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Obesity Genes and Risk of Major Depressive Disorder in a Multiethnic Population:
A Cross-Sectional Study

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ABSTRACT

Objective: Observational studies have shown a positive association between obesity (body mass index [BMI] ≥ 30 kg/m^2) and depression. Around 120 obesity-associated loci have been identified, but genetic variants associated with depression remain elusive. Recently, our team reported that the fat mass and obesity-associated (*FTO*) gene rs9939609 obesity-risk variant is paradoxically inversely associated with the risk of depression. This finding raises the question as to whether other obesity-associated genetic variants are also associated with depression.

Method: Twenty-one obesity gene variants other than *FTO* were selected from a custom ~50,000 single-nucleotide polymorphisms (SNPs) genotyping array (ITMAT-Broad-CARe array). Associations of these 21 SNPs and an unweighted genotype score with BMI and major depressive disorder (determined using the *DSM-IV* diagnostic criteria) were tested in 3,209 cases and 14,195 noncases, using baseline data collected from July 2001 to August 2003 from the multiethnic EpiDREAM study.

Results: Body mass index was positively associated with depression status (odds ratio [OR] = 1.02; 95% CI, 1.02–1.03 per BMI unit; $P = 2.9 \times 10^{-12}$, adjusted for age, sex, and ethnicity). Six of 21 genetic variants (rs1514176 [*TNN13K*], rs2206734 [*CDKAL1*], rs11671664 [*GIPR*], rs2984618 [*TAL1*], rs3824755 [*NT5C2*], and rs7903146 [*TCF7L2*]) and the genotype score were significantly associated with BMI ($1.47 \times 10^{-14} \leq P \leq .04$). Of the 21 SNPs, *TAL1* rs2984618 obesity-risk allele was associated with a higher risk of major depressive disorder ($P = 1.79 \times 10^{-4}$, adjusted for age, sex, BMI, and ethnicity), and *BDNF* rs1401635 demonstrated significant ethnic-dependent association with major depressive disorder (OR = 0.88; 95% CI, 0.80–0.97; $P = .01$ in non-Europeans and OR = 1.11; 95% CI, 1.02–1.20; $P = .02$ in Europeans; $P_{interaction} = 2.73 \times 10^{-4}$). The genotype score, calculated with or without *FTO* rs9939609, and adjusted for the same covariates, was not associated with depression status.

Conclusions: Our data support the view that the association between obesity and major depressive disorder at the observational level may be explained, at least in part, by shared genetic factors.

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According to the World Health Organization, 350 million people suffer from depression, and the burden of this disorder is on the rise globally.[1] A number of modifiable and nonmodifiable factors increase the risk for depression. These include sex, age, socioeconomic status, early trauma, stressful life events (violence, mourning, divorce), and chronic illness.[2] Family and twin studies have reported that 35%–75% of interindividual variability for depression may be accounted for by genetic factors, but specific genetic variants associated with depression remain elusive.[2,3] No gene responsible for highly penetrant Mendelian forms of depression has been described to date. In addition, large-scale genome-wide association studies (GWAS)[4–6] have been mostly unsuccessful in identifying common genetic variants associated with modest increase in the risk of depression.

The World Health Organization reported that worldwide prevalence of obesity more than doubled between 1980 and 2014.[7] An estimated total of 600 million adults are considered obese (body mass index [BMI] ≥ 30 kg/m^2).[7] A number of environmental factors have been attributed to the obesity epidemic, most importantly changes in eating habits and decreased physical activity.[8] Heritability studies support a genetic basis for obesity.[9] Recently, candidate gene studies, genecentric studies, and GWAS have identified around 120 loci conclusively associated with BMI variation or obesity risk.[10,11] Variation in the intron 1 of the fat mass and obesity-associated (*FTO*) gene is the most significant contributor to polygenic obesity.[12,13]

Growing evidence supports an association between obesity and depression in longitudinal studies. In a meta-analysis of 8 longitudinal studies (N = 55,387), obesity (BMI ≥ 30 kg/m^2) at baseline was associated with a 1.55-fold increase in the incidence of depression at follow-up.[14] Conversely, a reciprocal meta-analysis of 9 longitudinal studies (N = 6,436) by the same group[14] showed that depression at baseline was associated with a 1.58 times increase in the risk of developing obesity over time.

Previous studies[15–18] suggested that shared genetic architecture may account, at least in part, for the association between obesity and depression.

Clinical Points

- Previous studies suggest that the association between obesity and depression, 2 comorbid conditions, may be explained by shared genetic architecture.
- Of the 21 obesity-associated single-nucleotide polymorphisms included in this study, *TAL1* rs3824755 was found to be positively associated with major depressive disorder in a multiethnic context. In addition, *BDNF* rs1401635 demonstrated an ethnic-dependent association with major depressive disorder.

A modestly powered twin study[15] estimated that 12% of the genetic component of depression may be shared with obesity. A recent meta-analysis[17] using 4 independent studies demonstrated an inverse association between the *FTO* rs9939609 obesity-risk variant and risk of depression independent of its effect on BMI. However, it is unclear whether the association between the *FTO* rs9939609 A variant and depression is exclusive to *FTO* or is present in other obesity gene variants. The effect of 21 obesity-/BMI-associated single-nucleotide polymorphisms (SNPs) (analyzed separately and together as a genotype score) on BMI variation and the risk of major depressive disorder was therefore assessed in 17,404 subjects using baseline clinical data from 6 ethnic groups (EpiDREAM study [Epidemiology arm of the Diabetes REduction Assessment with ramipril and rosiglitazone Medication]).

METHOD

Participants

EpiDREAM is a longitudinal study that enrolled 24,872 individuals who were at risk for type 2 diabetes and were recruited from 21 countries, including subjects who participated in the Diabetes REduction Assessment with ramipril and rosiglitazone Medication (DREAM) trial (ClinicalTrials.gov identifier: NCT00095654). All individuals who were deemed to be at risk for dysglycemia defined by family history, ethnicity, and abdominal obesity, between the ages of 18–85 years, were screened using a 75-g oral glucose tolerance test (OGTT) from July 2001 to August 2, 2003. Detailed methods and description of the study cohort have been reported earlier.[19,20] The current study used cross-sectional data from the baseline screening visit for the EpiDREAM and DREAM studies. A subset of 17,404 subjects from 6 ethnic groups (East Asian, South Asian, European, African, Latin American, and Native North American) had both phenotypic and genotypic information available at baseline and was included in the study (Supplementary eFigure 1). Self-reported ethnicity has been validated in the 17,404 individuals using the eigensoft software (http://genetics.med.harvard.edu/reich/Reich_Lab/Software.html). The EpiDREAM and DREAM studies have been approved by local ethics committees, and informed consent was obtained from each subject before participating in the studies, in accordance with the Declaration of Helsinki.

Genotyping

Deoxyribonucleic acid was successfully extracted from buffy coats in 19,498 participants of the EpiDREAM study (Supplementary eFigure 1) using the Qiagen Gentra Systems. The Illumina CVD ITMAT-Broad-CARe (IBC) bead chip microarray was used in this study.[21] Genotyping was performed at the McGill University and Genome Quebec Innovation Centre, Montreal, Quebec, Canada, using the Illumina BeadStudio genotyping module, version 3.2. A list of SNPs that reached genome-wide significance ($P < 5 \times 10^{-8}$) with BMI or binary obesity status in populations of European ancestry was established. Three different strategies were used to optimize the SNP selection procedure using a keyword search (eg, *BMI*) on (1) the National Human Genome Research Institute (NHGRI) GWAS Catalog (http://www.genome.gov/gwastudies/), (2) the HuGE Navigator GWAS Integrator (www.hugenavigator.net/HuGENavigator/gWAHitStartPage.do), and (3) the PubMed database (http://www.ncbi.nlm.nih.gov/pubmed). Using this strategy, 119 independent SNPs were found to be associated with BMI or binary obesity status. For SNPs that were not available in the Cardio-MetaboChip (Illumina, Inc), we searched for proxy SNPs using the Broad Institute website tool SNAP (SNP Annotation and Proxy Search).[22] For those highlighted as missing in the Cardio-MetaboChip, we checked their availability using their chromosomal position in the Illumina product file.[23] We used the following criteria to select proxy SNPs: (1) SNPs included in the Cardio-MetaboChip, (2) $r^2 > 0.90$ within the same ethnic group from the 1000 Genomes Project as reported in the GWAS report, and (3) selection of a coding nonsynonymous SNP if available in the list of proxy; otherwise, selection of the SNP located closest to the GWAS lead SNP. From this list, 21 SNPs other than *FTO* were available on versions 1 and 2 of the IBC 50,000 SNP array (Supplementary eTable 1). The 21 SNPs include rs1514176 (*TNNI3K*), rs6235 (*PCSK1*), rs6232 (*PCSK1*), rs2206734 (*CDKAL1*), rs2272903 (*TFAP2B*), rs1211166 (*NTRK2*), rs6265 (*BDNF*), rs1401635 (*BDNF*), rs997295 (*MAP2K5*), rs1805081 (*NPC1*), rs2075650 (*TOMM40/APOE/APOC1*), rs11671664 (*GIPR*), rs2984618 (*TAL1*), rs1011527 (*LEPR*), rs7605927 (*POMC*), rs611203 (*USP37*), rs2535633 (*ITIH4*), rs3824755 (*NT5C2*), rs7903146 (*TCF7L2*), rs671 (*ALDH2*), and rs749767 (*KAT8*) (see Table 2 for full gene names). Single-nucleotide polymorphisms in/near *PCSK1* (rs6232/rs6235) and *BDNF* (rs6265/rs1401635) are independent in EpiDREAM ($r^2 < 0.2$, Supplementary eTable 1).

