

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

Article

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

2 Biobank

3

4 Short title: gene-depression interaction

5

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28 the study. This project was conducted under UK Biobank application number 10171.

29

30 **Abstract**

31

32 **Background:** This study aimed to explore the association between depression and body mass
33 index (BMI), and to investigate whether genetic susceptibility to high BMI is different among
34 individuals with or without depression.

35 **Methods:** We used data on 251,125 individuals of white British ancestry from the UK
36 Biobank. We conducted Mendelian randomisation (MR) analysis to test for a causal
37 association between depression and BMI using a major depressive disorder (MDD)-related
38 genetic risk score (GRS_{MDD}) as an instrument for depression. We also examined whether
39 depression modifies genetic susceptibility to high BMI, by investigating the interaction
40 between depression and the BMI-related genetic risk score (GRS_{BMI}).

41 **Results:** We found observational and genetic evidence for an association between depression
42 and BMI (MR beta: 0.09, 95% CI 0.04-0.13). Further, the contribution of genetic risk to high
43 BMI was higher among individuals with depression compared to controls. Carrying ten
44 additional BMI increasing alleles was associated with 0.24 SD (95% CI 0.23-0.25) higher
45 BMI among depressed individuals compared to 0.20 SD (95% CI 0.19-0.21) higher in
46 controls, which corresponds to 3.4 kg and 2.8 kg extra weight for an individual of average
47 height. Amongst the individual loci, the evidence for interaction was most notable for a
48 variant near *MC4R*, a gene known to affect both appetite regulation and the hypothalamic
49 pituitary adrenal axis ($P_{interaction}=5.7 \times 10^{-5}$). **Conclusion:** Genetic predisposition to high BMI
50 was higher among depressed than to non-depressed individuals. This study provides support
51 for a possible role of *MC4R* in the link between depression and obesity.

52

53 **Key words:** “gene-lifestyle factors interaction”, “genetic risk score”, “*MC4R*”, “depression”,
54 “BMI”, “predisposition”, and “UK-Biobank”.

55

56 **Introduction**

57

58 The obesity epidemic is worsening globally, with prevalence tripling over the last three
59 decades (Afshin et al., 2017). From 1980 to 2015, excess fat accumulation contributed to an
60 estimated 4 million deaths through its association with cardiovascular, metabolic, cancer and
61 other diseases, leading to a loss of 120 million disability-adjusted life years (Afshin et al.,
62 2017). An obesogenic environment, characterised by sedentary behaviour and abundance of
63 energy-rich food, is among a very large number of potential contributors to high body mass
64 index (BMI) at the population level (Townshend & Lake, 2017). However, genetic factors are
65 also a known to affect BMI (Locke et al., 2015; Zaitlen et al., 2013), and heritability studies
66 have indicated that 40-70% of BMI variability can be attributed to genetic factors (Zaitlen et
67 al., 2013). Genome-wide association studies (GWAS) have identified over 700 BMI related
68 genetic variants, which only explain 5% of the variability in BMI (Yengo et al., 2018). Some
69 of this missing heritability of BMI could be explained by an interaction between these genetic
70 variants and lifestyle factors.

71

72 Previous interaction studies on BMI-related genetic variants and lifestyle factors highlight the
73 importance of modifying diet and physical activity to decrease high BMI risk in genetically
74 predisposed individuals (Celis-Morales et al., 2016; Vimalaswaran et al., 2016). Another
75 possible factor that may modify genetic susceptibility to high BMI is comorbid depression.
76 Prior research has demonstrated that depressed individuals tend to lead more sedentary
77 lifestyles, be less physically active and have worse dietary habits, each of which may
78 contribute to high BMI (Jacka, Cherbuin, Anstey, & Butterworth, 2014; Roshanaei-
79 Moghaddam, Katon, & Russo, 2009). There is evidence that obesity is a causal risk factor for

80 depression (Tyrrell J et al., 2018), and prospective observational evidence that depression
81 itself may lead to obesity (Mannan, Mamun, Doi, & Clavarino, 2016).

82

83 Recent success in identifying genetic variants affecting susceptibility to major depressive
84 disorder (MDD) (Wray et al., 2018), enables the use of Mendelian randomization (MR) for
85 testing the causal association between depression and BMI. Compared to traditional
86 observational approaches, MR studies are less prone to bias by confounding or reverse
87 causation (Zheng et al., 2017). To our knowledge there are no earlier MR studies examining
88 the causal effect of depression on BMI, and only a few studies have investigated whether
89 depression influences genetic susceptibility to high BMI (Hung et al., 2014; Rivera et al.,
90 2012).

