8.6E-02
Neuronal GRS§	All	0.29	0.025	0.0134	2.5E-28	0.21	0.006	0.0095	0.0E+00	2.9E-04	3.3E-04
	Women	0.31	0.036	0.0134	4.5E-18	0.22	0.005	0.0088	0.0E+00	2.3E-03	2.1E-03
	Men	0.25	0.036	0.0126	2.6E-11	0.20	0.005	0.0111	0.0E+00	1.0E-01	1.2E-01
Non-neuronal GRS§	All	0.24	0.038	0.0039	2.5E-09	0.20	0.007	0.0039	0.0E+00	4.7E-01	4.5E-01
	Women	0.25	0.051	0.0039	3.5E-06	0.22	0.010	0.0039	0.0E+00	6.6E-01	6.4E-01
	Men	0.22	0.056	0.0043	9.7E-05	0.19	0.010	0.0042	0.0E+00	6.5E-01	6.4E-01
rs6567160	All	0.11	0.021	0.0035	1.3E-08	0.05	0.003	0.0008	0.0E+00	5.7E-05	6.5E-05
	Women	0.14	0.026	0.0051	8.8E-08	0.05	0.005	0.0009	3.5E-23	1.7E-04	1.8E-04
	Men	0.07	0.028	0.0014	2.2E-02	0.04	0.006	0.0008	1.6E-24	3.5E-01	3.6E-01

† Two-way interaction between genetic variable and depression on BMI.

‡ Two-way interaction in a model further adjusted for anti-depressant medication use.

§ Per 10 allele higher. However, for rs6567160 is per an allele higher.

Supplementary table 6. Association between BMI genetic risk score (or rs6567160 variant near *MC4R* gene) and BMI among individuals with and without single episode or recurrent depressive disorder

			Depression case				Control				P-interaction†
			Beta	SE	P	r^2	Beta	SE	P	r^2	
Single episode depressive disorder (F32)	Total GRS‡	All	0.266	0.017	0.0E+00	0.0174	0.221	0.004	0.0E+00	0.0151	3.8E-03
		Women	0.270	0.024	2.3E-30	0.0159	0.230	0.006	0.0E+00	0.0140	5.0E-02
		Men	0.260	0.025	2.3E-24	0.0207	0.210	0.005	0.0E+00	0.0175	4.8E-02
	Neuronal GRS‡	All	0.283	0.021	0.0E+00	0.0136	0.227	0.005	0.0E+00	0.0109	2.9E-03
		Women	0.290	0.028	4.2E-24	0.0125	0.240	0.007	0.0E+00	0.0098	3.3E-02
		Men	0.270	0.030	1.6E-19	0.0164	0.220	0.006	0.0E+00	0.0128	5.3E-02
	Non-neuronal GRS‡	All	0.235	0.032	2.5E-13	0.0041	0.218	0.007	0.0E+00	0.0045	5.5E-01
		Women	0.240	0.043	2.3E-08	0.0038	0.240	0.011	0.0E+00	0.0044	7.6E-01
		Men	0.220	0.046	1.7E-06	0.0046	0.200	0.009	0.0E+00	0.0049	6.5E-01
	rs6567160	All	0.097	0.016	1.2E-09	0.0029	0.045	0.003	0.0E+00	0.0007	7.4E-05
		Women	0.100	0.021	9.4E-07	0.0030	0.049	0.005	2.1E-19	0.0007	3.6E-03
		Men	0.083	0.023	4.1E-04	0.0026	0.041	0.004	4.0E-22	0.0008	4.5E-02
Recurrent depressive disorder (F33)	Total GRS‡	All	0.240	0.015	0.0E+00	0.0152	0.221	0.004	0.0E+00	0.0151	1.5E-01
		Women	0.260	0.020	0.0E+00	0.0162	0.230	0.006	0.0E+00	0.0140	1.1E-01
		Men	0.200	0.021	4.7E-20	0.0135	0.210	0.005	0.0E+00	0.0175	5.2E-01
	Neuronal GRS‡	All	0.246	0.018	0.0E+00	0.0109	0.227	0.005	0.0E+00	0.0109	2.8E-01
		Women	0.270	0.024	2.2E-30	0.0120	0.240	0.007	0.0E+00	0.0098	1.2E-01
		Men	0.190	0.026	9.1E-14	0.0089	0.220	0.006	0.0E+00	0.0128	3.4E-01
	Non-neuronal GRS‡	All	0.240	0.027	5.3E-19	0.0046	0.218	0.007	0.0E+00	0.0045	2.6E-01
		Women	0.260	0.036	8.0E-13	0.0047	0.240	0.011	0.0E+00	0.0044	4.3E-01
		Men	0.210	0.039	8.2E-08	0.0046	0.200	0.009	0.0E+00	0.0049	8.8E-01
	rs6567160	All	0.052	0.013	1.2E-04	0.0009	0.045	0.003	0.0E+00	0.0007	6.3E-01
		Women	0.065	0.018	3.2E-04	0.0012	0.049	0.005	2.1E-19	0.0007	3.8E-01
		Men	0.028	0.019	1.5E-01	0.0004	0.041	0.004	4.0E-22	0.0008	4.5E-01

