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

Short title: gene-depression interaction

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Abstract

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

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

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

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

Introduction

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

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

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

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

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

Methods

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

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 classified as obese (WHO, 2016). For analysis, BMI was inverse normal transformed, with one SD corresponding to 4.74 kg/m^2. Secondary analysis used alternate measures of adiposity, including waist circumference (WC) and body fat percentage (BFP) (Supplementary Methods). Lifestyle and socioeconomic information was self-reported, and derived from the baseline assessment (Sudlow et al., 2015) (Supplementary Methods).

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

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

Genetic variants and genetic risk score

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

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

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

$$\text{Weighted genetic risk score} = \frac{(\beta_1 \times SNP_1 + \beta_2 \times SNP_2 + \ldots \beta_n \times SNP_n) \times \text{Number of SNPs}}{\text{Sum of } \beta \text{ coefficients}}$$

Where:
SNP_1 to SNP_n are number of risk increasing alleles contributing to the genetic risk score.
β_1 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 $GRS_{BMI.}$

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

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

Statistical analysis

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

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

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

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

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

Results

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

Observational and genetic evidence for association between depression and BMI

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

Association between genetic variants and BMI

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

Genetic contribution to BMI is modified by depression status

Depression modified the association of genetic variants with BMI (Table 4). Genetic susceptibility to BMI was higher in depressed individuals compared to non-depressed individuals ($P_{interaction}=9.1 \times 10^{-4}$), and carrying ten additional risk alleles was associated with 0.24 SD, (95% CI 0.23 to 0.25) and 0.20 SD (95% CI 0.19 to 0.21) higher BMI among depressed and non-depressed individuals. Here, one SD represents 4.72 kg/m^2 difference in BMIs hence, these data are equivalent 3.4 kg and 2.8 kg extra weight for 1.73 m tall average depressed and non-depressed individual, respectively. This interaction was also observed when using WC or BFP as an outcome ($P_{interaction}<0.004$), but not with obesity (Supplementary table 3).

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

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

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

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

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

Discussion

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

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

This study utilised BMI-associated variants from different biological pathways to explore the link between depression and high BMI. Although related differences between neuronal GRS_{BMI} and non-neuronal GRS_{BMI} were small, the evidence of an interaction from the former, suggests a role of the CNS in the link between depression and high BMI. Previous studies have indicated that the hypothalamic-pituitary-adrenal (HPA) axis is involved in the pathogenesis of depression and obesity (Bose, Olivan, & Laferrere, 2009; Varghese & Brown, 2001). This is supported further by our finding that rs6567160 near the *MC4R* gene was the main variant driving the interaction with depression on BMI. Interestingly rs17782313, which is in perfect LD with rs6567160, has previously been reported to interact with stress, and influence obesity risk (Park et al., 2016).The importance of the *MCR4* gene in the depression-high BMI relationship is also evident in animal-based pharmacological studies, in which the antagonist of *MCR4* receptor has shown anxiolytic and antidepressant effects, particularly under conditions of high stress (Chaki & Okubo, 2007). This antagonist was suggested for treatment of cachexia through the effect on increasing food intake, and decreasing energy expenditure (Weyermann et al., 2009).

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

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

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

Conclusions

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

Availability of Data and Materials

All data is available through the UK Biobank.

Supplementary information is available at Depression and Anxiety online.

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Tables

Table 1. Mean BMI and the prevalence of obesity by participant characteristics in the UK 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¶		$<1.0x10^{-300}$	$<1.0x10^{-300}$

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

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		

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

‡ 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, assessment centre, type of array, and 15 PCs.

§ 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 Biobank.

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

NA not applicable.

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

		Beta	SE	r^2	P	P-interaction†
Total GRSBMI‡	All	0.21	0.003	0.013	$<1.0x10^{300}$	$1.0x10^{-4}$
	Women	0.22	0.005	0.012	$<1.0x10^{-300}$	
	Men	0.20	0.004	0.015	$<1.0x10^{-300}$	
Neuronal GRSBMI‡	All	0.21	0.004	0.009	$<1.0x10^{-300}$	$1.9x10^{-3}$
	Women	0.22	0.006	0.009	$<1.0x10^{-300}$	
	Men	0.20	0.005	0.011	$<1.0x10^{-300}$	
Non-neuronal GRSBMI‡	All	0.20	0.006	0.004	$1.0x10^{-285}$	$9.0x10^{-3}$
	Women	0.22	0.008	0.004	$1.0x10^{-143}$	
	Men	0.19	0.007	0.004	$2.0x10^{-151}$	
rs6567160	All	0.05	0.003	0.001	$6.1x10^{-78}$	$1.4x10^{-2}$
	Women	0.06	0.004	0.001	$7.3x10^{-44}$	
	Men	0.04	0.004	0.001	$1.1x10^{-35}$	

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

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

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

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

		Depression case				Control				P-interaction†	P-interaction‡
		Beta	**SE**	**r2**	**P**	**Beta**	**SE**	**r2**	**P**		
Total GRS_{BMI}§	All	0.24	0.0051	0.015	$2.1x10^{-123}$	0.20	0.0051	0.013	$<1.0x10^{-300}$	$9.1x10^{-4}$	
	Women	0.25	0.0051	0.015	$8.0x10^{-77}$	0.22	0.0051	0.012	$<1.0x10^{-300}$	0.01	
	Men	0.21	0.0051	0.015	$2.3x10^{-50}$	0.19	0.0051	0.015	$<1.0x10^{-300}$	0.02	0.35
Neuronal GRS_{BMI}§	All	0.24	0.0051	0.011	$4.0x10^{-93}$	0.21	0.0051	0.01	$<1.0x10^{-300}$	0.006	
	Women	0.26	0.0051	0.011	$1.1x10^{-57}$	0.22	0.0051	0.009	$1.1x10^{-231}$	0.03	
	Men	0.22	0.0051	0.011	$1.2x10^{-38}$	0.20	0.0051	0.011	$<1.0x10^{-300}$	0.31	0.32
Non-neuronal GRS_{BMI}§	All	0.23	0.0051	0.004	$6.1x10^{-34}$	0.20	0.0051	0.004	$5.4x10^{-223}$	0.08	
	Women	0.25	0.0102	0.004	$3.6x10^{-22}$	0.22	0.0102	0.004	$1.1x10^{-104}$	0.21	
	Men	0.20	0.0102	0.004	$1.0x10^{-13}$	0.19	0.0102	0.004	$2.2x10^{-123}$	0.62	0.67

† Two-way interaction between GRSBMI and depression on BMI.

‡ Three-way interaction among GRSBMI, sex and depression on BMI.

§ Per 10 allele increase.

Figure legends

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

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

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