

Genetic Association of Major Depression With Atypical Features and Obesity-Related Immunometabolic Dysregulations

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IMPORTANCE The association between major depressive disorder (MDD) and obesity may stem from shared immunometabolic mechanisms particularly evident in MDD with atypical features, characterized by increased appetite and/or weight (A/W) during an active episode.

OBJECTIVE To determine whether subgroups of patients with MDD stratified according to the A/W criterion had a different degree of genetic overlap with obesity-related traits (body mass index [BMI] and levels of C-reactive protein [CRP] and leptin).

DESIGN, SETTING, AND PATIENTS This multicenter study assembled genome-wide genotypic and phenotypic measures from 14 data sets of the Psychiatric Genomics Consortium. Data sets were drawn from case-control, cohort, and population-based studies, including 26 628 participants with established psychiatric diagnoses and genome-wide genotype data. Data on BMI were available for 15 237 participants. Data were retrieved and analyzed from September 28, 2015, through May 20, 2017.

MAIN OUTCOMES AND MEASURES Lifetime *DSM-IV* MDD was diagnosed using structured diagnostic instruments. Patients with MDD were stratified into subgroups according to change in the *DSM-IV* A/W symptoms as decreased or increased.

RESULTS Data included 11 837 participants with MDD and 14 791 control individuals, for a total of 26 628 participants (59.1% female and 40.9% male). Among participants with MDD, 5347 (45.2%) were classified in the decreased A/W and 1871 (15.8%) in the increased A/W subgroups. Common genetic variants explained approximately 10% of the heritability in the 2 subgroups. The increased A/W subgroup showed a strong and positive genetic correlation (SE) with BMI (0.53 [0.15]; $P = 6.3 \times 10^{-4}$), whereas the decreased A/W subgroup showed an inverse correlation (-0.28 [0.14]; $P = .06$). Furthermore, the decreased A/W subgroup had a higher polygenic risk for increased BMI (odds ratio [OR], 1.18; 95% CI, 1.12-1.25; $P = 1.6 \times 10^{-10}$) and levels of CRP (OR, 1.08; 95% CI, 1.02-1.13; $P = 7.3 \times 10^{-3}$) and leptin (OR, 1.09; 95% CI, 1.06-1.12; $P = 1.7 \times 10^{-3}$).

CONCLUSIONS AND RELEVANCE The phenotypic associations between atypical depressive symptoms and obesity-related traits may arise from shared pathophysiologic mechanisms in patients with MDD. Development of treatments effectively targeting immunometabolic dysregulations may benefit patients with depression and obesity, both syndromes with important disability.

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← Editorial page 1189

+ Supplemental content

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Epidemiologic evidence has identified robust associations between depression and obesity.^{1,2} This link may be attributable to shared pathophysiologic mechanisms, such as immunometabolic pathways characterized by increased proinflammatory response and dysregulation of homeostatic hormones responsible for energy metabolism.³ Obesity is characterized by low-grade proinflammatory activation.⁴ Peripheral immune activation could trigger brain inflammatory responses participating in depressive neurochemical and/or endocrine processes (ie, depletion and degradation of tryptophan toward neurotoxic end products⁵ or hyperactivation of the hypothalamic-pituitary-adrenal axis⁶). Disrupted central signaling of the adipocyte-derived hormone leptin (suppressing food intake and promoting energy expenditure⁷) may influence mood. Development of central functional resistance blunts leptin anorexigenic (disinhibiting feeding⁷), pro-cognitive, and antidepressant effects.⁸⁻¹⁰ Leptin mood regulation may be exerted directly via receptors expressed in the hippocampus and amygdala by influencing neurogenesis and neuroplasticity in the hippocampus and cortex or by modulating the hypothalamic-pituitary-adrenal axis.¹¹⁻¹³

Establishing the role in depression of such mechanisms has been difficult. Although meta-analytic evidence provides mean effect sizes, strength and direction of the associations of depression with obesity-related indexes and biomarkers may vary considerably across different subgroups of patients owing to clinical heterogeneity. In the past decade, evidence has emerged suggesting that the link between depression and immunometabolic dysregulations is stronger, or specific, for MDD with atypical features, such as increased appetite and/or weight (A/W) and hypersomnia.¹⁴⁻²³ Other clinical characteristics linked to atypical depression are preponderance of female sex, earlier age at onset, and higher severity.^{24,25} Specific atypical symptoms may constitute major axes of variation for the associations of MDD with obesity-related features. Recently, the Netherlands Study of Depression and Anxiety (NESDA) showed that increased appetite during an active depressive episode was more strongly associated with body mass index (BMI) and levels of C-reactive protein (CRP)²⁶ and leptin.²⁷ Other atypical symptoms that commonly cluster with increased appetite showed a weaker association (increased weight)²⁷ or no association (hypersomnia)^{26,27} with these markers. Whether this covariance between depressive symptoms and obesity-related traits reflects shared genetic liabilities needs to be established. In prior work^{28,29} including approximately 3000 Dutch individuals, the contribution of BMI risk variants could be specifically detected only in patients with MDD who endorsed increased A/W symptoms.