† Two-way interaction between genetic variable and depression on BMI

‡ Per 10 allele higher. However, for rs6567160 is per an allele higher.

Supplementary table 7. Association of between BMI genetic risk score excluding *MC4R* variant and BMI among individuals with and without depression

		Depression case				Control				P-interaction†
		Beta	SE	P	r^2	Beta	SE	P	r^2	
Total GRS† excluding *MC4R* gene	All	0.244	0.0108	0.00E+00	0.0149	0.218	0.0038	0.00E+00	0.0143	0.01
	Women	0.250	0.0144	0.00E+00	0.0144	0.230	0.0060	0.00E+00	0.0133	0.06
	Men	0.230	0.0157	0.00E+00	0.0167	0.210	0.0047	0.00E+00	0.0166	0.21
Neuronal GRS† excluding *MC4R* gene	All	0.021	0.0011	0.00E+00	0.0109	0.019	0.0004	0.00E+00	0.0101	0.02
	Women	0.260	0.0175	0.00E+00	0.0103	0.230	0.0073	0.00E+00	0.0091	0.07
	Men	0.240	0.0189	1.10E-35	0.0125	0.210	0.0058	0.00E+00	0.0120	0.22

† Two-way interaction between genetic variable and depression on BMI.

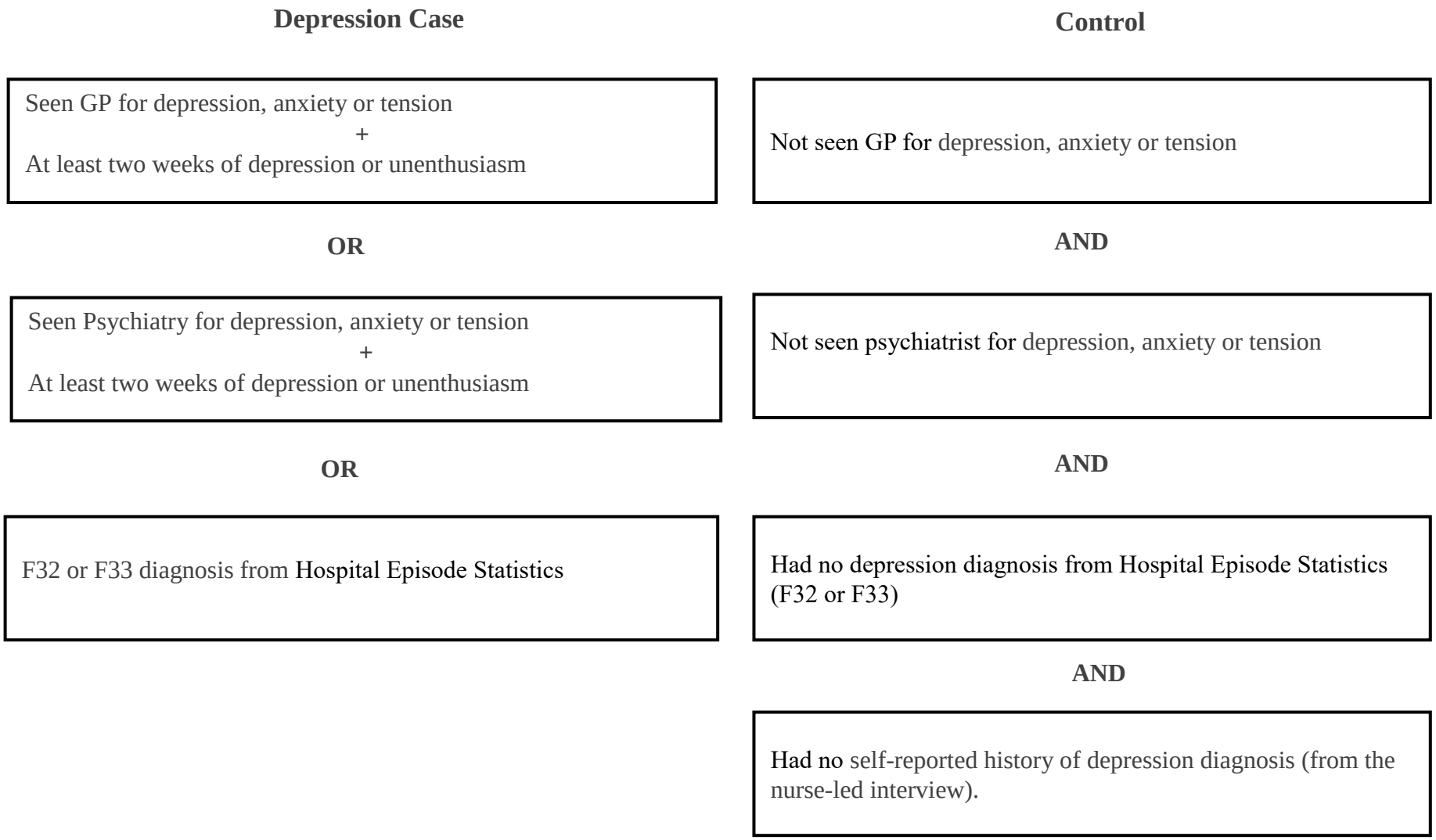
‡ Per 10 allele higher. However, for rs6567160 is per an allele higher.

Supplementary table 8. Association of between BMI genetic risk score and BMI among individuals with and without depression after adjusting for antidepressant use