The 21 SNPs showed no deviation from Hardy-Weinberg equilibrium (HWE) within ethnic group in the overall sample as well as in the depressed and nondepressed subgroups (all P values $\geq 1 \times 10^{-6}$, Supplementary eTable 2). The call rate for each of the 21 SNPs was between 99.98% and 100% (Supplementary eTable 2).

Phenotyping

Demographic data as well as direct anthropometric measurements were obtained from study participants using a standardized protocol. Height (m) and weight (kg) were

measured in clinical centers by trained staff. Standing height was measured to the nearest 0.1 cm with the participant looking straight ahead in bare feet and with his/her back against a wall. Weight was measured to the nearest 0.1 kg with the participant in light clothing. BMI was calculated as weight in kilograms (kg) divided by height in meters squared (m^2).

The assessment of a major depressive episode was performed using diagnostic criteria from the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*) as described elsewhere.[17] Interviews were conducted face-to-face by trained professionals, and a structured case report form was completed to assess depression (a major depressive episode in the past 12 months). Participants were asked whether they had experienced any of the following symptoms during the past 12 months and whether these symptoms were persistent on a daily basis and lasted for at least 2 weeks: feeling sad, blue, or depressed; loss of interest in most things; feeling tired or low energy; changing body weight; having difficulty sleeping; having difficulty concentrating; thinking about death; and having low self-esteem or confidence. A depressive episode was considered present if the individual had 5 or more of the above symptoms.

Statistical Analyses

All statistical analyses were performed using the SPSS 14.0 software. The power of our depression case-control study was assessed using QUANTO software version 1.2.4 (University of Southern California, Los Angeles). The comparison of baseline characteristics between depression cases and controls was done using *t* tests or χ^2 tests. Genotypes were coded as 0, 1, and 2, depending on the number of copies of the obesity-risk alleles as determined in the literature. All genetic association studies were performed under an additive mode of inheritance. A genotype score was calculated by summing the alleles of 21 obesity-associated SNPs. A separate genotype score with the addition of the *FTO* rs9939609 SNP was created.[17] An unweighted genotype score was used as previously recommended by Dudbridge.[24] Individuals with more than 2 missing genotypes out of 21 were discarded from the calculation of the genotype score, and the remaining missing values were imputed using the method of the mean. This imputation was performed for each SNP individually in each separate ethnicity using the arithmetic average of the coded genotypes observed for all successfully genotyped individuals. The association of SNPs/genotype score with binary traits (eg, major depressive disorder) was tested using a logistic regression model adjusted for age, sex, and ethnicity. We also tested this association with BMI as an additional covariate. The association of SNPs/genotype score with continuous traits (eg, BMI) was tested using a linear regression model adjusted for age, sex, and ethnicity. A *P* value of .05 was considered significant for the data presented in Table 1 and 2, due to their high prior likelihood of association. Two-sided $P < .05$ before Bonferroni correction was considered nominally significant. After applying the Bonferroni correction for multiple testing, $P < .0007$ (= .05/71) was considered statistically significant. This value was calculated by dividing .05 by the total number of statistical tests performed in the study. In Table 3, we tested the association of the 21 SNPs and the 2 genotype scores with major depressive disorder 2 times (once

Table 1. Baseline Characteristics by Depression Status in the EpiDREAM Study

Characteristic	All	Depression	No Depression	*P*[a]
Overall				
Age, mean (SD), y	52.65 (11.37)	51.08 (10.55)	53.01 (11.52)	6.917×10^{-20}
BMI, mean (SD)	30.16 (6.22)	31.58 (6.78)	29.84 (6.04)	4.648×10^{-40}
Sex, n (%)				
Female	10,606 (60.9)	2,429 (75.7)	8,177 (57.6)	1.079×10^{-93}
Male	6,798 (39.1)	780 (24.3)	6,018 (42.4)	
Ethnicity, n (%)				
South Asian	2,760 (15.9)	193 (6.0)	2,567 (18.1)	1.980×10^{-93}
East Asian	225 (1.3)	23 (0.7)	202 (1.4)	
European	9,378 (53.9)	1,750 (54.5)	7,628 (53.7)	
African	1,249 (7.2)	227 (7.1)	1,022 (7.2)	
Latin American	3,292 (18.9)	914 (28.5)	2,378 (16.8)	
Native North American	500 (2.9)	102 (3.2)	398 (2.8)	
Total	17,404 (100)	3,209 (100)	14,195 (100)	
South Asian				
Age, mean (SD), y	44.86 (9.38)	44.54 (8.97)	44.89 (9.41)	.604
BMI, mean (SD)	26.43 (4.35)	26.04 (4.81)	26.45 (4.31)	.250
Sex, n (%)				
Female	1,334 (48.3)	119 (61.7)	1,251 (48.1)	1.225×10^{-4}
Male	1,426 (51.7)	74 (38.3)	1,352 (51.9)	
East Asian				
Age, mean (SD), y	53.14 (11.09)	52.09 (11.58)	53.26 (11.05)	.648
BMI, mean (SD)	26.07 (4.28)	26.08 (3.35)	26.06 (4.38)	.983
Sex, n (%)				
Female	129 (57.3)	18 (78.3)	111 (55.0)	.032
Male	96 (42.7)	5 (21.7)	91 (45.0)	
European				
Age, mean (SD), y	54.97 (10.82)	52.50 (10.34)	55.54 (10.85)	2.170×10^{-27}
BMI, mean (SD)	30.63 (6.14)	31.72 (6.70)	30.38 (5.98)	2.112×10^{-14}
Sex, n (%)				
Female	5,699 (60.8)	1,291 (73.8)	4,408 (57.8)	4.798×10^{-35}
Male	3,679 (39.2)	459 (26.2)	3,220 (42.2)	
African				
Age, mean (SD), y	54.05 (10.98)	50.01 (10.37)	54.95 (10.92)	4.460×10^{-10}
BMI, mean (SD)	32.63 (6.14)	34.28 (7.71)	31.97 (6.80)	3.909×10^{-5}
Sex, n (%)				
Female	897 (71.8)	185 (81.5)	712 (69.7)	3.385×10^{-4}
Male	352 (28.2)	42 (18.5)	310 (30.3)	
Latin American				
Age, mean (SD), y	52.59 (11.65)	50.69 (10.62)	53.32 (11.94)	9.057×10^{-10}
BMI, mean (SD)	31.05 (6.16)	31.71 (6.34)	30.79 (6.08)	1.634×10^{-4}
Sex, n (%)				
Female	2,199 (66.8)	732 (80.1)	1,467 (61.7)	1.041×10^{-23}
Male	1,093 (33.2)	182 (19.9)	911 (38.3)	
Native North American				
Age, mean (SD), y	48.89 (10.92)	44.82 (9.10)	49.93 (11.11)	2.920×10^{-6}
BMI, mean (SD)	32.49 (6.39)	33.76 (7.24)	32.17 (6.13)	.044
Sex, n (%)				
Female	348 (69.6)	84 (82.4)	264 (66.3)	.002
Male	152 (30.4)	18 (17.6)	134 (33.7)	

[a]*P* values are reported for unadjusted univariate analyses (χ^2 or Student *t* tests).
Abbreviations: BMI = body mass index, SD = standard deviation.