In the present study, we scaled up genetic analyses to more than 25 000 samples from different countries from the Psychiatric Genomics Consortium (PGC) with established psychiatric diagnoses and genome-wide association study (GWAS) data. Compared with the latest study,²⁹ we were able to estimate the genetic correlations between BMI and MDD subgroups. Furthermore, we derived polygenic risk scores with enhanced predictive accuracy owing to larger discovery samples and newly developed methods. Finally, we included leptin polygenic risk scores previously not investigated. First, after strati-

Key Points

Question Is the genetic overlap with obesity-related traits (body mass index and levels of C-reactive protein and leptin) stronger in patients with major depression and the atypical symptoms of increased appetite and/or weight during an active episode?

Findings Data from a large international consortium showed that patients with depression and increased appetite and/or weight (approximately 15% of cases) carried a higher number of genetic risk variants for body mass index and levels of C-reactive protein and leptin.

Meaning The established phenotypic associations between atypical depressive symptoms and obesity-related traits may arise from shared pathophysiologic mechanisms, and development of treatments effectively targeting immunometabolic dysregulations may benefit this subgroup of patients.

fying patients according to A/W symptoms during the MDD index episodes, we validated the resulting subgroups against established clinical characteristics. Next, we estimated the contribution of common genetic variants to the underlying liabilities of the subgroups and their reciprocal correlations. Finally, we tested whether the subgroups had a differential genetic overlap with BMI and levels of CRP and leptin. Based on previous findings,^{28,29} we hypothesized a specific underlying connection between immunometabolic traits and patients with MDD endorsing the *DSM-IV* increased A/W symptoms.

Methods

Study Sample

Data were derived from the PGC MDD Working Group (PGC-MDD2) (<http://www.biorxiv.org/content/early/2017/07/24/167577>), which assembled genome-wide genotypic and phenotypic measures from 29 data sets (24 contributing cohorts), including 42 455 samples of European ancestry. Eleven data sets did not provide *DSM* items coding for A/W; in addition, 4 data sets were excluded owing to very low endorsement (<14 samples) of A/W symptoms. Thus, the main analytic sample (**Table 1**) was based on the remaining 14 data sets totaling 26 628 participants, of whom 11 837 had MDD (cases diagnosed according to *DSM-IV* lifetime MDD using structured diagnostic instruments, clinician-administered *DSM-IV* checklists, or medical record) and 14 791 were control individuals (screened in 11 of 14 data sets). Data collection was approved by each center's local institutional review board or medical ethics committee (all participating centers are listed at the end of the article), which waived the need for informed consent for use of the deidentified data sets.

Stratification of MDD Cases

Data were retrieved and analyzed from September 28, 2015, through May 20, 2017. The selected data sets included information on *DSM-IV* MDD symptoms endorsed during the index depressive episode. Items on neurovegetative symptoms were disaggregated to code separately for increase and decrease. As in previous work,²⁹ stratification of MDD cases in

Table 1. Characteristics of the PGC Data Sets Selected

Data Set	Country	Sample, No.	Female, No. (%)	No. of Control Individuals	MDD Status ^a			
					No. of Patients	A/W Subtype, No. (%)		
					Decreased	No Change	Increased	
BOMA	Germany	1648	895 (54.3)	1062	586	355 (60.6)	146 (24.9)	55 (9.4)
PsyCoLaus	Switzerland	1952	976 (50.0)	1445	507	246 (48.5)	205 (40.4)	56 (11.0)
GenRED1	United States	2363	1283 (54.3)	1344	1019	499 (49.0)	210 (20.6)	253 (24.8)
GenRED2	United States	1304	919 (70.5)	474	830	404 (48.7)	170 (20.5)	190 (22.9)
GSK/MPIP	Germany	1741	1171 (67.3)	861	880	552 (62.7)	229 (26.0)	67 (7.6)
NESDA/NTR	Netherlands	3096	1996 (64.4)	1602	1494	548 (36.7)	415 (27.8)	349 (23.4)
QIMR substudy qi3c	Australia	1443	870 (60.3)	579	864	369 (42.7)	307 (35.5)	129 (14.9)
QIMR substudy qi6c	Australia	1089	713 (65.5)	590	499	153 (30.7)	189 (37.9)	50 (10.0)
QIMR substudy qio2	Australia	1091	708 (64.8)	526	565	203 (35.9)	222 (39.3)	73 (12.9)
RADIANT-United Kingdom	United Kingdom	3269	2158 (66.0)	1397	1872	948 (50.6)	395 (21.1)	279 (14.9)
RADIANT-Germany	Germany	549	330 (60.1)	227	322	174 (54.0)	89 (27.6)	44 (13.7)
SHIPO	Germany	1453	726 (50.0)	1087	366	205 (56.0)	109 (29.8)	34 (9.3)
STAR*D	United States	1870	986 (52.7)	934	936	291 (31.1)	290 (31.0)	197 (21.0)
TwinGene	Sweden	3760	1978 (51.9)	2663	1097	400 (36.5)	445 (40.6)	95 (8.7)