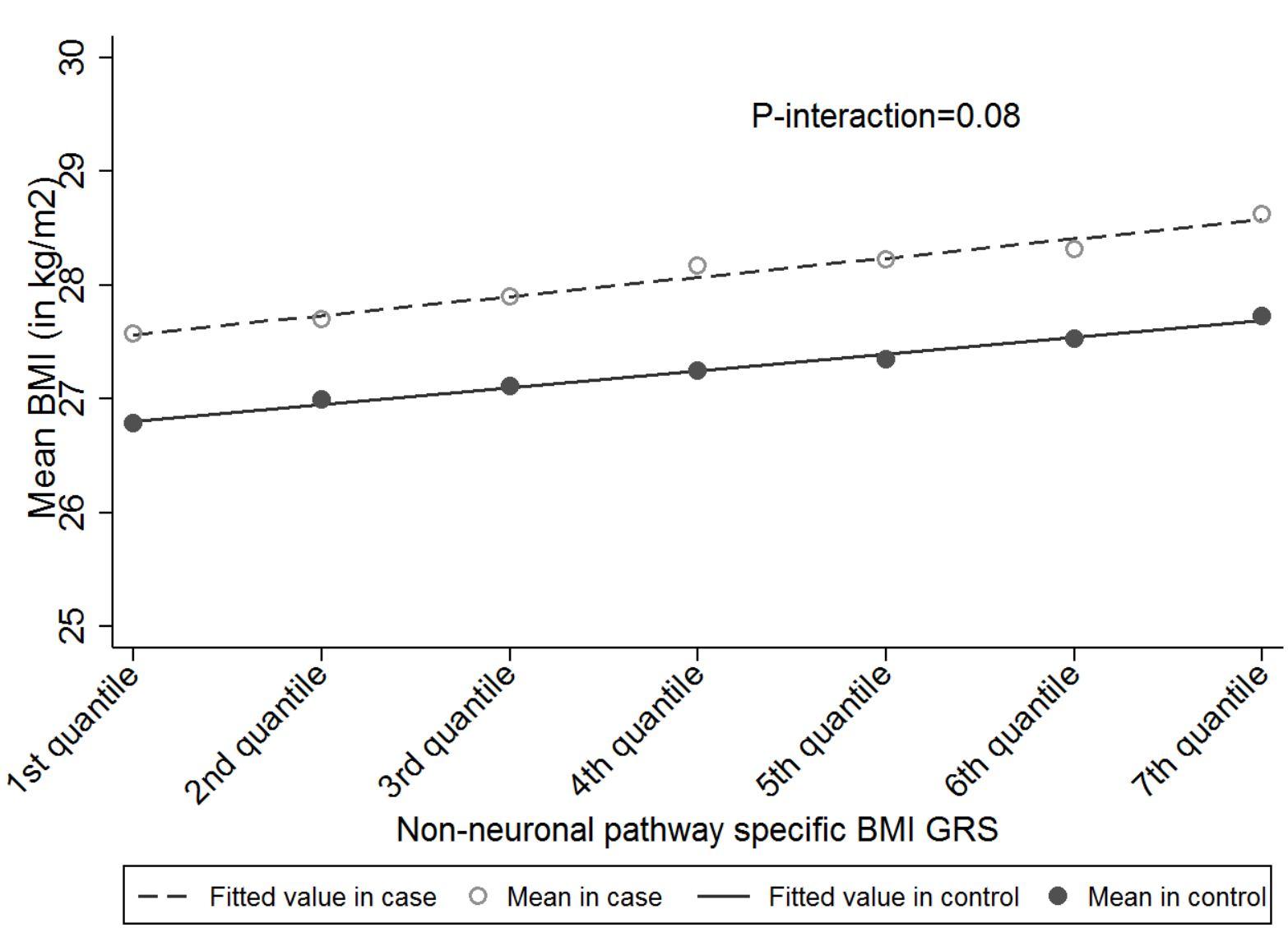
		Depression case				Control				P-interaction†
		Beta	SE	r^2	P	Beta	SE	r^2	P	
Total GRS‡	All	0.24	0.010	0.015	0E+00	0.20	0.004	0.013	0E+00	0.001
	Women	0.25	0.014	0.015	0E+00	0.22	0.006	0.012	0E+00	0.012
	Men	0.21	0.015	0.015	0E+00	0.19	0.005	0.015	0E+00	0.213
Neuronal GRS‡	All	0.24	0.013	0.011	0E+00	0.21	0.004	0.010	0E+00	0.006
	Women	0.26	0.017	0.011	0E+00	0.22	0.007	0.009	0E+00	0.023
	Men	0.22	0.018	0.011	2E-32	0.20	0.006	0.011	0E+00	0.353
Non-neuronal GRS‡	All	0.23	0.019	0.004	3E-34	0.20	0.007	0.004	0E+00	0.079
	Women	0.25	0.026	0.004	1E-22	0.22	0.011	0.004	0E+00	0.224
	Men	0.20	0.028	0.004	1E-13	0.19	0.008	0.004	0E+00	0.550
rs6567160	All	0.07	0.010	0.002	2E-14	0.04	0.003	0.001	0E+00	0.002
	Women	0.08	0.013	0.002	6E-11	0.05	0.005	0.001	2E-19	0.009
	Men	0.06	0.014	0.001	7E-05	0.04	0.004	0.001	2E-22	0.339

† P-interaction in further adjusted for history of anti-depressant medication usage model.

‡ Per 10 allele higher. However, for rs6567160 is per an allele higher.



Supplementary figure 1. Depression case and control definition (GP: general practitioner, F32 and F33 ICD-10 code for single episode and recurrent depressive disorders respectively)



Supplementary figure 2. Association between non-neuronal genetic risk score and BMI among individuals with and without depression (The lines show the changes in BMI per change in non-neuronal GRS, where the dotted line represents depression case group, and the solid line represents control group)

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