Table 2. Association of SNPs and the Genotype Score With BMI in EpiDREAM

Gene	SNP	Risk Allele	β	SE	P[a,b]
TNNI3K	rs1514176	G	0.20	0.06	**.002**
PCSK1	rs6235	C	0.00	0.07	.96
PCSK1	rs6232	G	0.06	0.16	.68
CDKAL1	rs2206734	C	0.24	0.08	**.002**
TFAP2B	rs2272903	G	0.15	0.09	.09
NTRK2	rs1211166	A	0.05	0.08	.52
BDNF	rs6265	G	0.11	0.08	.18
BDNF	rs1401635	C	0.10	0.07	.15
MAP2K5	rs997295	T	0.04	0.06	.56
NPC1	rs1805081	A	0.07	0.07	.33
TOMM40/APOE/APOC1	rs2075650	A	0.06	0.09	.53
GIPR	rs11671664	G	0.25	0.10	**.015**
TAL1	rs2984618	T	0.32	0.06	**7.325×10^{-7}**
LEPR	rs1011527	A	−0.09	0.10	.41
POMC	rs7605927	G	−0.02	0.07	.78
USP37	rs611203	G	0.02	0.07	.80
ITIH4	rs2535633	G	−0.02	0.06	.72
NT5C2	rs3824755	C	0.18	0.09	**.04**
TCF7L2	rs7903146	C	0.34	0.07	**1.074×10^{-6}**
ALDH2/MYL2	rs671	G	0.17	0.66	.80
KAT8	rs749767	A	0.07	0.07	.29
Genotype score without *FTO* rs9939609			0.10	0.02	**1.038×10^{-9}**
Genotype score with *FTO* rs9939609			0.12	0.02	**1.473×10^{-14}**

[a]*P* values are adjusted for sex, age, and ethnicity.
[b]Bold means $P < .05$.
Abbreviations: BMI = body mass index, SE = standard error, SNP = single-nucleotide polymorphism.
Gene abbreviations: *TNNI3K* = TNNI3 interacting kinase; *PCSK1* = proprotein convertase subtilisin/kexin type 1; *CDKAL1* = CDK5 regulatory subunit associated protein 1-like 1; *TFAP2B* = transcription factor AP-2 β (activating enhancer binding protein 2 β); *NTRK2* = neurotrophic tyrosine kinase, receptor, type 2; *BDNF* = brain-derived neurotrophic factor; *MAP2K5* = mitogen-activated protein kinase kinase 5; *NPC1* = Niemann-Pick disease, type C1; *TOMM40/APOE/APOC1* = translocase of outer mitochondrial membrane 40 homolog (yeast)/apolipoprotein E/apolipoprotein C-I; *GIPR* = gastric inhibitory polypeptide receptor; *TAL1* = T-cell acute lymphocytic leukemia 1; *LEPR* = leptin receptor; *POMC* = proopiomelanocortin; *USP37* = ubiquitin specific peptidase 37; *ITIH4* = inter-alpha-trypsin inhibitor heavy chain family, member 4; *NT5C2* = 5′-nucleotidase, cytosolic II; *TCF7L2* = transcription factor 7-like 2 (T-cell specific, HMG-box); *ALDH2/MYL2* = aldehyde dehydrogenase 2 family (mitochondrial)/myosin, light chain 2, regulatory, cardiac, slow; *KAT8* = K(lysine) acetyltransferase 8; *FTO* = fat mass and obesity-associated.

with BMI as a covariate and once without), giving a total of 46 tests. In Supplementary eTable 4, we tested for interaction between European/non-European ancestry and each of the 21 SNPs as well as the 2 genotype scores mentioned above on major depressive disorder status, giving a total of 23 tests. Finally, we performed 2 tests on *BDNF* rs1401635 (once in Europeans and once in non-Europeans). Altogether, this gives a total of 71 statistical tests.

RESULTS

Baseline Characteristics of Depression Cases and Controls

Table 1 shows the main baseline characteristics by depression status in the EpiDREAM study. Subjects with major depressive disorder represented 18.4% of the total EpiDREAM sample. On average, the depressed group was 2 years younger and had a 1.75 unit higher BMI than the nondepressed group, and there was a greater proportion of women in the depressed (75.7%) than in the nondepressed (57.6%) group. Strong ethnic variation in depression rates was observed. Specifically, East Asians and South Asians were less likely and Latin Americans were more likely to report depression (Table 1 and Supplementary eTable 3).

Association Between BMI and Major Depressive Disorder

In a multivariate logistic regression model adjusted for sex, age, and ethnicity, baseline BMI was positively associated with major depressive disorder status (odds ratio [OR] = 1.02; 95% CI, 1.02–1.03 per BMI unit; $P = 2.9\times10^{-12}$).

Association Between Obesity SNPs, the Genotype Score, and BMI

Genotype distributions of the 21 obesity-associated gene variants are presented by ethnic group in Supplementary eTable 2. Associations between the 21 obesity SNPs, the genotype score, and baseline BMI are reported in Table 2. Association tests have been adjusted for sex, age, and ethnicity. The direction of effect for 18 of 21 obesity-risk alleles included in the study was consistent with previous literature.[10,12,25–31] Only *LEPR* rs1011527, *POMC* rs7605927, and *ITIH4* rs2535633 had a negative β value. Six of the 21 SNPs achieved nominal evidence of association with BMI: rs1514176 (*TNN13K*), rs2206734 (*CDKAL1*), rs11671664 (*GIPR*), rs2984618 (*TAL1*), rs3824755 (*NT5C2*), and rs7903146 (*TCF7L2*) (*P* comprised between .04 and 7.33×10^{-7}, Table 2). The genotype score was also associated with increased BMI ($\beta = 0.10 \pm 0.02$, $P = 1.04\times10^{-9}$). When the *FTO* rs9939609 SNP was added to the genotype score, the association with BMI became stronger ($\beta = 0.12 \pm 0.02$, $P = 1.47\times10^{-14}$). No significant interaction between European/non-European ancestry and the SNPs/genotype score was found on BMI (data not shown).

Association Between Obesity SNPs, the Genotype Score, and Major Depression

Associations between the 21 obesity SNPs, the genotype score, and major depressive disorder at baseline are reported in Table 3. Association tests were adjusted for sex, age, and ethnicity. Results are also provided with further adjustment for BMI (Table 3). *TAL1* rs2984618 was found to be significantly associated with major depressive disorder when adjusted for sex, age, and ethnicity (OR = 1.11; 95% CI, 1.05–1.18; $P = 1.79\times10^{-4}$). The association was slightly attenuated by further adjustment for BMI (OR = 1.10; 95% CI, 1.04–1.17; $P = .001$). No significant association between the other 20 obesity SNPs and major depressive disorder ($.08 \le P \le .98$) was observed. For these 20 SNPs, further adjustment for BMI gave similar results ($.08 \le P \le .99$). The genotype score, with or without adjustment for BMI, was not associated with major depressive disorder (OR = 1.01; 95% CI, 0.99–1.02; $P = .43$ and OR = 1.01; 95% CI, 0.99–1.02; $P = .46$, respectively). No association with major depressive disorder at baseline was found, even after adding the *FTO* rs9939609 SNP to the genotype

Table 3. Association of Obesity SNPs With Major Depressive Disorder in EpiDREAM

Gene[a]	SNP	Risk Allele	Adjusted OR (95% CI)[b]	P[c]	Adjusted OR (95% CI)[b] Including BMI as Covariate	P[c]
TNN13K	rs1514176	G	1.04 (0.99–1.10)	.14	1.05 (0.99–1.11)	.12
PCSK1	rs6235	C	1.02 (0.96–1.09)	.45	1.02 (0.96–1.09)	.53
PCSK1	rs6232	G	0.96 (0.83–1.10)	.55	0.95 (0.82–1.10)	.51
CDKAL1	rs2206734	C	0.98 (0.91–1.05)	.58	0.97 (0.91–1.04)	.45
TFAP2B	rs2272903	G	1.06 (0.98–1.15)	.15	1.06 (0.98–1.15)	.14
NTRK2	rs1211166	A	0.98 (0.92–1.05)	.64	0.97 (0.91–1.04)	.46
BDNF	rs6265	G	1.01 (0.93–1.08)	.87	1.01 (0.94–1.09)	.73
BDNF	rs1401635	C	0.99 (0.94–1.06)	.98	0.99 (0.93–1.06)	.88
MAP2K5	rs997295	T	0.98 (0.93–1.04)	.58	0.98 (0.93–1.04)	.56
NPC1	rs1805081	A	1.01 (0.95–1.07)	.73	1.02 (0.96–1.09)	.47
TOMM40/APOE/APOC1	rs2075650	A	1.03 (0.95–1.12)	.44	1.03 (0.95–1.12)	.43
GIPR	rs11671664	G	1.02 (0.93–1.12)	.67	1.01 (0.92–1.11)	.78
TAL1	rs2984618	T	1.11 (1.05–1.18)	**1.787×10^{-4}**	1.10 (1.04–1.17)	**.001**
LEPR	rs1011527	A	0.95 (0.86–1.04)	.27	0.95 (0.86–1.05)	.35
POMC	rs7605927	G	1.00 (0.94–1.06)	.97	1.00 (0.94–1.06)	.99
USP37	rs611203	G	1.01 (0.96–1.07)	.71	1.01 (0.95–1.07)	.72
ITIH4	rs2535633	G	0.99 (0.93–1.04)	.60	0.88 (0.70–1.11)	.29
NT5C2	rs3824755	C	0.94 (0.87–1.02)	.14	0.94 (0.87–1.02)	.15
TCF7L2	rs7903146	C	1.02 (0.96–1.08)	.53	1.01 (0.95–1.07)	.72
ALDH2/MYL2	rs671	G	0.58 (0.31–1.08)	.08	0.57 (0.31–1.06)	.08
KAT8	rs749767	A	0.97 (0.91–1.02)	.25	0.95 (0.91–1.03)	.28
Genotype score without *FTO* rs9939609			1.01 (0.99–1.02)	.46	1.01 (0.99–1.02)	.43
Genotype score with *FTO* rs9939609			1.01 (0.99–1.02)	.82	1.00 (0.99–1.02)	.85

[a]See Table 2 for full gene names.
[b]All regressions adjusted for sex, age, and ethnicity.
[c]Bold means $P < .05$.
Abbreviations: BMI = body mass index, SE = standard error, SNP = single-nucleotide polymorphism.

score (OR = 1.00; 95% CI, 0.99–1.02; $P = .85$ and OR = 1.01; 95% CI, 0.99–1.02; $P = .82$, with or without adjustment for BMI).