91

92 In this study we have used information from 251,125 UK Biobank participants to investigate
93 the observational and genetic associations between depression and BMI, and to test whether
94 genetic susceptibility to high BMI is modified by the presence of depression. To explore this
95 relationship further, we performed secondary analyses according to biological pathway-based
96 genetic risk score of BMI (GRS_{BMI}), and using each genetic variant individually in the
97 interaction tests.

98 **Methods**

99

100 The UK Biobank is a population-based cohort of over 500 000 individuals (age ranging 37 to
101 73 years old at recruitment) living in the United Kingdom (Allen et al., 2012) (Supplementary
102 Methods). We used information on 251 125 individuals of white British ancestry (as
103 evidenced by self-report and genetic ancestry analyses) who have complete data on
104 genotypes, BMI and depression status. Related individuals, and those with a mismatch
105 between self-reported and genetically determined sex, and/or who have failed genotype and
106 imputation quality control (Bycroft et al., 2018), were excluded from the analyses.

107 Measured weight (kg) and height (m) were used to derive BMI (kg/m^2). Individuals with a
108 BMI greater than or equal to 30kg/m^2 were classified as obese (WHO, 2016). For analysis,
109 BMI was inverse normal transformed, with one SD corresponding to 4.74 kg/m^2 . Secondary
110 analysis used alternate measures of adiposity, including waist circumference (WC) and body
111 fat percentage (BFP) (Supplementary Methods). Lifestyle and socioeconomic information
112 was self-reported, and derived from the baseline assessment (Sudlow et al., 2015)
113 (Supplementary Methods).

114

115 We used depression-related information from touchscreen questionnaires, nurse-led
116 interviews, and hospital-linked data to classify depression cases, and to identify controls
117 (Sudlow et al., 2015). Participants who had seen a general practitioner or a psychiatrist for
118 anxiety, tension, nervousness or depression, and reported depression or unenthusiasm of at
119 least two weeks duration were recoded as having depression. Additional cases were identified
120 from hospital diagnoses (ICD-10 F32 or F33 or the corresponding ICD-9 codes) obtained
121 from Hospital Episode Statistics (HES) (Supplementary figure 1).

122

123 Individuals in the control group were those who had not seen a general practitioner or
124 psychiatrist for anxiety, tension, nervousness or depression, and who had no hospital
125 diagnosed depression, and no self-reported depression. For further sensitivity analysis, we
126 categorized depression into single episode depressive disorder and recurrent depressive
127 disorder depending the number of depressive episodes; and used the HES data defined
128 depression variables as alternative outcomes.

129

130 **Genetic variants and genetic risk score**

131 To investigate the causal association between depression and BMI, we used 44 MDD related
132 genetic variants (Supplementary table 1) identified in a recent genome-wide association
133 meta-analysis which included 135,458 MDD cases and 344,901 controls (Wray et al., 2018).

134 To test for an interaction between depression and BMI-related genetic risk, we selected BMI
135 increasing variants from the largest GWAS meta-analysis (N=339 224) which did not include
136 the UK Biobank (Locke et al., 2015). This study included 339 224 individuals and identified
137 97 BMI increasing variants (Locke et al., 2015). Among these, 77 variants were identified in
138 European ancestry sex-combined analysis, of which rs7903146 (*TCF7L2*) is a primary variant
139 for type 2 diabetes, and hence was excluded from the current analyses. Three other variants
140 were excluded because of their strong association with traits other than BMI (horizontal
141 pleiotropy). These included rs11030104 (reward phenotype), rs13107325 (HDL level and
142 blood pressure), and rs3888190 (multiple traits) (MacArthur et al., 2017). Subsequently our
143 GRS_{BMI} comprised 73 variants (Supplementary table 2).

144

145 Based on the number of risk alleles associated with depression or BMI, each genetic variant
146 was coded as 0 (no risk alleles), 1 (one risk allele) and 2 (two risk alleles). We used an
147 additive genetic model, and constructed a weighted GRS by summing the product of the
148 number of risk-increasing alleles by each genetic variant's weight taken from the primary
149 GWAS (Locke et al., 2015; Wray et al., 2018). The weighted GRS was re-scaled using the
150 formula below to express the change in effect size per number of risk increasing alleles (See
151 the equation below).

152

$$\text{Weighted genetic risk score} = \frac{(\beta_1 \times \text{SNP}_1 + \beta_2 \times \text{SNP}_2 + \dots \beta_n \times \text{SNP}_n) \times \text{Number of SNPs}}{\text{Sum of } \beta \text{ coefficients}}$$

Where:

SNP₁ to SNP_n are number of risk increasing alleles contributing to the genetic risk score.
β₁ to β_n is a coefficient from variant-exposure association of n variants taken from the
GWAS discovery analyses, i.e. MDD GWAS (Wray et al., 2018) for genetic score of
MDD (GRS_{MDD}) and BMI GWAS (Locke et al., 2015) for GRS_{BMI}.