Abbreviations: A/W, appetite and/or weight symptoms; BOMA, Bonn/Mannheim Study; GenRED, Genetics of Recurrent Early-Onset Depression; GSK/MPIP, GlaxoSmithKline/Max Planck Institute of Psychiatry; MDD, major depressive disorder; NESD/NTR, Netherlands Study of Depression and Anxiety/Netherlands Twin Registry; PGC, Psychiatric Genomics Consortium; PsyCoLaus, psychiatric arm of Cohorte Lausannoise; QIMR, Queensland

Institute of Medical Research; SHIPO, Study of Health in Pomerania; STAR*D, Sequenced Treatment Alternatives to Relieve Depression study.

^a A small proportion of cases, set as missing, could not be classified owing to reporting simultaneously reported increase and decrease in the 2 items (5.9%) or owing to missing both items (4.2%).

all data sets was based on 2 items coding separately for decrease in A/W and increase in A/W. Among the patients with MDD, the following 3 subgroups were identified (Table 1 and eMethods 1 in the Supplement): decreased A/W (5347 [45.2%]), no change (3421 [28.9%]), and increased A/W (1871 [15.8%]).

Additional Phenotypes

Information on age at onset was available for 10 452 patients with MDD (eTable 1 in the Supplement). The number of endorsed symptoms calculated as the sum of *DSM-IV*-positive criteria (range, 5-12; 3 symptoms disaggregated in 6 items coding separately for increase or decrease) to index overall severity was available in 10 991 cases. Analyses using BMI were based on 2 panels of data sets, including 9 data sets providing BMI for 15 237 samples (42%-100% of the samples across data sets; the GlaxoSmithKline/Max Planck Institute of Psychiatry and Sequenced Treatment Alternatives to Relieve Depression studies were excluded owing to lack of BMI data; the Bonn/Mannheim Study, RADIANT-United Kingdom, and RADIANT-Germany were excluded owing to availability of BMI in <18% of samples) and 7 data sets providing BMI for 13 448 samples (83%-100% of the samples across data sets; additional removal of Genetics of Recurrent Early-Onset Depression studies 1 and 2 providing BMI only in cases).

Genotype Data Selection

Genotype data underwent centralized quality control and imputation as extensively described in the PGC-MDD2 GWAS (<http://www.biorxiv.org/content/early/2017/07/24/167577>). Two panels of single-nucleotide polymorphisms (SNPs) were selected for the present analyses (eMethods 1 in the Supplement). The first panel of 1 169 543 SNPs passing postimputation quality

control in at least 2 of 14 data sets and present in the HapMap3 reference was selected to build a genomic relationship matrix (eTable 2 in the Supplement). The second panel of 2 548 638 SNPs passing quality control in all 14 data sets constituted the base to build genomic profile risk scores (GPRSs).

