

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

Article

Supplemental Material

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1 **Supplementary Material**

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

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5 Anwar Mulugeta^{1,2*}, Ang Zhou¹, Karani Santhanakrishnan Vimalaswaran³, Cameron Dickson¹, and Elina Hyppönen^{1,4,5*}

6
7 ¹ Australian Centre for Precision Health, University of South Australia Cancer Research Institute, Adelaide, Australia

8 ² Department of Pharmacology, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

9 ³ Hugh Sinclair Unit of Human Nutrition, Department of Food and Nutritional Sciences and Institute for Cardiovascular and
10 Metabolic Research (ICMR), University of Reading, Reading, UK

11 ⁴ Population, Policy and Practice, UCL Great Ormond Street Institute of Child Health, London, UK

12 ⁵ South Australian Health and Medical Research Institute, Adelaide, Australia

13
14 *** Corresponding Authors**

15 Professor Elina Hyppönen, Australian Centre for Precision Health, University of South Australia Cancer Research Institute,
16 Adelaide, Australia, GPO Box 2471, Adelaide SA 5001,

17 Elina.hypponen@unisa.edu.au
18

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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 $30\text{kg}/\text{m}^2$ were grouped as those with obesity, and those below $30\text{kg}/\text{m}^2$ 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,

70 overcrowding, no-house ownership, and unemployment (Phillimore, Beattie, & Townsend, 1994). Educational status was based
71 on highest qualification and grouped as “none”, “A-levels and below” and “degree or professional”. Sedentary behaviour was
72 based on a questions on daily time spent watching TV, using a computer, and driving, with information on these three questions
73 combined to a single indicator and classified as ”less than five hours” vs. “five hours or more”. Participants were also asked about
74 the number of days they had spent at least 10 minutes at a time walking, or undertaking moderate and vigorous activities, and each
75 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
76 included the average daily consumption of fruit, vegetables and salad. Further adjustments included smoking (“never”,
77 “previous”, and “current”), alcohol consumption (“never”, “previous”, and “current”), and general health status (“excellent”,
78 “good”, “fair”, and “poor”). Information on antidepressant medication use (“yes” and “no”) was based on self-reported regular use
79 of prescription medications, and included selective serotonin reuptake inhibitors (SSRI), tricyclic antidepressants (TCA),
80 monoamine oxidase inhibitors (MAOI) and others (“UK Biobank”).

81 82 **Statistical analysis**

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

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

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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)			Log (OR) in MDD per one risk allele higher (PGC)			
								logOR	SE	P	EAF (PGC)	logOR	SE	P
rs12129573	<i>LINC01360</i>	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	<i>NEGR1</i>	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	<i>RERE, SLC45A1</i>	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	<i>DENND1B</i>	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	<i>VRK2</i>	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	<i>LINC01876, NR4A2, GPD2</i>	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	<i>RSRC1, LOC1000996447, MLF1</i>	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†	<i>TOPAZ1, TCAIM, ZNF445</i>	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	<i>SLC30A9, LINC00682, DCAF4L1</i>	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	<i>LINC00461, MEF2C</i>	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‡	<i>LOC101927421</i>	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	<i>TENM2</i>	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‡	<i>extended MHC</i>	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	<i>C6orf168, FBXL4</i>	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†	<i>TMEM106B, VWDE</i>	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	<i>PUM3, LINC01231</i>	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	<i>DENND1A, LHX2</i>	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	<i>ASTN2</i>	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	<i>SORCS3</i>	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	<i>DKFZp686K1684, PAUPAR, ELP4</i>	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	<i>SOX5</i>	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	<i>OLFM4, LINC01065</i>	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	<i>ENOX1, LACCI, CCDC122</i>	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	<i>BAG5, APOPT1</i>	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†	<i>DLST, PROX2, RPS6KL1</i>	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	<i>LRFN5</i>	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	<i>SYNE2, MIR548H1, ESR2</i>	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	<i>PMFBP1, DHX38</i>	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	<i>RBFOX1</i>	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	<i>SHISA9, CPPED1</i>	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	<i>RBFOX1</i>	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
rs1772765	<i>CRYBA1, MYO18A, NUFIP2</i>	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	<i>DCC, MIR4528</i>	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	<i>TCF4, MIR4529</i>	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	<i>RAB27B, CCDC68</i>	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	<i>MIR924HG</i>	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	<i>L3MBTL2, EP300-AS1, CHADL</i>	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 $MAF \leq 0.01$), hence we replaced them with a proxy variant. ‡ These indicate SNPs with two alternative alleles. † 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.

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

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		Depression case				Control				P-interaction [†]
		Beta	SE	P	r ²	Beta	SE	P	r ²	
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/m ²)	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

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

117 [‡] Per 10 allele higher. For rs6567160 is per an allele higher.