153

154 To investigate the biological mechanism of how depression modifies genetic susceptibility to
155 high BMI, we grouped the 73 genetic variants as neuronal and non-neuronal, based on their
156 proximity to genes enriched in the respective pathways (Locke et al., 2015). Locke et al
157 manually reviewed literature for gene activity and function with respect to all 405 genes
158 within 500kb and r²>0.2 from the 97 BMI-associated lead variants, resulting in classification
159 of the variants into 25 biological categories including peripheral and central biological
160 mechanisms (Locke et al., 2015). Forty-three of the 73 BMI-associated genes are expressed
161 predominantly in the central nervous system (CNS), and are understood to affect neuronal
162 development, neuronal and hypothalamus expression, and energy metabolism (Locke et al.,
163 2015). Accordingly, these were grouped as neuronal variants (Supplementary table 2). The

164 remaining 30 BMI-related variants were hypothesized to affect BMI through processes other
165 than the CNS (Locke et al., 2015), and were subsequently classified as non-neuronal. GRS_{BMI}
166 for neuronal and non-neuronal variants were constructed. A third GRS_{BMI} (termed ‘total’)
167 was also constructed incorporating all 73 BMI related genetic variants.

168

169 **Statistical analysis**

170 Our depression to BMI association analysis comprised linear regression on BMI, with
171 adjustment first for age, sex and assessment centre, then further adjustment for broader
172 covariates including Townsend deprivation index, education, physical activity, sedentary
173 behaviour, vegetable and fruit consumption, cigarette smoking, alcohol consumption and
174 general health status. This was followed by one-sample MR analysis using two-stage least
175 squares regression to establish evidence for a causal relationship between depression and
176 BMI. The genetic analysis further adjusted for genotyping array and 15 principal
177 components. Sensitivity analyses used two-sample MR with complementary approaches
178 including inverse-variance weight (MR IVW), weighted median, and MR-Egger methods
179 (Supplementary Methods).

180

181 In depression by variant interaction analysis, we first checked the association of the GRS_{BMI}
182 and each genetic variant with BMI using linear regression. To test for the interaction between
183 total GRS_{BMI} and depression on BMI, we included an interaction term in the linear regression
184 model. We repeated the test using pathway-specific GRS_{BMI} , and also performed interaction
185 tests for each BMI-related genetic variant. All analyses were adjusted for age, sex,
186 assessment centre, type of genotyping array, 15 principal components, and socioeconomic
187 and lifestyle factors including Townsend deprivation index, education, physical activity,

188 sedentary behaviour, vegetable and fruit consumption, cigarette smoking, alcohol
189 consumption and general health status.

190

191 To check whether any significant interactions were also seen with other measures of
192 adiposity, we repeated the analyses using inverse normal transformed WC, and BFP as
193 outcomes in a linear regression model. Logistic regression was used to test the interaction
194 with respect to obesity. Upon a significant interaction, we stratified the association between
195 GRS_{BMI} and BMI by depression status. For statistical significance, we used P-value threshold
196 of 0.05 for tests involving total GRS_{BMI} . Analyses involving multiple testing used a
197 Bonferroni corrected p-value to minimise the likelihood of a false-positive result. Bonferroni
198 corrected significant thresholds of 0.025 (i.e. $0.05/2$) and 0.0007 (i.e. $0.05/73$) were used for
199 the pathway-based GRS', and single variant analyses respectively.

200

201 Sensitivity analyses were also completed using by severity of depression, as follows: single
202 episode, recurrent depressive disorder, and any hospital diagnosed depression based on HES
203 data. To clarify whether the interaction was driven by only a few genetic variants, we tested
204 the hypothesis using a GRS_{BMI} from which the variants observed to have significant
205 interaction with depression had been omitted. To further clarify whether this interaction was
206 due to concomitant use of antidepressants, we adjusted the models for current use of
207 antidepressant medications.

208 **Results**

209

210 Table 1 shows mean BMI and percentage of obesity of individuals stratified by lifestyle
211 factors, depression status, and high BMI genetic load. Men were observed to have a higher
212 mean BMI and obesity prevalence ($P < 4.9 \times 10^{-57}$). Notably, prevalence of obesity was
213 observed to increase with reducing levels of self-reported general health ($P < 1.0 \times 10^{-300}$).
214 Individuals who had a history of depression including single episode, recurrent depressive
215 disorder, and hospital diagnosed depression all had higher mean BMIs and higher prevalence
216 of obesity, than controls ($P < 4.9 \times 10^{-78}$). Antidepressant medication use was also associated
217 with BMI and obesity ($P < 3.0 \times 10^{-285}$). The mean BMI and prevalence of obesity were higher
218 in the 50% of people having more BMI genetic load compared with the 50% of people having
219 low BMI genetic load ($P < 1.0 \times 10^{-300}$).