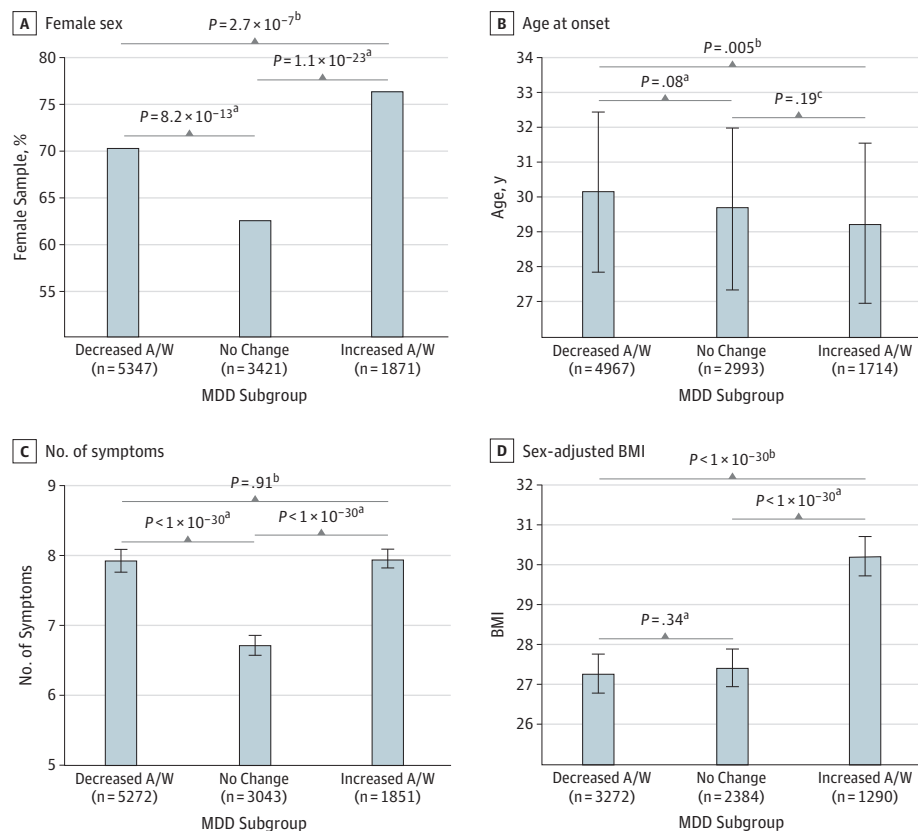
Genomic Profile Risk Scores

We used GWAS meta-analyses from large international consortia to generate the following obesity-related trait GPRSs (eMethods 1 in the Supplement): BMI (approximately 160 000 samples)³⁰ and circulating blood concentrations of CRP (approximately 70 000 samples),³¹ leptin, and BMI-adjusted leptin (approximately 32 000 samples).³² Psychiatric trait GPRSs were also built, including schizophrenia (approximately 36 000 patients and 113 000 controls)³³ and MDD (approximately 50 000 patients and 110 000 controls) (<http://www.biorxiv.org/content/early/2017/07/24/167577>). Overlapping SNPs (approximately 400 000 to 700 000) between the approximately 2.5 million selected and those filtered from the discovery GWAS were used to build GPRSs with linkage disequilibrium (LD) according to the LDpred method,³⁴ which has shown an improved predictive performance compared with other methods by modeling a prior on effect sizes and LD information. The fraction of causal SNPs was set at 5%, consistent with the estimate for schizophrenia.³⁵

Statistical Analysis

Analyses are extensively described in eMethods 1 and URLs of the software used in the analyses are given in eMethods 2 in the Supplement. In brief, differences in sex, age at onset, number of *DSM-IV* symptoms, and sex-adjusted BMI across the subgroups of patients were examined. Data were pooled using a multilevel analysis approach with (generalized) linear mixed

Figure 1. Phenotype Validation Against Established Clinical Characteristics



Differences in sex, age at onset, number of *DSM-IV* symptoms, and sex-adjusted body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) are shown across subgroups of patients with major depressive disorder (MDD). The patients were compared by subgroups with increased appetite and/or weight symptoms (A/W), decreased A/W, or no change using generalized linear mixed models. A, Raw data for female patients include 3758 (70.3%) for the decreased A/W subgroup, 2141 (62.6%) for the no-change subgroup, and 1430 (76.4%) for the increased A/W subgroup. B, Estimated mean (SE) age at onset was 30.1 (2.3) years in the decreased A/W subgroup, 29.7 (2.3) years in the no-change subgroup, and 29.2 (2.3) years in the increased

A/W subgroup. C, Estimated mean (SE) number of symptoms was 7.9 (0.1) in the decreased A/W subgroup, 6.7 (0.1) in the no-change subgroup, and 7.9 (0.1) in the increased A/W subgroup. D, Sex-adjusted BMI analyses included 9 of 14 data sets providing BMI data for more than 80% of patients. Estimated mean (SE) sex-adjusted BMIs were 27.3 (0.5) in the decreased A/W subgroup, 27.4 (0.5) in the no-change subgroup, and 30.2 (0.5) in the increased A/W. Error bars indicate SEs.

^a Compared with the no-change subgroup.