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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.

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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

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[†] 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.

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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

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

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

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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 <i>MC4R</i> 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 <i>MC4R</i> 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

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

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

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

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

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

Depression Case

Seen GP for depression, anxiety or tension
+
At least two weeks of depression or unenthusiasm

OR

Seen Psychiatry for depression, anxiety or tension
+
At least two weeks of depression or unenthusiasm

OR

F32 or F33 diagnosis from Hospital Episode Statistics

Control

Not seen GP for depression, anxiety or tension

AND

Not seen psychiatrist for depression, anxiety or tension

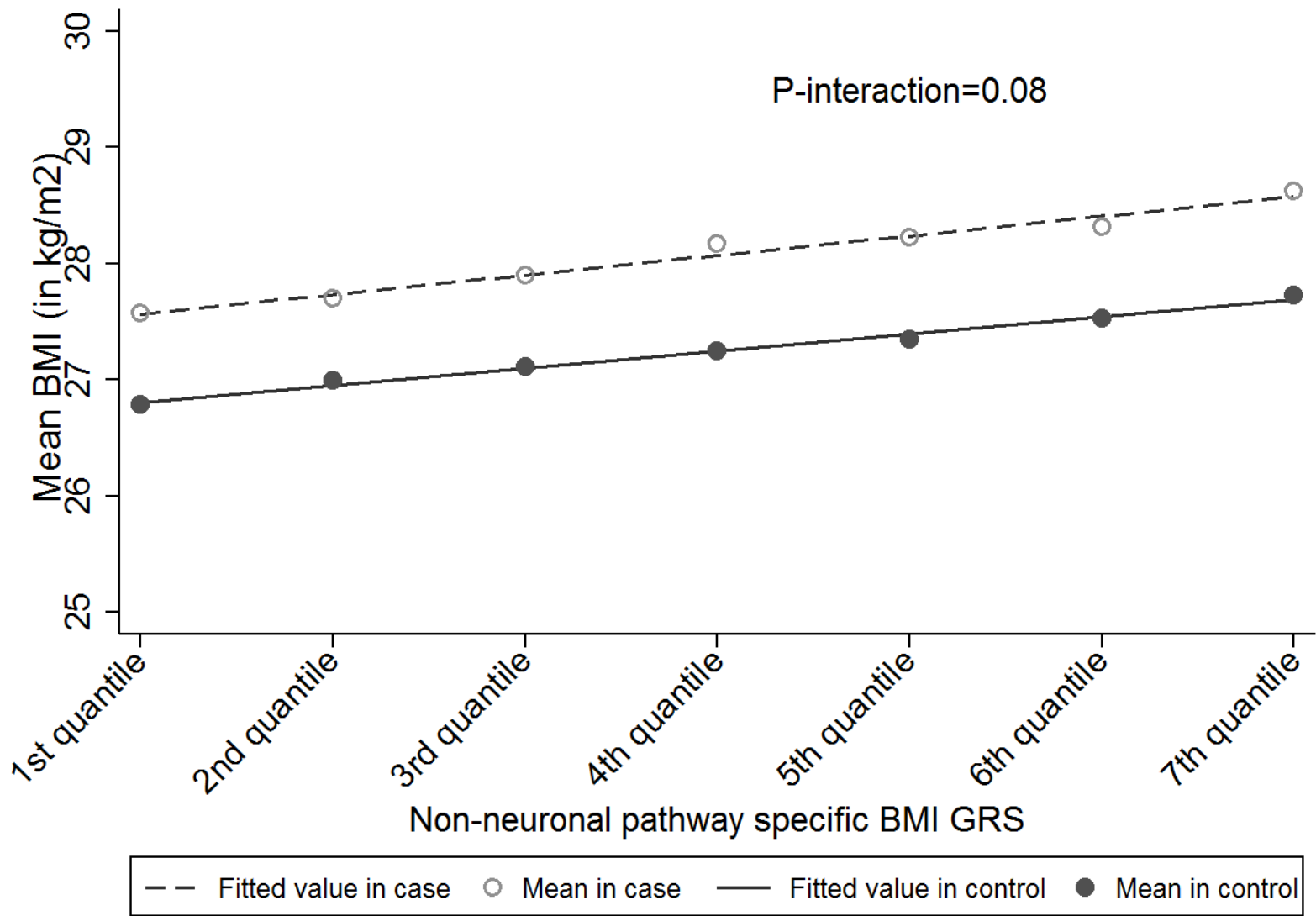
AND

Had no depression diagnosis from Hospital Episode Statistics
(F32 or F33)

AND

Had no self-reported history of depression diagnosis (from the
nurse-led interview).

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)



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153 **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
 154 non-neuronal GRS, where the dotted line represents depression case group, and the solid line represents control group)

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