Interaction Between Ethnicity, Obesity SNPs, the Genotype Score, and Major Depression

Since ethnicity was significantly associated with the prevalence of major depressive disorder in our sample, we tested the impact of European (54%)/non-European (46%) ancestry on the association between obesity SNPs, the genotype score, and major depressive disorder (Supplementary eTable 4). The rs1401635 in *BDNF* showed a significant interaction with European/non-European ancestry on depression (OR = 1.27; 95% CI, 1.12–1.44; $P_{interaction} = 2.73 \times 10^{-4}$). While the *BDNF* rs1401635 obesity-risk allele is nominally associated with a lower risk of depression in non-Europeans (OR = 0.88; 95% CI, 0.80–0.97; $P = .01$), an inverse nominal association is observed in Europeans (OR = 1.11; 95% CI, 1.02–1.20; $P = .02$).

DISCUSSION

Our data suggest that shared common genetic variants may play a minor role in explaining the positive association between obesity and depression observed in the literature[14,32] as well as in our sample. We had a statistical power > 80% to detect odds ratios as modest as 1.10 at the nominal level of significance and an odds ratio of 1.15 at the Bonferroni-adjusted significance level across a broad range of allele frequencies in our sample (Supplementary eFigure 2).

Of the 21 obesity gene variants in this study, the *TAL1* rs2984618 obesity-risk allele was positively associated with major depressive disorder in a multiethnic context. *TAL1* (also named *SCL* or *TCL5*) is a transcriptionally complex gene that is expressed throughout development, activating or repressing transcription in hematopoietic, neural, and endothelial precursors.[33] Interestingly, rare homozygous mutations in the SCL/TAL1 interrupting locus (*STIL*) gene result in microcephaly and mental retardation.[34] Furthermore, *BDNF* rs1401635 had a significant association with major depressive disorder, but since the direction of effect was discovered to be ethnic-dependent, this association was detectable only after stratifying by European/non-European ancestry. *BDNF* rs1401635 obesity-risk allele protected against major depressive disorder in non-Europeans but contributed to the risk of major depressive disorder in Europeans. A likely explanation for this observation is that the effect of *BDNF* rs1401635 is not causal, but rather, the SNP is in linkage disequilibrium with the actual causal variant for major depressive disorder with flip-flop phenomenon across ethnic groups.[35] Gene × gene or gene × environment interactions are other possible explanations for this observation.[36] *BDNF* is an excellent candidate gene to link obesity and mood disorders. Brain-derived neurotrophic factor and its high-affinity receptor tropomyosin-related kinase B regulate the development, survival, and differentiation of neurons.[37] The absence of one functional copy of BDNF is associated with hyperphagic obesity, impaired cognitive function, and hyperactivity in humans.[38] In a recent meta-analysis,[39] common genetic variation at the *BDNF* locus was associated with suicidal behavior.

The relationship between inherited obesity and depression seems to be more complex than initially thought. Our

former and current data suggest that obesity-risk alleles can both protect against (*FTO* rs9939609)[17] and contribute to (*TAL1* rs2984618) the risk of major depressive disorder, possibly in interaction with the ethnic background (*BDNF* rs1401635). The promising associations described in this study deserve further confirmation in additional large-scale multiethnic studies. No association between a genotype score, combining the information of all of the obesity SNPs, and depression with or without the *FTO* rs9939609 SNP was observed. Taken together, our results from 21 obesity gene variants suggest that the association between obesity and depression at the clinical level may be explained, at least in part, by genetic factors.

Our results are in line with the twin study by Afari et al[15] that reported that only a minority (12%) of genetic determinants of obesity are shared with depression. On the contrary, our results are inconsistent with the recent report that an obesity genotype score (based on the information of 31 SNPs) was positively associated with depressive symptoms.[18] However, their particular study[18] differs from our present study in the following ways: (1) a modest sample size (N = 1,731 persons), (2) lack of correction for multiple tests, (3) a different SNP selection, and (4) a non-multiethnic population. Therefore, because there are inherent differences between the study by Jokela et al[18] and our present study, our conclusions are not mutually exclusive. Supporting this view, and more consistent with our findings, an adequately powered study[40] in 2,430 depression cases and 792 controls from Europe found no association between depression and a 32 SNP obesity genotype score.

Environmental causes, well-documented in the literature, are likely to play a more important role in the pathogenesis of major depressive disorder than shared molecular determinants of obesity and depression.[14,32] For instance, weight gain is a well-recognized side effect of certain antidepressant medications.[41] Low self-esteem and psychological distress from negative body image and the stigmatization of obesity may also explain the link between obesity and subsequent risk of depression.[42,43]

The study of common genetic variants was able to provide additional information to investigate the hypothesis of a shared genetic architecture as suggested by a heritability study.[15] In our current study, we were able to demonstrate that the association between common obesity gene variants and major depressive disorder can go in both directions. Some common variants may protect against while others may contribute to the risk of major depressive disorder. Therefore, the use of genotype score for these types of studies should be interpreted with caution. Furthermore, ethnicity seems to be an additional factor that contributes to the complex association. Studying obesity-associated SNPs in multiethnic contexts may mask the apparent ethnic-dependent effect of the gene variant on major depressive disorder.

Only 6 of 21 SNPs displayed a nominal association with BMI in our sample. This is most likely due to the limited power of our study to detect the modest effect size of these SNPs on BMI. Reaching an appropriate statistical power has become an issue[36] with the emergence of large-scale discovery studies through international consortiums. However, the facts that (1) 18 of 21 SNPs show a direction of effect for BMI consistent with previous reports; (2) the genotype score was strongly associated with BMI ($P = 1.99 \times 10^{-10}$); and (3) no interaction between European/non-European ancestry and SNPs/genotype score was found on BMI confirm the worldwide relevance of SNPs identified in diverse ethnic groups.[44]

Strengths and Limitations

Our study has several strengths including a large and adequately powered sample representative of global ethnic diversity, objectively measured BMI, and a structured face-to-face assessment of major depressive disorder in the previous 12 months. In addition, our study includes the use of a genotype score that reflects the overall effect of genetic predisposition to obesity on major depressive disorder. However, we are aware that the use of such a genotype score is less relevant if obesity-risk alleles can both protect against and contribute to the risk of depression, which is the case for SNPs in *FTO* and *TAL1*.

There are some limitations in our study. Due to limited genotype data from our 50,000 SNP array, we were unable to analyze an exhaustive list of obesity-associated SNPs. Around 120 binary obesity-/BMI-associated gene loci have been identified to date, but we had genotype information for only 22 SNPs.[10,45] Also, the multiethnic nature of our sample may add genetic heterogeneity and lower the statistical power in the context of ethnic-specific associations. Furthermore, the efficiency of proxy SNPs identified by GWAS in a specific population to tag causal variants may not be optimal in other ethnic groups. We were not able to investigate the effects of rare mutations or structural variants contributing to monogenic forms of obesity on major depressive disorder, and such investigations may nicely complement the present study. Psychiatric symptoms including emotional lability have indeed been reported in monogenic obese children.[38,46,47] Testing the reciprocal association of depression SNPs on obesity-related traits may have strengthened our conclusions. However, no genetic variant to date has been definitively associated with depression in GWAS.[48] Our definition for major depressive disorder used for this study may be considered a limitation. Depression is a chronic illness, but we assessed for major depressive episode(s) only 12 months prior to the recording of baseline BMI. We also acknowledge that the diagnosis of depression may be biased by the stigma associated with mental illness or traditional illness beliefs within different ethnic groups. However, since major depressive disorder is a more severe form of depression, the risk of misclassification is lower. The cross-sectional nature of this study precludes causal inferences to be made about the association between obesity and depression. The enrichment of obese, impaired fasting glucose/impaired

glucose tolerance, and type 2 diabetes cases in EpiDREAM also prevents the generalization of our conclusions to the entire population.