^b Compared with the increased A/W subgroup.

models with random intercept (data set). Analyses based on genomic relationship matrix-restricted maximum likelihood methods were applied to estimate (1) the variance in liability to MDD subgroups explained by the joint effect of all SNPs (h^2 SNP value) and (2) genetic correlations (r_g value) across MDD subgroups and with BMI. The association of GPRS-LDpred with MDD subgroups was estimated using logistic mixed models with random intercept (data set). The proportion of variance explained by GPRS on the liability scale for MDD subgroups was estimated according to Lee et al.³⁶ Statistical significance level was set at $P < .05$ (2-tailed).

Results

Phenotype Validation

Data included 11 837 patients with MDD and 14 791 controls, for a total of 26 628 participants (59.1% female and 40.9% male). We

validated MDD subgroup phenotypes against established clinical characteristics (Figure 1). The increased A/W subgroup was more likely to be female compared with the decreased A/W (odds ratio [OR], 1.39; 95% CI, 1.22-1.57) and no-change (OR, 1.94; 95% CI, 1.71-2.22) subgroups and had slightly earlier age at onset compared with the decreased A/W subgroup ($\beta = -0.91$; SE = 0.32). The increased A/W ($\beta = 1.24$; SE = 0.04) and decreased A/W ($\beta = 1.23$; SE = 0.03) subgroups had higher similar severity indexed by number of endorsed symptoms than the no-change subgroup. Finally, the increased A/W subgroup had higher BMI than the decreased A/W ($\beta = 2.94$; SE = 0.18) and no-change ($\beta = 2.78$; SE = 0.19) subgroups. In addition, the increased A/W subgroup had higher BMI than controls ($\beta = 2.00$; SE = 0.70) (eFigure 1 in the Supplement); all other subgroups did not differ from controls. Direct comparisons of the increased A/W with decreased A/W subgroups by using meta-analyses highlighted moderate to substantial heterogeneity across data sets ($I^2 = 15\%$ -91%) (eMethods 1 and eFigure 2 in the Supplement).

Table 2. SNP Heritability and Genetic Correlation Estimates for MDD Subgroups

MDD Subgroup	MDD Subgroup, Estimate (SE) ^{a,b}			
	All MDD	Decreased A/W	No Change	Increased A/W
All MDD	h^2 -SNP = 0.14 (0.08)	NA	NA	NA
Decreased A/W	NA	h^2 -SNP = 0.11 (0.02)	NA	NA
No change	NA	rg = 1.00 (0.23)	h^2 -SNP = 0.08 (0.02)	NA
Increased A/W	NA	rg = 0.82 (0.25)	rg = 1.00 (0.40)	h^2 -SNP = 0.11 (0.03)

Abbreviations: A/W, appetite and/or weight symptoms; MDD, major depressive disorder; NA, not applicable; SNP, single-nucleotide polymorphism.

^a Results are derived from (bivariate) genomic relationship matrix-restricted maximum likelihood analyses adjusted for sex, 10 ancestry-informative principal components, and 13 data set dummy variables as genetic correlation

(rg value) or joint effect of all SNPs (h^2 -SNP value). Lifetime risk for MDD, 0.150; decreased A/W subgroup (45% of patients), 0.0675; no-change subgroup (30% of patients), 0.045; and increased A/W (16% of patients), 0.024.

^b $P < 1 \times 10^{-4}$ for estimates greater than 0.

MDD Subgroup SNP Heritability and Correlations

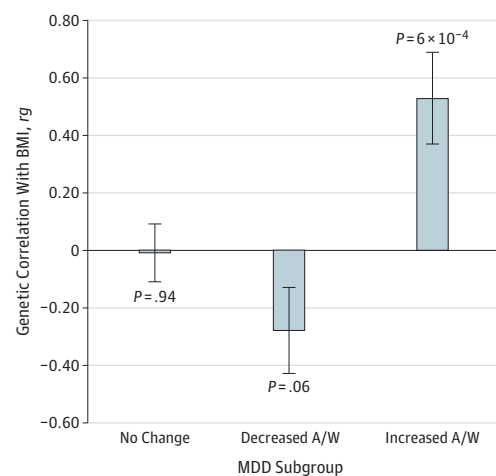
The genomic relationship matrix-restricted maximum likelihood analyses (Table 2) showed that the joint effect of common SNPs (h^2 -SNP) significantly captured approximately 10% of variance in liability for MDD and the subgroups (eTable 3 in the Supplement for h^2 -SNP at varying lifetime risk). The h^2 -SNP estimates were consistent with those obtained from concurrent techniques (eMethods 1 in the Supplement). Bivariate genomic relationship matrix-restricted maximum likelihood analyses across subgroups showed an rg of 1.00 between the no-change subgroup and the increased and decreased A/W subgroups. A smaller correlation ($rg = 0.82$), although with large SEs owing to restricted sample sizes, was found between the decreased and increased A/W and MDD subgroups, suggesting the possibility of a specific small divergence between these 2 subgroups that otherwise shared most of their genetic background.