220

221 **Observational and genetic evidence for association between depression and BMI**

222 In the phenotypic analysis, individuals with depression had 0.19 SD (95% CI 0.18 to 0.20, P
223 $= 5.0 \times 10^{-215}$) higher BMIs compared to those without depression (Table 2). This association
224 was supported by genetic evidence, and in MR analyses a higher genetic risk of depression
225 was associated with higher BMI (OR 0.09 SD, 95% CI 0.04 to 0.13, $P = 0.0001$). MR-IVW,
226 weighted median, and MR-Egger estimates from two-sample MR were directionally
227 consistent with estimates from one-sample MR, but with wider confidence intervals (Table
228 2). MR-Egger intercept was not significantly different from zero ($P = 0.06$) with no evidence
229 for directional pleiotropy.

230

231 **Association between genetic variants and BMI**

232 Each of the 73 BMI genetic variants explained 0.11% to 0.39% of the variability in BMI
233 (Supplementary table 2). Among these variants, *FTO* gene, and *MC4R* gene were the two
234 strongest influences on the variability in BMI (r^2 of *FTO*=0.39%, r^2 of *MC4R* =0.23%). The
235 ‘C’ allele of rs6567160 near *MC4R* is a risk-increasing allele for BMI and obesity and
236 individuals with *TC* and *CC* genotypes had higher BMIs and obesity prevalence compared to
237 homozygous T allele carriers ($P < 3.8 \times 10^{-36}$, Table 1). The GRS_{BMI} ’ showed normal
238 distribution and was associated with high BMI (Figure 1). Total GRS_{BMI} (including 73
239 genetic variants) explained 1.3% of the variability in BMI, neuronal GRS_{BMI} (including 43
240 genetic variants) explained 0.94% of the variability, and the non-neuronal GRS_{BMI} explained
241 0.40% of the variability (Table 3). The contribution of GRS_{BMI} ’ or a variant near the *MC4R*
242 gene on BMI was different between men and women ($P_{interaction} < 0.01$, Table 3). In the
243 analyses using the GRS_{BMI} ’ and for *MC4R*, women had a greater increase in BMI compared
244 to men for every increase in risk allele (Table 3).

245

246 **Genetic contribution to BMI is modified by depression status**

247 Depression modified the association of genetic variants with BMI (Table 4). Genetic
248 susceptibility to BMI was higher in depressed individuals compared to non-depressed
249 individuals ($P_{interaction} = 9.1 \times 10^{-4}$), and carrying ten additional risk alleles was associated with
250 0.24 SD, (95% CI 0.23 to 0.25) and 0.20 SD (95% CI 0.19 to 0.21) higher BMI among
251 depressed and non-depressed individuals. Here, one SD represents 4.72 kg/m² difference in
252 BMIs hence, these data are equivalent 3.4 kg and 2.8 kg extra weight for 1.73 m tall average
253 depressed and non-depressed individual, respectively. This interaction was also observed
254 when using WC or BFP as an outcome ($P_{interaction} < 0.004$), but not with obesity
255 (Supplementary table 3).

256

257 We next compared the association between depression and BMI with respect to effect
258 modification by pathway-specific GRS_{BMI} (neuronal vs. non-neuronal). Statistical evidence
259 for interaction by depression in the genetic contribution to BMI was seen for neuronal
260 pathway-related genetic variants, but not for non-neuronal pathway variants (neuronal
261 GRS_{BMI} $P_{interaction}=0.009$, non-neuronal GRS $P_{interaction}=0.10$). However, differences in the
262 estimated effect sizes were negligible (Figure 2 and Supplementary figure 2).

263

264 To check whether the interaction was driven by a particular genetic variant, each variant was
265 tested for interaction with depression. Before correction for multiple testing there were seven
266 variants showing evidence of interaction at $P<0.05$, but none of the associations remained
267 after Bonferroni-correction, with a suggestive interaction coming only from rs6567160 near
268 *MC4R* gene ($P_{interaction}=2.3 \times 10^{-3}$, Supplementary table 4).