In conclusion, our data support the claim that the association between obesity and major depressive disorder at the observational epidemiology level may be explained, at least in part, by shared genetic factors. However, the contribution of genetics to this relationship is complex due to factors such as bidirectional contributions by different genetic variants and ethnic-dependent genetic effects. This study is the first to our knowledge that combines the power of both observational epidemiology and molecular genetics to decipher the associations between obesity and depression in a multiethnic context.

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Author contributions: Dr Meyre conceived this study and designed the methods. Drs Samaan and Meyre and Ms Lee analyzed and interpreted the data. Dr Meyre and Ms Lee wrote the manuscript. Drs Samaan, Gerstein, Engert, Bosch, Mohan, Diaz, Yusuf, and Anand critically reviewed the manuscript. Drs Gerstein, Engert, Bosch, Mohan, Diaz, Yusuf, and Anand collected the data for the EpiDREAM study. All authors read and approved the final manuscript.

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Supplementary material: See accompanying pages.

Additional information: The data coordination site of the EpiDREAM and DREAM studies is the Population Health Research Institute (Hamilton, Ontario, Canada). The Population Health Research Institute controls the access to the EpiDREAM and DREAM data and owns the databases.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Obesity Genes and Risk of Major Depression in a Multiethnic Population

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List of Supplementary Material for the article

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Supplementary Table 1. LD parameters between *PCSK1* rs6232 & rs6235 *BDNF* rs6265 & rs1401635

	Gene	*PCSK1* rs6232 and *PCSK1* s6235		*BDNF* rs6265 and *BDNF* rs1401635	
		r2	D'	r2	D'
Ethnicity	South Asian	0.084	0.801	0.087	1
	East Asian	0.199	1	0.082	1
	European	0.106	0.896	0.083	0.993
	African	0.089	0.879	0.097	1
	Latin American	0.118	0.934	0.078	1
	Native North American	0.11	0.893	0.089	1
Notes		Calculated from Epidream		Calculated from Epidream	

Supplementary Table 2. Genotype distributions of 21 obesity SNPs in the EpiDREAM Study.

				All						Depression cases						Depression controls					
Ethnicity	Major allele	Minor allele	Obesity risk allele	Genotype count			Obesity risk allele frequency	Call rate (%)	HWE *P*-value	Genotype count			Obesity risk allele frequency	Call rate (%)	HWE *P*-value	Genotype count			Obesity risk allele frequency	Call rate (%)	HWE *P*-value
rs1514176 – *TNNI3K*																					
				AA	GA	GG				AA	GA	GG				AA	GA	GG			
South Asian	A	G	G	566	1360	834	0.549	100	0.788	40	98	55	0.539	100	0.763	526	1262	779	0.549	100	0.719
East Asian				35	70	120	0.689	100	0.00004	3	5	15	0.761	100	0.054	32	65	105	0.681	100	0.0002
European				3173	4551	1654	0.419	100	0.751	580	853	317	0.425	100	0.913	2593	3698	1337	0.418	100	0.767
African				137	552	560	0.669	100	0.956	29	101	97	0.650	100	0.736	108	451	463	0.674	100	0.906
Latino				806	1565	921	0.518	100	0.006	192	440	282	0.549	100	0.401	614	1125	639	0.505	100	0.009
Native*				97	246	157	0.560	100	0.971	22	37	43	0.603	100	0.014	75	209	114	0.549	100	0.228
Total				4814	8344	4246	0.484	100	N.A.	866	1534	809	0.491	100	N.A.	3948	6810	3437	0.482	100	N.A.
rs6235 – *PCSK1*																					
				CC	CG	GG				CC	CG	GG				CC	CG	GG			
South Asian	G	C	C	261	1096	1402	0.293	99.964	0.029	18	83	91	0.310	99.482	0.882	243	1013	1311	0.292	100	0.021
East Asian				20	93	112	0.296	100	0.912	2	12	9	0.348	100	0.472	18	81	103	0.290	100	0.717
European				685	3612	5080	0.266	99.989	0.218	131	664	955	0.265	100	0.296	554	2948	4125	0.266	99.987	0.387
African				27	329	893	0.153	100	0.607	7	68	152	0.181	100	0.856	20	261	741	0.147	100	0.590
Latino				157	1086	2049	0.213	100	0.396	44	299	571	0.212	100	0.548	113	787	1478	0.213	100	0.531
Native*				27	189	284	0.243	100	0.539	3	41	58	0.230	100	0.178	24	148	226	0.246	100	0.972
Total				1177	6405	9820	0.252	99.989	N.A.	205	1167	1836	0.246	99.969	N.A.	972	5238	7984	0.253	99.993	N.A.
rs6232 – *PCSK1*																					
				AA	GA	GG				AA	GA	GG				AA	GA	GG			
South Asian	A	G	G	2435	309	16	0.062	100	0.073	168	24	1	0.067	100	0.887	2267	285	15	0.061	100	0.067
East Asian				223	2	0	0.004	100	0.947	22	1	0	0.022	100	0.915	201	1	0	0.003	100	0.972
European				8490	865	23	0.049	100	0.845	1589	159	2	0.047	100	0.334	6901	706	21	0.049	100	0.513
African				1231	18	0	0.007	100	0.798	225	2	0	0.004	100	0.947	1006	16	0	0.008	100	0.801
Latino				3104	185	3	0.029	100	0.887	864	50	0	0.027	100	0.395	2240	135	3	0.030	100	0.517
Native*				471	29	0	0.029	100	0.504	100	2	0	0.010	100	0.920	371	27	0	0.034	100	0.484
Total				15954	1408	42	0.043	100	N.A.	2968	238	3	0.038	100	N.A.	12986	1170	39	0.044	100	N.A.
rs2206734 – *CDKAL1*																					
				CC	TC	TT				CC	TC	TT				CC	TC	TT			
South Asian	C	T	C	1627	973	160	0.766	100	0.363	114	60	19	0.746	100	0.013	1513	913	141	0.767	100	0.832
East Asian				102	94	29	0.662	100	0.321	12	11	0	0.761	100	0.132	90	83	29	0.651	100	0.174
European				6012	3019	346	0.802	99.989	0.169	1107	576	67	0.797	100	0.459	4905	2443	279	0.803	99.987	0.240
African				715	462	72	0.757	100	0.817	126	90	11	0.753	100	0.315	589	372	61	0.758	100	0.824
Latino				2107	1049	136	0.799	100	0.705	587	293	34	0.803	100	0.731	1520	756	102	0.798	100	0.515
Native*				299	183	18	0.781	100	0.118	65	34	3	0.804	100	0.563	234	149	15	0.775	100	0.140
Total				10862	5780	761	0.790	99.994	N.A.	2011	1064	134	0.793	100	N.A.	8851	4716	627	0.799	99.993	N.A.
rs2272903 – *TFAP2B*																					
				AA	AG	GG				AA	AG	GG				AA	AG	GG			
South Asian	G	A	G	132	946	1682	0.781	100	0.945	3	67	123	0.811	100	0.067	129	879	1559	0.779	100	0.723
East Asian				8	77	140	0.793	100	0.513	0	7	16	0.848	100	0.389	8	70	124	0.787	100	0.628
European				119	1778	7481	0.893	100	0.251	15	342	1393	0.894	100	0.230	104	1436	6088	0.892	100	0.066
African				121	487	641	0.708	100	0.045	18	90	119	0.723	100	0.865	103	397	522	0.705	100	0.035
Latino				72	784	2436	0.859	100	0.342	22	221	671	0.855	100	0.456	50	563	1765	0.861	100	0.517
Native*				4	100	396	0.892	100	0.395	0	15	87	0.927	100	0.423	4	85	309	0.883	100	0.486
Total				456	4172	12776	0.854	100	N.A.	58	742	2409	0.866	100	N.A.	398	3430	10367	0.851	100	N.A.