Differential Associations With Obesity-Related Liability

To investigate whether the smaller resemblance between the decreased and increased A/W subgroups could be attributed to a different underlying liability to obesity, we estimated their genetic correlation with BMI (estimated h^2 -SNP = 0.18; SE = 0.02; $P = 2.9 \times 10^{-15}$). As depicted in Figure 2 (MDD reported as the benchmark), BMI was significantly correlated with increased A/W ($rg = 0.53$; SE = 0.16) and inversely correlated with decreased A/W ($rg = -0.28$; SE = 0.15).

Furthermore, associations with GPRS-LDpred for obesity-related traits confirmed partially distinct polygenic signatures (Figure 3 and eTable 4 in the Supplement) for both A/W subgroups. The GPRS-LDpred for BMI was significantly associated with a higher likelihood of increased A/W (OR, 1.18; 95% CI, 1.12-1.25; h^2 for liability = 0.56%) and with a slightly reduced likelihood of decreased A/W (OR, 0.96; 95% CI, 0.93-0.99; h^2 for liability = 0.03%; false discovery rate, $q < 0.05$, accounting for multiple testing) (eMethods 1 in the Supplement). Moreover, the association between GPRS-LDpred for CRP levels and MDD (OR, 1.01; 95% CI, 1.01-1.06; h^2 for liability = 0.03%) seemed to be completely driven by increased A/W (OR, 1.08; 95% CI, 1.02-1.13; h^2 for liability = 0.09%). Finally, increased A/W was associated with GPRS-LDpred for leptin levels (OR, 1.09; 95% CI, 1.06-1.12; h^2 for liability = 0.14%) and, although with a reduced effect size, GPRS-LDpred for leptin levels adjusted for BMI (OR, 1.06; 95% CI, 1.01-1.12; h^2 for liability = 0.07%). Of note, GPRS-LDpred for leptin levels adjusted

Figure 2. Genetic Correlations Between Major Depressive Disorder (MDD) and Body Mass Index (BMI)



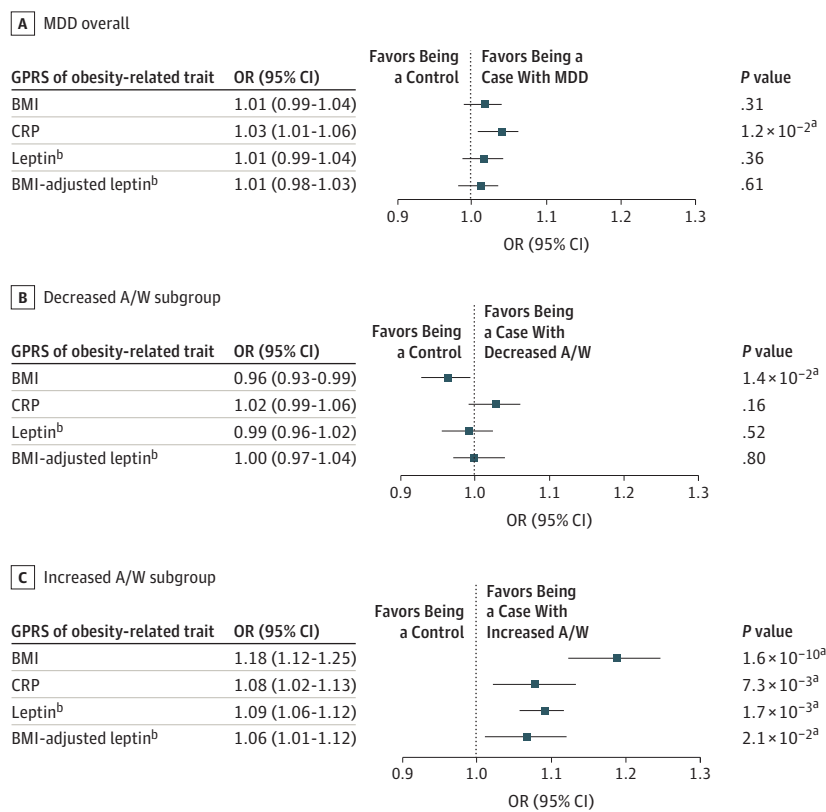
Results from bivariate genomic relationship matrix-restricted maximum likelihood analyses were adjusted for sex, 10 ancestry-informative principal components, and 8 data set dummy variables. Analyses were based on 7 data sets providing BMI data in more than 80% of the samples, including control individuals. P values test the hypothesis that h^2 values are significantly greater than 0. A/W indicates appetite and/or weight symptoms. Error bars indicate SEs; rg , genetic correlation.