269

270 In sensitivity analysis restricted the depression outcome to HES data, the interaction between
271 depression and total GRS_{BMI} remained significant ($P_{interaction}=6.8 \times 10^{-4}$, Supplementary table
272 5). This interaction was predominately driven by neuronal pathway specific variants, as was
273 the case with our main finding (neuronal GRS_{BMI} $P_{interaction}=2.9 \times 10^{-4}$, non-neuronal GRS_{BMI}
274 $P_{interaction}=0.47$, Supplementary table 5). Specifically, rs6567160 was observed to be
275 influential ($P_{interaction}=5.7 \times 10^{-5}$, Figure 3). Having ten additional neuronal-specific BMI risk
276 alleles was associated with 0.21 SD (95% CI 0.20 to 0.23) higher BMI in non-depressed
277 individuals, compared to 0.29 SD, (95% CI 0.24 to 0.34) in depressed individuals
278 (Supplementary table 5). For the non-neuronal GRS_{BMI} , the ten additional BMI risk alleles
279 were associated with a 0.20 SD, (95% CI 0.19 to 0.22) and 0.24 SD, (95% CI 0.16 to 0.31)

280 higher BMI among individuals without and with depression, respectively. The risk allele (C)
281 at *MC4R* variant rs6567160 contributed to 0.05 SD, (95%CI 0.04 to 0.06) and 0.11 SD,
282 (95%CI 0.07 to 0.15) higher BMI in non-depressed and depressed individuals, respectively
283 (Supplementary table 5).

284

285 When looking at effect modification on the genetic influence on BMI by alternative
286 depression classifications, evidence for interaction by single episode depressive disorder was
287 seen for total GRS_{BMI} ($P_{interaction}=0.004$), neuronal GRS_{BMI} ($P_{interaction}=0.003$), and a variant
288 near *MC4R* ($P_{interaction}=7 \times 10^{-5}$). No significant interactions were apparent for recurrent
289 depressive disorder (for all, $P_{interaction}>0.15$, Supplementary table 6). To understand whether
290 the interaction between total GRS_{BMI} and neuronal pathway specific GRS_{BMI} with depression
291 is solely contributed to by *MC4R*, we constructed a GRS_{BMI} excluding rs6567160 (near
292 *MC4R*). The interaction between depression and neuronal GRS_{BMI} ($P_{interaction}=0.02$) was only
293 borderline significant at Bonferroni corrected p-value ($P=0.025$, Supplementary table 7),
294 suggesting that the interaction is in part driven by a variant near the *MC4R* gene. For total
295 GRS_{BMI} , the interaction by depression was also attenuated by the absence of the variant
296 nearby *MC4R*, again highlighting its influence (Supplementary table 7). Adjusting for
297 recurrent use of antidepressant medication had a negligible influence on the interaction
298 between GRS_{BMI} and depression (Supplementary table 8).

299 **Discussion**

300 Using 251 125 individuals of white British ancestry, we found observational and genetic
301 evidence for an association between depression and BMI, and an increased genetic
302 predisposition to higher BMI among individuals with depression compared to controls.
303 Depression is known to have broad influences on an individual's behaviour and lifestyles
304 (Roshanaei-Moghaddam et al., 2009). There is also evidence to show that heritability of
305 obesity is notably higher in obesogenic compared to non-obesogenic environments
306 (Schrempft et al., 2018). Like obesogenic environments, depression may act to endorse
307 unhealthy lifestyle choices, allowing the genetic potential for higher BMI to be expressed.
308 While our study also suggested that the interaction between genetic predisposition to higher
309 BMI and depression is likely to be most pronounced for variants implicated in neuronal
310 pathways, potentially influencing behaviours (Locke et al., 2015), further studies are required
311 to establish underlying mechanisms and patterns of mediation.

312

313 As expected, the BMI-related GRS was associated with BMI. This association was more
314 apparent in depressed individuals compared to non-depressed, and the total GRS_{BMI} (73
315 variants) explained 1.7% and 1.3% of the variability of BMI in individuals with and without
316 hospital diagnosed depression, respectively. This finding is consistent with a previous study
317 in which a GRS of 32 variants explained 1.6% of the variability in BMI among depressed
318 individuals compared to 0.3% among non-depressed individuals (Hung et al., 2015). In
319 keeping with our results, this prior study also noted a stronger association of their GRS_{BMI}
320 with BMI among depressed individuals when the depression outcome measure is derived
321 from hospital episode statistics, than data collected from the general population (Hung et al.,
322 2015).

323

324 This study utilised BMI-associated variants from different biological pathways to explore the
325 link between depression and high BMI. Although related differences between neuronal
326 GRS_{BMI} and non-neuronal GRS_{BMI} were small, the evidence of an interaction from the
327 former, suggests a role of the CNS in the link between depression and high BMI. Previous
328 studies have indicated that the hypothalamic-pituitary-adrenal (HPA) axis is involved in the
329 pathogenesis of depression and obesity (Bose, Oliván, & Laferrere, 2009; Varghese &
330 Brown, 2001). This is supported further by our finding that rs6567160 near the *MC4R* gene
331 was the main variant driving the interaction with depression on BMI. Interestingly
332 rs17782313, which is in perfect LD with rs6567160, has previously been reported to interact
333 with stress, and influence obesity risk (Park et al., 2016). The importance of the *MC4R* gene
334 in the depression-high BMI relationship is also evident in animal-based pharmacological
335 studies, in which the antagonist of *MC4R* receptor has shown anxiolytic and antidepressant
336 effects, particularly under conditions of high stress (Chaki & Okubo, 2007). This antagonist
337 was suggested for treatment of cachexia through the effect on increasing food intake, and
338 decreasing energy expenditure (Weyermann et al., 2009).