rs1211166 – *NTRK2*																		
				AA	GA	GG				AA	GA	GG				AA	GA	GG			
South Asian	A	G	A	1440	1104	216	0.722	100	0.828	104	68	21	0.715	100	0.060	1336	1036	195	0.722	100	0.765
East Asian				151	63	11	0.811	100	0.196	14	9	0	0.804	100	0.243	137	54	11	0.812	100	0.076
European				6118	2893	365	0.807	99.979	0.320	1119	559	72	0.799	100	0.835	4999	2334	293	0.809	99.974	0.319
African				568	541	139	0.672	99.920	0.552	95	107	24	0.657	99.559	0.447	473	434	115	0.675	100	0.308
Latino				2117	1021	154	0.798	100	0.032	590	287	37	0.803	100	0.777	1527	734	117	0.797	100	0.019
Native*				379	111	10	0.869	100	0.577	79	18	5	0.863	100	0.010	300	93	5	0.871	100	0.459
Total				10773	5733	895	0.7847	99.983	N.A.	2001	1048	159	0.787	99.969	N.A.	8772	4685	736	0.783	99.986	N.A.
rs6265 – *BDNF*																					
				AA	AG	GG				AA	AG	GG				AA	AG	GG			
South Asian	G	A	G	146	954	1660	0.774	100	0.558	11	77	105	0.744	100	0.522	135	877	1555	0.777	100	0.434
East Asian				46	117	62	0.536	100	0.497	3	13	7	0.587	100	0.427	43	104	55	0.530	100	0.636
European				345	2807	6226	0.814	100	0.196	67	506	1177	0.817	100	0.175	278	2301	5049	0.813	100	0.430
African				4	74	1171	0.967	100	0.018	0	15	212	0.967	100	0.607	4	59	959	0.967	100	0.004
Latino				94	862	2336	0.841	100	0.182	23	226	665	0.851	100	0.470	71	636	1671	0.836	100	0.270
Native*				14	128	358	0.844	100	0.534	4	29	69	0.819	100	0.667	10	99	289	0.851	100	0.663
Total				649	4942	11813	0.821	100	N.A.	108	866	2235	0.831	100	N.A.	541	4076	9578	0.818	100	N.A.
rs1401635 – *BDNF*																					
				CC	CG	GG				CC	CG	GG				CC	CG	GG			
South Asian	G	C	C	424	1255	1080	0.381	99.964	0.060	20	84	89	0.321	100	0.978	404	1171	991	0.386	99.961	0.062
East Asian				4	28	193	0.080	100	0.020	1	6	16	0.174	100	0.659	3	22	177	0.069	100	0.027
European				823	3801	4753	0.290	99.989	0.109	167	734	849	0.305	100	0.648	656	3067	3904	0.287	99.987	0.125
African				77	478	694	0.253	100	0.659	16	76	135	0.238	100	0.248	61	402	559	0.256	100	0.312
Latino				156	1120	2016	0.218	100	0.978	47	289	578	0.209	100	0.170	109	831	1438	0.221	100	0.425
Native*				28	169	303	0.225	100	0.491	3	33	66	0.191	100	0.641	25	136	237	0.234	100	0.360
Total				1512	6851	9039	0.284	99.989	N.A.	254	1222	1733	0.270	100	N.A.	1258	5629	7306	0.287	99.986	N.A.
rs997295 – *MAP2K5*																					
				GG	GT	TT				GG	GT	TT				GG	GT	TT			
South Asian	T	G	T	838	1336	586	0.454	100	0.212	59	89	45	0.464	100	0.312	779	1247	541	0.454	100	0.311
East Asian				151	63	11	0.189	100	0.196	14	8	1	0.217	100	0.915	137	55	10	0.186	100	0.157
European				1597	4497	3284	0.590	100	0.390	316	842	592	0.579	100	0.582	1281	3655	2692	0.592	100	0.499
African				262	617	370	0.543	100	0.872	49	111	67	0.540	100	0.811	213	506	303	0.544	100	0.948
Latino				995	1586	710	0.457	99.970	0.098	285	420	209	0.458	100	0.024	710	1166	501	0.456	99.958	0.582
Native*				168	223	109	0.441	100	0.033	37	38	27	0.451	100	0.012	121	185	82	0.445	100	0.470
Total				4011	8322	5070	0.530	99.994	N.A.	760	1508	941	0.528	100	N.A.	3251	6814	4129	0.531	99.993	N.A.
rs1805081 – *NPC1*																					
				AA	GA	GG				AA	GA	GG				AA	GA	GG			
South Asian	A	G	A	1634	971	155	0.768	100	0.497	107	70	16	0.736	100	0.350	1527	901	139	0.770	100	0.686
East Asian				133	77	15	0.762	100	0.402	15	8	0	0.861	100	0.313	118	69	15	0.755	100	0.275
European				3549	4387	1442	0.612	100	0.155	680	801	269	0.617	100	0.193	2869	3586	1173	0.611	100	0.342
African				1085	158	6	0.932	100	0.923	200	26	1	0.938	100	0.876	885	132	5	0.931	100	0.974
Latino				1591	1373	328	0.692	100	0.209	454	370	90	0.700	100	0.254	1167	1003	238	0.693	100	0.297
Native*				224	232	44	0.680	100	0.139	55	40	7	0.735	100	0.940	169	192	37	0.666	100	0.094
Total				8216	7198	1990	0.679	100	N.A.	1511	1315	383	0.674	100	N.A.	6705	5883	1607	0.680	100	N.A.
rs2075650 – *APOE*																					
				AA	GA	GG				AA	GA	GG				AA	GA	GG			
South Asian	A	G	A	2088	621	51	0.869	100	0.541	149	41	3	0.878	100	0.926	1939	580	48	0.866	100	0.546
East Asian				173	47	5	0.873	100	0.402	19	3	1	0.913	100	0.117	154	44	4	0.871	100	0.682
European				6951	2246	181	0.861	100	0.978	1318	398	34	0.867	100	0.537	5633	1848	147	0.860	100	0.749

African				958	278	13	0.878	100	0.146	176	48	3	0.881	100	0.893	782	230	10	0.878	100	0.123
Latino				2598	647	47	0.888	100	0.355	715	188	11	0.885	100	0.730	1883	459	36	0.888	100	0.189
Native*				399	96	5	0.894	100	0.771	80	22	0	0.892	100	0.222	319	74	5	0.895	100	0.763
Total				13167	3935	302	0.870	100	N.A.	2457	700	52	0.875	100	N.A.	10710	3235	250	0.868	100	N.A.
rs11671664 – *GIPR*																					
				AA	AG	GG				AA	AG	GG				AA	AG	GG			
South Asian	G	A	G	33	524	2203	0.893	100	0.770	2	38	153	0.891	100	0.832	31	486	2050	0.903	100	0.717
East Asian				41	89	95	0.620	100	0.016	7	8	8	0.522	100	0.146	34	81	87	0.631	100	0.049
European				121	1766	7488	0.893	99.968	0.145	21	356	1373	0.886	100	0.699	100	1410	6115	0.894	99.961	0.069
African				15	256	978	0.886	100	0.702	2	39	186	0.905	100	0.978	13	217	792	0.881	100	0.666
Latino				29	532	2730	0.910	99.970	0.585	9	131	774	0.919	100	0.196	20	401	1956	0.907	99.958	0.912
Native*				3	102	395	0.892	100	0.189	0	16	86	0.922	100	0.390	3	86	309	0.884	100	0.256
Total				242	3269	13889	0.892	99.977	N.A.	41	588	2580	0.896	100	N.A.	201	2681	11309	0.891	99.972	N.A.
rs2984618 – *TALI*																					
				GG	GT	TT				GG	GT	TT				GG	GT	TT			
South Asian	G	T	T	556	1315	889	0.560	100	0.083	41	90	62	0.554	100	0.435	515	1225	827	0.561	100	0.113
East Asian				3	19	203	0.944	100	0.003	1	0	22	0.957	100	0.000002	2	19	181	0.943	100	0.078
European				3412	4445	1521	0.399	100	0.251	584	836	330	0.427	100	0.315	2828	3609	1191	0.393	100	0.481
African				87	485	677	0.736	100	0.991	15	97	115	0.720	100	0.363	72	388	562	0.740	100	0.653
Latino				767	1515	1010	0.537	100	0.00002	184	424	305	0.566	100	0.099	582	1091	705	0.526	100	0.0001
Native*				116	248	136	0.520	100	0.886	19	54	29	0.549	100	0.485	97	194	107	0.513	100	0.625
Total				4941	8027	4436	0.485	100	N.A.	845	1501	863	0.503	100	N.A.	4096	6526	3573	0.482	100	N.A.
rs1011527 – *LEPR*																					
				GG	AG	AA				GG	AG	AA				GG	AG	AA			
South Asian	G	A	A	1362	1146	252	0.299	100	0.624	95	81	17	0.298	100	0.964	1267	1065	235	0.299	100	0.603
East Asian				184	40	1	0.093	100	0.449	21	2	0	0.043	100	0.827	163	38	1	0.099	100	0.439
European				8040	1282	56	0.074	100	0.529	1489	249	12	0.078	100	0.653	6551	1033	44	0.073	100	0.636
African				930	293	26	0.138	100	0.605	175	50	2	0.119	100	0.443	755	243	24	0.142	100	0.400
Latino				2851	428	13	0.069	100	0.471	811	101	2	0.057	100	0.535	2040	327	11	0.073	100	0.586
Native*				451	47	2	0.051	100	0.518	91	11	0	0.054	100	0.565	360	36	2	0.050	100	0.296
Total				13818	3236	350	0.113	100	N.A.	2682	494	33	0.087	100	N.A.	11136	2742	317	0.119	100	N.A.
rs7605927 – *POMC*																					
				CC	GC	GG				CC	GC	GG				CC	GC	GG			
South Asian	C	G	G	795	1366	599	0.464	100	0.788	47	107	39	0.479	100	0.124	748	1259	560	0.463	100	0.484
East Asian				39	113	73	0.576	100	0.675	4	10	9	0.609	100	0.675	35	103	64	0.572	100	0.558
European				5417	3380	581	0.242	100	0.081	1023	610	117	0.241	100	0.047	4394	2770	464	0.242	100	0.324
African				407	579	263	0.442	100	0.033	76	109	42	0.425	100	0.791	331	470	221	0.446	100	0.026
Latino				1283	1493	516	0.384	100	0.019	343	429	142	0.390	100	0.682	940	1064	374	0.381	100	0.012
Native*				208	215	77	0.369	100	0.087	43	39	20	0.387	100	0.050	165	176	57	0.364	100	0.366
Total				8149	7146	2109	0.326	100	N.A.	1536	1304	369	0.318	100	N.A.	6613	5842	1740	0.328	100	N.A.
rs611203 – *USP37*																					
				AA	GA	GG				AA	GA	GG				AA	GA	GG			
South Asian	A	G	G	1351	1106	303	0.310	100	0.001	89	85	19	0.319	100	0.843	1262	1021	284	0.310	100	0.0004
East Asian				149	66	10	0.191	100	0.442	13	9	1	0.239	100	0.718	136	57	9	0.186	100	0.343
European				3262	4515	1601	0.411	100	0.566	572	877	301	0.423	100	0.260	2690	3638	1300	0.409	100	0.242
African				452	618	179	0.391	100	0.165	85	109	33	0.479	100	0.838	367	509	146	0.392	100	0.151
Latino				1095	1632	565	0.420	100	0.305	325	451	138	0.398	100	0.365	770	1181	427	0.428	100	0.483
Native*				218	220	62	0.344	100	0.575	47	38	17	0.353	100	0.063	171	182	45	0.342	100	0.743
Total				6527	8157	2720	0.391	100	N.A.	1131	1569	509	0.403	100	N.A.	5396	6588	2211	0.388	100	N.A.
rs2535633 – *ITIH4*																					