for BMI was not associated with BMI ($\beta = 0.07$; SE = 0.04; $P = .08$). The associations between increased A/W and the GPRS-LDpred for obesity-related traits were similar across sex (GPRS-LDpred \times sex interaction terms, $P > .3$) In supplementary analyses, GPRS-LDpred for MDD and schizophrenia were similarly associated across subgroups (eTable 4 in the Supplement). For completeness of information, eTable 5 in the Supplement reports the association between the no-change A/W MDD subgroup and GPRS-LDpred.

Additional Analyses With GWAS

The association of decreased and increased A/W with single genetic variants was estimated in the following 3 GWAS meta-analyses: (1) decreased A/W subgroup vs controls, (2) increased A/W subgroup vs controls, and (3) decreased vs increased A/W subgroups (eMethods 1 in the Supplement). Owing to small sample size, the 3 GWASs performed were substantially underpowered to detect significant association with

Figure 3. Associations of Polygenic Risk for Obesity-Related Traits With Major Depressive Disorder (MDD)



Results (odds ratios [ORs] and 95% CIs) from binary (using controls for reference values) logistic mixed models adjusted for sex and 5 ancestry-informative principal components. BMI indicates body mass index; CRP, C-reactive protein.

^a False discovery rate, $q < 0.05$.

^b Analyses were based on 13 of 14 data sets available that are not included in the discovery genome-wide association study.

single genetic variants. Only when comparing the decreased and increased A/W subgroups, 1 SNP reached genome-wide statistical significance (*rs7598414*; $P = 4.7 \times 10^{-8}$), harbored in a locus on chromosome 2 overlapping several genes, including *SOS1* (NG_007530.1), *CDKL4* (NC_000002.12), and *MAP4K3* (NG_028007.1) (eFigures 3-5 in the Supplement); *CDKL4* was statistically significant in gene-based test analyses ($P = 8.3 \times 10^{-7}$).

Discussion

Using data from more than 25 000 samples from the PGC-MDD2, we examined whether subgroups of patients with MDD stratified according to the DSM A/W symptoms had a different degree of genetic overlap with obesity-related traits. The findings showed that the derived subgroups largely shared their genetic background but were specifically divergent in their liability to immunometabolic traits, with approximately 15% of patients reporting increased A/W symptoms during an active episode carrying a higher number of common risk variants for BMI and CRP and leptin levels.

Despite the simple clinical subphenotyping strategy, the subgroups recapitulated some clinical features that were reported in previous research on classic MDD subtypes; patients with increased A/W (approximating an atypical subtype) were more likely to be female and had an earlier age at onset, higher severity, and higher BMI.^{24,25} Common vari-

ants explained approximately 10% of MDD heritability, in line with the estimation from the latest PGC-MDD2 GWAS (<http://www.biorxiv.org/content/early/2017/07/24/167577>). The SNP heritability was similar for MDD subgroups, indicating an overall common genetic background. Reciprocal genetic correlations confirmed the close association of the subgroups. Nevertheless, the correlation of 0.82 (affected by large uncertainty owing to limited sample size) for the decreased vs increased A/W subgroups was suggestive of a possible small divergence between these 2 subgroups otherwise sharing most of their genetic background. We tested whether this divergence was attributable to obesity-related genetic variants of traits. Results confirmed that BMI had a genetic correlation with increased A/W. Similarly, the increased A/W subgroup had a higher genetic risk load for CRP and leptin levels.

Evidence from observational studies suggests stronger links with obesity immunometabolic dysregulations in depression with atypical features¹⁴⁻²³; in particular, the role of increased appetite in connection to BMI and levels of CRP and leptin has been highlighted.^{26,27} The present findings suggest that these phenotypic interrelationships may be rooted in a shared genetic base and common pathophysiologic mechanisms. Adipose tissue produces proinflammatory cytokines, which in turn act on peripheral cellular targets, leading to the synthesis of acute phase proteins (CRP from hepatocytes) responsible for systemic inflammation.³ Systemic inflammation in turn could trigger brain inflammatory responses participating in depression neu-

rochemical and endocrine processes.⁵ Obesity-related inflammation can disrupt the central signaling of leptin (CRP directly inhibits the binding of leptin to its receptors³⁷), blunting its anorexigenic effect and consequently disinhibiting feeding.⁷ In parallel, reduced central signaling affects leptin's antidepressant effects.⁸⁻¹⁰ The hypothesis of a divergent mechanism acting in MDD along the A/W axis is strengthened by the finding of a dissociable neural response among subgroups of patients stratified according to appetite symptom, in particular with those endorsing increased appetite showing a specific hyperactivation of mesocorticolimbic reward circuitry in response to food stimuli.³⁸