339

340 *MC4R* is found mainly in the CNS including the paraventricular nucleus of the hypothalamus,
341 a centre involved in appetite and energy regulation, and HPA axis function (Chaki & Okubo,
342 2007; Krashes, Lowell, & Garfield, 2016). Activation of the *MC4R* receptor in the
343 hypothalamus has been associated with decreased appetite and food intake through
344 stimulation of the satiety centre, and inhibition of the hunger centre (Krashes et al., 2016).
345 Individuals with depression have stress-induced dysregulation of the HPA axis, a process that
346 involves secretion of corticotrophin-releasing factor (CRF) from the hypothalamus (Chaki &

347 Okubo, 2007). Also, *MC4R* partly mediates secretion of CRF from corticotrophin neurons in
348 the hypothalamus (Chaki & Okubo, 2007; Von Frijtag, Croiset, Gispén, Adan, & Wiegant,
349 1998). We did not observe an independent association between *MC4R* and depression. This
350 might suggest that the interaction between *MC4R* and depression on BMI may be due to a
351 direct impact on appetite regulation – rather than depression associated activation of the HPA
352 axis.

353

354 Our study has some limitations. Firstly, UK Biobank participants are relatively healthy
355 compared to the general population (Fry et al., 2012), which may limit the chance of
356 detecting a robust gene-lifestyle interaction. As with other observational investigations, our
357 gene-depression interaction study could have been affected by unmeasured confounding
358 factors. However, to minimise such influence, our analyses included a wide range of lifestyle
359 factors including the Townsend deprivation index, education, physical activity, sedentary
360 behaviour, vegetable and fruit consumption, cigarette smoking, alcohol consumption, and
361 general health status. We also conducted adjusted analyses to account for potential weight
362 gain attributable to antidepressant use; however, the observed interaction between
363 depression and the genetic contribution to BMI remained unaffected.

364

365 **Conclusions**

366 Our study provides genetic evidence for causal effect of depression on BMI. Furthermore,
367 genetic predisposition to high BMI was increased among depressed compared to non-
368 depressed individuals, suggesting that depression might increase the expression of an
369 individual's genetic disposition to obesity. Our study provided some support for a possible
370 role of *MC4R* in the link between depression and obesity. This result may strengthen the case
371 for *MC4R* as a potential target for pharmaceutical interventions for obesity.

372

373 **Availability of Data and Materials**

374 All data is available through the UK Biobank.

375

376 Supplementary information is available at Depression and Anxiety online.

377

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482

484 **Table 1.** Mean BMI and the prevalence of obesity by participant characteristics in the UK
485 Biobank