				CC	CG	GG				CC	CG	GG				CC	CG	GG			
South Asian	C	G	G	1014	1288	458	0.399	100	0.153	72	92	29	0.389	100	0.965	942	1196	429	0.400	100	0.136
East Asian				87	111	27	0.260	100	0.351	12	7	4	0.326	100	0.140	75	104	23	0.371	100	0.144
European				3314	4495	1569	0.407	100	0.498	606	834	310	0.415	100	0.432	2708	3661	1259	0.405	100	0.715
African				125	539	585	0.684	100	0.959	26	106	95	0.652	100	0.662	99	433	490	0.691	100	0.814
Latino				894	1620	778	0.482	100	0.403	246	470	198	0.474	100	0.344	648	1150	580	0.486	100	0.119
Native*				131	245	124	0.493	100	0.658	27	46	29	0.510	100	0.324	104	199	95	0.489	100	0.992
Total				5565	8198	3541	0.442	100	N.A.	989	1555	665	0.450	100	N.A.	4576	6743	2876	0.440	100	N.A.
rs3824755 – *NT5C2*																					
				GG	GC	CC				GG	GC	CC				GG	GC	CC			
South Asian	G	C	C	1620	962	178	0.239	100	0.031	113	70	10	0.233	100	0.843	1507	892	168	0.239	100	0.022
East Asian				110	100	15	0.289	100	0.220	7	16	0	0.348	100	0.011	103	84	15	0.282	100	0.706
European				7610	1664	104	0.100	100	0.224	1447	286	17	0.091	100	0.495	6163	1378	87	0.102	100	0.313
African				808	396	45	0.195	100	0.681	155	66	6	0.172	100	0.744	653	330	39	0.200	100	0.736
Latino				2292	906	94	0.166	100	0.696	632	254	28	0.170	100	0.687	1660	652	66	0.165	100	0.837
Native*				369	123	8	0.139	100	0.535	74	26	2	0.147	100	0.871	295	97	6	0.137	100	0.535
Total				12809	4151	444	0.145	100	N.A.	2428	718	63	0.132	100	N.A.	10381	3433	381	0.148	100	N.A.
rs7903146 – *TCF7L2*																					
				TT	TC	CC				TT	TC	CC				TT	TC	CC			
South Asian	C	T	C	272	1174	1314	0.689	100	0.680	21	86	86	0.668	100	0.942	251	1088	1228	0.690	100	0.658
East Asian				2	22	201	0.942	100	0.126	1	4	18	0.870	100	0.263	1	18	183	0.950	100	0.450
European				956	3904	4518	0.690	100	0.009	170	731	849	0.694	100	0.490	786	3173	3669	0.689	100	0.010
African				112	522	615	0.701	100	0.935	22	93	112	0.698	100	0.675	90	429	503	0.702	100	0.914
Latino				280	1307	1705	0.716	100	0.190	72	359	483	0.725	100	0.643	208	948	1222	0.713	100	0.214
Native*				10	145	345	0.835	100	0.241	2	32	68	0.824	100	0.423	8	113	277	0.838	100	0.365
Total				1632	7074	8698	0.703	100	N.A.	288	1305	1616	0.707	100	N.A.	1344	5769	7082	0.702	100	N.A.
rs671 – *ALDH2*																					
				AA	AG	GG				AA	AG	GG				AA	AG	GG			
South Asian	G	T	G	0	1	2759	1.000	100	0.992	0	0	193	1.000	100	N.A.	0	1	2566	1.000	100	0.992
East Asian				12	54	159	0.827	100	0.015	4	5	14	0.717	100	0.026	8	49	145	0.839	100	0.149
European				0	1	9377	1.000	100	0.996	0	0	1750	1.000	100	N.A.	0	1	7627	1.000	100	0.995
African				0	3	1246	0.999	100	0.966	0	0	227	1.000	100	N.A.	0	3	1019	0.999	100	0.963
Latino				0	1	3291	1.000	100	0.993	0	1	913	0.999	100	0.987	0	0	2378	1.000	100	N.A.
Native*				0	0	500	1.000	100	N.A.	0	0	102	1.000	100	N.A.	0	0	398	1.000	100	N.A.
Total				12	60	17332	0.998	100	N.A.	4	6	3199	0.998	100	N.A.	8	54	14133	0.998	100	N.A.
rs749767– *KAT8*																					
				GG	GA	AA				GG	GA	AA				GG	GA	AA			
South Asian	A	G	A	54	622	2084	0.868	100	0.342	3	45	145	0.868	100	0.817	51	577	1939	0.868	100	0.294
East Asian				154	60	11	0.182	100	0.114	17	5	1	0.152	100	0.450	137	55	10	0.186	100	0.157
European				1434	4479	3465	0.608	100	0.830	288	839	623	0.596	100	0.845	1146	3640	2842	0.611	100	0.726
African				111	497	641	0.712	100	0.299	20	97	110	0.698	100	0.833	91	400	531	0.715	100	0.211
Latino				717	1561	1014	0.545	100	0.012	206	420	288	0.545	100	0.026	511	1141	726	0.545	100	0.113
Native*				109	233	158	0.549	100	0.187	18	49	35	0.583	100	0.905	91	184	123	0.540	100	0.166
Total				2579	7452	7373	0.638	100	N.A.	552	1455	1202	0.601	100	N.A.	2027	5997	6171	0.646	100	N.A.

*Native = Native North American

Supplementary Table 3. Distribution of depression cases and controls within each ethnicity.