	All, n (%)	BMI [†] , mean (SD)	Obesity [‡] , n (%)
Sex			
Women	123 496 (49.97)	26.9 (5.1)	28 053 (22.4)
Men	123 629 (50.03)	27.8 (4.2)	31 478 (25.1)
P		<1.0x10 ⁻³⁰⁰	4.9x10 ⁻⁵⁷
Age (in years)			
39-45	29 649 (11.8)	26.8 (4.8)	6 015 (20.3)
46-51	39 298 (15.7)	27.1 (4.8)	8 916 (22.7)
52-57	47 624 (19.0)	27.4 (4.9)	11 691 (24.6)
58-63	70 571 (28.1)	27.5 (4.6)	17 527 (24.8)
64-72	63 983 (25.4)	27.5 (4.3)	15 382 (24.0)
P		<1.0x10 ⁻³⁰⁰	5.9x10 ⁻³⁸
Depression (self-reported + hospital diagnosed)			
Control	217 882 (86.8)	27.2 (4.5)	49 714 (22.8)
Case	33 243 (13.2)	28.1 (5.4)	9 817 (29.5)
p§		3.0x10 ⁻²³⁷	9.0x10 ⁻¹⁸⁶
Single episode depressive (F32)			
Control	217 882 (86.8)	27.2 (4.5)	49 714 (22.8)
Case	12 955 (5.2)	28.4 (5.6)	4 097 (31.6)
p§		1.0x10 ⁻¹⁶⁹	2.0x10 ⁻¹³¹
Recurrent depressive disorder (F33)			
Control	217 882 (86.8)	27.2 (4.5)	49 714 (22.8)
Case	16 889 (6.7)	27.9 (5.2)	4 799 (28.4)
p§		6.0x10 ⁻¹⁰⁶	4.9x10 ⁻⁷⁸
Hospital diagnosed Depression			
Control	218 407 (96.4)	27.3 (4.6)	55 988 (23.2)
Case	8 042 (3.6)	29.0 (6.0)	3 543 (36.7)
p§		2.3x10 ⁻²⁵³	4.0x10 ⁻²¹⁵
Anti-depressant medication usage			
No	239 176 (95.2)	27.3 (4.6)	55 102 (23.0)
Yes	11 949 (4.8)	29.0 (5.8)	4 429 (37.1)
p§		<1.0x10 ⁻³⁰⁰	3.0x10 ⁻²⁸⁵
BMI GRS (group using median)			
≤65	125 573 (50.0)	26.9 (4.4)	25 487 (20.3)
>65	125 552 (50.0)	27.8 (4.9)	34 044 (27.1)
p¶		<1.0x10 ⁻³⁰⁰	<1.0x10 ⁻³⁰⁰
rs6567160 (MC4R)			
TT	146 965 (58.6)	27.3 (4.6)	33 674 (22.9)
TC	90 083 (35.9)	27.5 (4.7)	22 083 (24.5)
CC	13 881 (5.5)	27.8 (4.9)	3 728 (26.9)
p¶		3.5x10 ⁻⁴⁹	3.8x10 ⁻³⁶
General health			
Excellent	45 665 (18.2)	25.5 (3.5)	5 555 (12.3)
Good	148 629 (59.2)	27.1 (4.3)	34 832 (23.7)
Fair	47 272 (18.8)	29.3 (5.3)	18 300 (39.6)
Poor	8 798 (3.5)	30.8 (6.7)	4 292 (51.0)
Missing	761 (0.3)	29.2 (5.9)	304 (41.3)
p¶		<1.0x10 ⁻³⁰⁰	<1.0x10 ⁻³⁰⁰

486 † P-value from linear regression. ‡ Obesity = BMI \geq 30, and the P-values are from logistic
487 regression. § adjusted for age and sex. ¶ further adjusted for types of genotyping array and 15
488 principal components

489

490 **Table2.** Instrument validation and observational and Mendelian randomisation analyses of depression on body mass index in the UK Biobank.

		All	Women	Men
Association between GRS_{MDD} and depression	OR (95% CI)	1.021 (1.018, 1.023)	1.019 (1.015, 1.023)	1.023 (1.019, 1.028)
	P	2.1E-45	4.5E-24	6.2E-24
	r ² (in %)	0.17	0.20	0.18
Observational association between depression and BMI[†]				
Simple model	Beta (95% CI)	0.19 (0.18, 0.20)	0.25 (0.24, 0.27)	0.10 (0.08, 0.11)
	P	5.0E-215	2.0E-190	2.0E-29
Adjusted model	Beta (95% CI)	0.06 (0.05, 0.07)	0.09 (0.07, 0.11)	-0.002 (-0.02, 0.01)
	P	5.5E-22	2.1E-25	0.79
Genetic association between depression and BMI				
MR: two-stage least square regression, one sample [‡]	Beta (95% CI)	0.09 (0.04, 0.13)	0.11 (0.04, 0.18)	0.06 (0.01, 0.11)
	P	0.0001	0.004	0.01
MR: inverse Variance weighted, two-sample [§]	Beta (95% CI)	0.06 (-0.02, 0.14)	NA	NA
	P	0.16		
MR: weighted median, two sample [§]	Beta (95% CI)	0.06 (-0.00, 0.12)	NA	NA
	P	0.07		
MR: Egger, two sample [§]	Beta (95% CI)	0.57 (0.04, 1.09)	NA	NA
	P	0.04		
	P _{intercept}	0.06		

491 [†] An observational association with estimates from linear regression analyses from two models: **simple model** involved adjustment for age, sex and assessment centre while
492 the **adjusted model** included further adjustment for Townsend deprivation index, education, physical activity, sedentary behaviour, vegetable and fruit consumption,
493 cigarette smoking, alcohol consumption and general health status.

494 [‡] A genetic association with estimates from one-sample MR analyses using the UK Biobank, results from two-stage least squares regression analyses adjusted for age, sex,
495 assessment centre, type of array, and 15 PCs.

496 [§] A genetic association with estimates from two-sample MR analyses using variant-MDD estimates from Wray et al (Wray et al., 2018), and variant-BMI estimates from UK
497 Biobank.

498 r² indicated the depression variability explained by the GRS_{MDD}. This was calculated by subtracting the r² value of a model containing only covariates without the GRS_{MDD},
499 from the r² of a full model inclusive of the GRS_{MDD}.