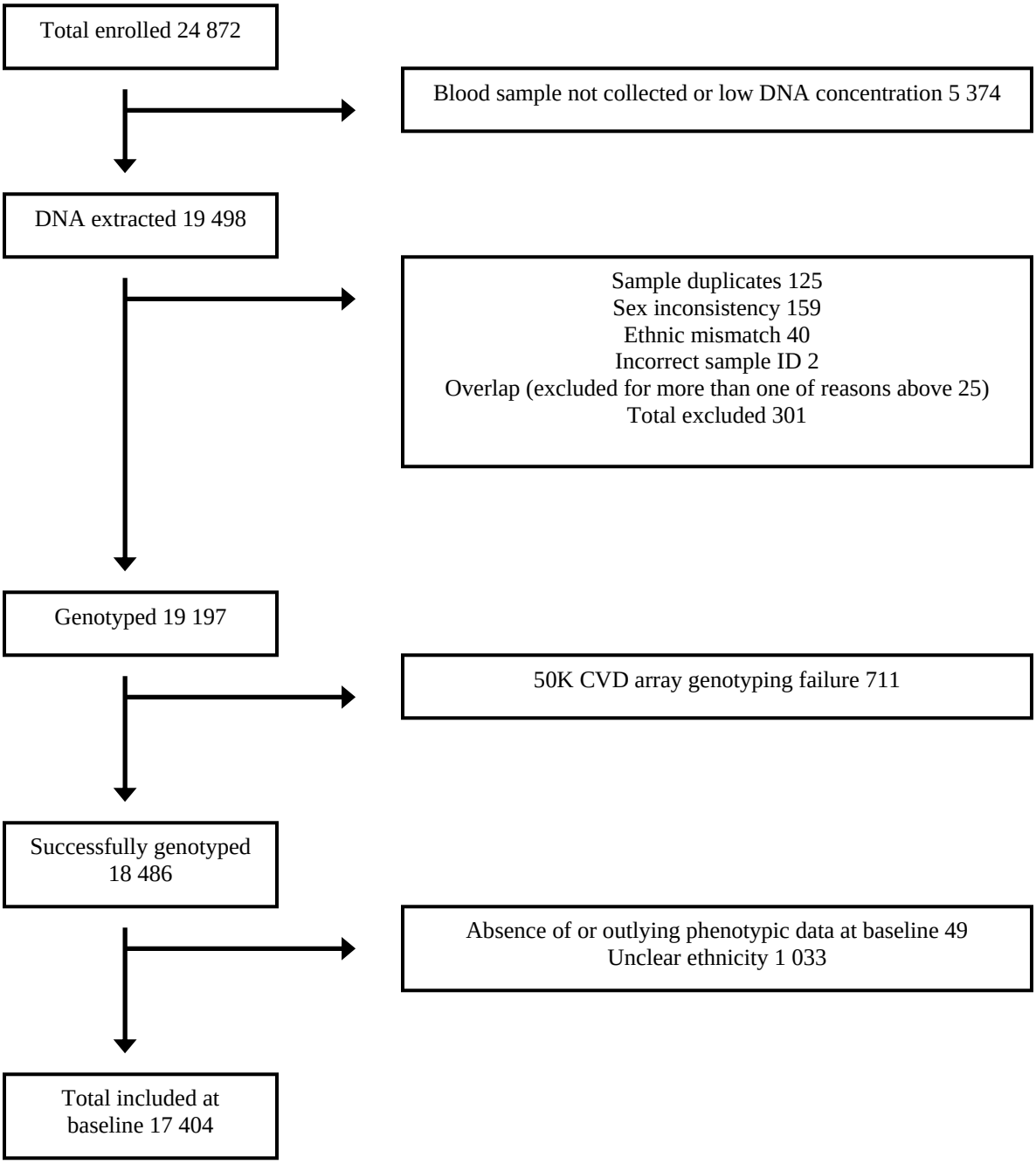
Ethnicity	Depression cases (%)	Controls (%)
South Asian	193 (7.0)	2567 (93.0)
East Asian	23 (10.2)	202 (89.8)
European	1750 (18.7)	7628 (81.3)
African	227 (18.2)	1022 (81.8)
Latin American	914 (27.8)	2378 (72.2)
Native North American	102 (20.4)	398 (79.6)

Supplementary Table 4. Interaction between obesity SNPs and European ancestry on depression status (adjusted for sex, age, BMI, European/Non-European subgroup, and population substructure).

		SNP Main effect		SNP x European ancestry Interaction	
Gene	**rs**	**OR [95% CI]**	***p***	**OR [95% CI]**	***p***
TNN13K	rs1514176	1.050 [0.964-1.143]	0.264	0.974 [0.870-1.091]	0.653
PCSK1	rs6235	1.077 [0.974-1.192]	0.147	0.922 [0.809-1.052]	0.228
PCSK1	rs6232	1.012 [0.789-1.297]	0.926	0.940 [0.693-1.275]	0.690
CDKAL1	rs2206734	0.998 [0.900-1.105]	0.964	0.963 [0.838-1.106]	0.593
TFAP2B	rs2272903	1.082 [0.967-1.210]	0.168	0.955 [0.810-1.126]	0.585
NTRK2	rs1211166	1.001 [0.907-1.106]	0.981	0.955 [0.833-1.094]	0.505
BDNF	rs6265	0.961 [0.854-1.082]	0.514	1.076 [0.925-1.253]	0.342
BDNF	rs1401635	0.880 [0.797-0.972]	**0.012**	1.269 [1.116-1.442]	**2.734×10^{-4}**
MAP2K5	rs997295	1.056 [0.970-1.105]	0.207	0.925 [0.826-1.036]	0.178
NPC1	rs1805081	1.028 [0.932-1.134]	0.583	0.951 [0.839-1.077]	0.428
APOE	rs2075650	1.001 [0.879-1.141]	0.987	1.023 [0.862-1.213]	0.794
GIPR	rs11671664	1.121 [0.972-1.293]	0.116	0.836 [0.695-1.006]	0.058
TAL1	rs2984618	1.023 [0.938-1.116]	0.607	1.107 [0.987-1.242]	0.082
LEPR	rs1011527	0.854 [0.742-0.982]	**0.026**	1.239 [1.017-1.509]	**0.034**
POMC	rs7605927	0.965 [0.885-1.052]	0.419	1.013 [0.897-1.145]	0.831
USP37	rs611203	0.956 [0.877-1.044]	0.317	1.115 [0.993-1.251]	0.065
ITIH4	rs2535633	0.913 [0.839-0.995]	**0.037**	1.128 [1.006-1.264]	**0.039**
NT5C2	rs3824755	0.952 [0.853-1.062]	0.378	0.931 [0.787-1.120]	0.406
TCF7L2	rs7903146	0.958 [0.872-1.053]	0.375	1.103 [0.975-1.248]	0.120
ALDH2	rs671	0.538 [0.287-1.010]	0.054	NA*	
KAT8	rs749767	1.010 [0.924-1.104]	0.828	0.953 [0.847-1.071]	0.419
Gene Score without *FTO* rs9939609		0.991 [0.970-1.013]	0.421	1.022 [0.992-1.052]	0.148
Gene Score with *FTO* rs9939609		0.987 [0.966-1.008]	0.232	1.022 [0.994-1.052]	0.129

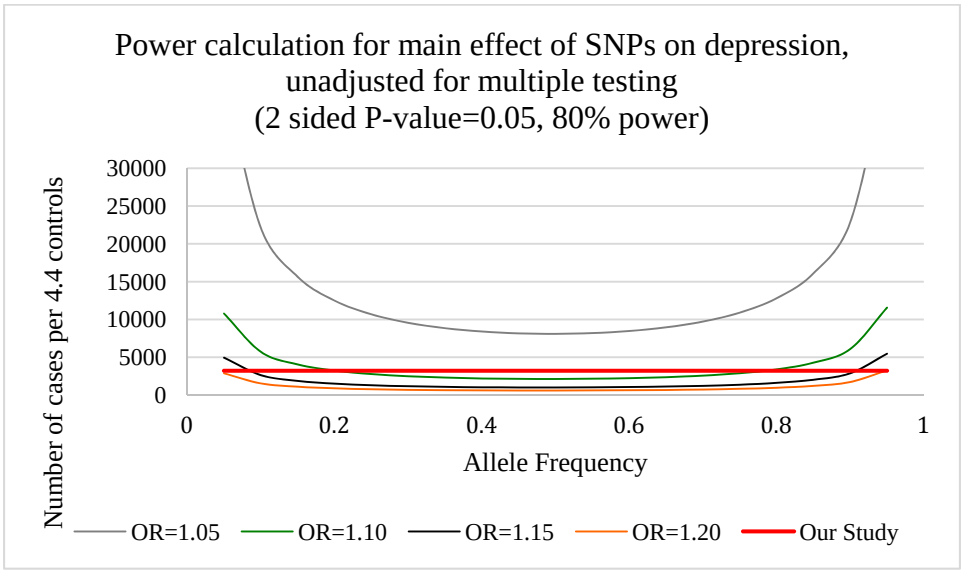
*Note: Only one TC and no TT carrier in the European group.

Supplementary Figure 1. Flow chart of the EpiDREAM study.



Supplementary Figure 2. Case numbers needed to achieve 80% of statistical power according to allele frequency and odds-ratio. The horizontal line corresponds to the EpiDREAM study (3 209 depression cases and 14 195 non depressed controls). **A**-Number of cases needed for a statistical power of 80% according to risk allele frequency and odds ratio, assuming a two-sided *P*-value of 0.05 unadjusted for multiple testing and an unequal number of cases and controls (1:4.4). **B**-Number of cases needed for a statistical power of 80% according to risk allele frequency and odds ratio, assuming a two-sided P-value of 0.05 after adjustment for multiple testing (corresponding to an unadjusted P-value of P of 0.0007) and an unequal number of cases and controls (1 *versus* 4.4).

A



B