500 NA not applicable.

501 **Table 3.** Association of the GRS_{BMI} and $MC4R$ variant with BMI in UK Biobank

		Beta	SE	r²	P	P-interaction[†]
Total GRS_{BMI}^{\ddagger}	All	0.21	0.003	0.013	$<1.0 \times 10^{-300}$	1.0×10^{-4}
	Women	0.22	0.005	0.012	$<1.0 \times 10^{-300}$	
	Men	0.20	0.004	0.015	$<1.0 \times 10^{-300}$	
Neuronal GRS_{BMI}^{\ddagger}	All	0.21	0.004	0.009	$<1.0 \times 10^{-300}$	1.9×10^{-3}
	Women	0.22	0.006	0.009	$<1.0 \times 10^{-300}$	
	Men	0.20	0.005	0.011	$<1.0 \times 10^{-300}$	
Non-neuronal GRS_{BMI}^{\ddagger}	All	0.20	0.006	0.004	1.0×10^{-285}	9.0×10^{-3}
	Women	0.22	0.008	0.004	1.0×10^{-143}	
	Men	0.19	0.007	0.004	2.0×10^{-151}	
rs6567160	All	0.05	0.003	0.001	6.1×10^{-78}	1.4×10^{-2}
	Women	0.06	0.004	0.001	7.3×10^{-44}	
	Men	0.04	0.004	0.001	1.1×10^{-35}	

502 [†] Two-way interaction between sex and genetic variants on BMI.

503 [‡] Associations shown for differences in BMI (SD) per 10 allele increase for the GRS_{BMI} , whereas for rs6567160
504 association are shown per one allele increase.

505 r^2 indicated the BMI variability explained by the GRS_{BMI} . This was calculated by subtracting the r^2 value of a
506 model containing only covariates without the GRS_{BMI} , from the r^2 of a full model inclusive of the GRS_{BMI} .

507

508

509 **Table 4.** Association between GRS_{BMI} and BMI among individuals with and without depression

		Depression case				Control				P-interaction [†]	P-interaction [‡]
		Beta	SE	r ²	P	Beta	SE	r ²	P		
Total GRS_{BMI} [§]	All	0.24	0.0051	0.015	2.1×10^{-123}	0.20	0.0051	0.013	$<1.0 \times 10^{-300}$	9.1×10^{-4}	
	Women	0.25	0.0051	0.015	8.0×10^{-77}	0.22	0.0051	0.012	$<1.0 \times 10^{-300}$	0.01	
	Men	0.21	0.0051	0.015	2.3×10^{-50}	0.19	0.0051	0.015	$<1.0 \times 10^{-300}$	0.02	0.35
Neuronal GRS_{BMI} [§]	All	0.24	0.0051	0.011	4.0×10^{-93}	0.21	0.0051	0.01	$<1.0 \times 10^{-300}$	0.006	
	Women	0.26	0.0051	0.011	1.1×10^{-57}	0.22	0.0051	0.009	1.1×10^{-231}	0.03	
	Men	0.22	0.0051	0.011	1.2×10^{-38}	0.20	0.0051	0.011	$<1.0 \times 10^{-300}$	0.31	0.32
Non-neuronal GRS_{BMI} [§]	All	0.23	0.0051	0.004	6.1×10^{-34}	0.20	0.0051	0.004	5.4×10^{-223}	0.08	
	Women	0.25	0.0102	0.004	3.6×10^{-22}	0.22	0.0102	0.004	1.1×10^{-104}	0.21	
	Men	0.20	0.0102	0.004	1.0×10^{-13}	0.19	0.0102	0.004	2.2×10^{-123}	0.62	0.67

510 [†] Two-way interaction between GRS_{BMI} and depression on BMI.

511 [‡] Three-way interaction among GRS_{BMI} , sex and depression on BMI.

512 [§] Per 10 allele increase.

513

514 **Figure legends**

515 **Figure 1. GRS_{BMI} and BMI in UK Biobank** (The histogram shows the distribution of BMI
516 GRS, with the line indicating the predicted relationship between GRS_{BMI} and BMI (Kg/m^2)).

517 **Figure 2. Association between neuronal GRS_{BMI} and BMI among individuals with, and
518 without depression** (The lines show the changes in BMI per change in neuronal GRS_{BMI} ,
519 where the dotted line represents depression case group, and the solid line represents control
520 group).

521 **Figure 3. Association between rs6567160 variant (near *MC4R* gene) and BMI among
522 individuals with and without depression** (Control (main) and case (main) indicators are
523 derived from the main depression outcome, self-report and hospital episode statistic
524 combined. Control (HES data) and case (HES data) are defined using depression diagnosis
525 history from Hospital episode statistics data).

526