The present findings indicate genetic overlap between increased A/W and immunometabolic traits. Therefore, the phenotypic association between increased A/W and obesity-related features may have resulted from shared genetic and biological pathways (ie, pleiotropy), such as increased inflammation or leptin system dysregulation, rather than from an overrepresentation of participants with higher BMI among this MDD subgroup independent from these pathways (ie, confounding). The 2 processes cannot be disentangled statistically in observational data; if a pleiotropic action between 2 traits is subsumed, reciprocal adjustment for the other trait (eg, BMI) may represent a potential bias-inducing overadjustment.³⁹ The example of leptin is emblematic of consistent pleiotropic (and BMI-independent) actions at different levels. In animal models, leptin resistance induced through selective deletion of leptin receptor in hypothalamus or hippocampus and cortex produces hyperleptinemia with obesity⁴⁰ or depressionlike phenotypes, respectively.^{41,42} Previous results from NESDA²⁷ showed that hyperleptinemia was linked with increased appetite in patients with MDD independently from BMI. In the present study, increased A/W was also associated with a polygenic score for BMI-adjusted leptin levels.

Although leptin may be an example of pleiotropic action of common genetic variants influencing increased A/W and obesity through specific pathways (eg, leptin effect in different brain areas⁴⁰⁻⁴²), pleiotropy also may occur when one trait is causally associated with another trait^{43,44}; in this case, a genetic overlap with inflammation may occur if, for instance, the genetically determined increase in appetite and feeding would be the main driver of proinflammatory activation. Reliable discrimination of different pleiotropy scenarios with recently developed techniques⁴³ will become possible with the availability in the future of adequately powered GWAS for MDD subgroups. By assuming the example of leptin dysregulation as a shared mechanism, the hypothetical model is that of a subgroup of patients expected to show phenotypically average higher appetite and weight compared with others.¹⁵ When depression ensues, the shared mechanism may become more dysregulated, and therefore, the behavioral phenotype will be more pronounced during an active episode. We confirmed using NESDA data (eResults in the [Supplement](#)) that the increased A/W subgroup had significantly higher BMI compared with other patients when the disorder was nonactive, but this difference was enhanced at the beginning of an active episode mainly owing to BMI increases in the increased A/W subgroup and decreases in the decreased A/W subgroup. This theoretical model is also consistent with the reported moderation effect of depression on the association of BMI and the *FTO* gene ([NG_012969.1](#)).^{45,46}

Furthermore, this model is consistent with a conceptual framework similar to Research Domain Criteria,⁴⁷ in which biology-based multilevel dimensions cut through symptom-based clinical categories. Obesity and atypical depression may partially overlap on the dimension of energy homeostasis, which could be measured at genetic, biomarker (immunometabolic mediators), and behavior (appetite and/or feeding) levels.

Limitations

In interpreting results from the present study, some limitations should be considered. First, A/W symptoms used for case stratification were based on a single MDD episode (index lifetime episode, generally with the highest severity). Nevertheless, these symptoms are consistently 75% to 85% stable across MDD episodes, especially atypical-like increase,⁴⁸⁻⁵⁰ indicating that they may be considered stable features of depression in an individual. Second, the data structure did not allow us to dissociate the specific effects of appetite from weight. Nevertheless, the correlation between these 2 symptoms during an active episode is high, and previous studies^{26,29,51} showed that higher genetic burden for BMI or immunometabolic biomarkers were detected in patients identified only by appetite. Finally, results cannot be generalized to a population of non-European ancestry.

Conclusions

The present findings showed that the increased A/W subgroup had a specific genetic overlap with obesity-related traits. An important follow-up study would be the identification of the specific genetic loci involved using unbiased genome-wide scans. The present results indicate that at the current stage, stratification of the existing MDD GWAS data set is not yet a viable option, because the reduction in power owing to reduced sample size would not be compensated by a higher heritability of the trait (similar to MDD), as shown by the substantially null results obtained using the present data. The significant locus detected in a case-only GWAS contrasting the decreased and increased A/W subgroups should be considered mainly as a stimulus to further pursue this analytic strategy in larger data sets. Furthermore, the present results identified only associations. Once the specific loci are identified, follow-up functional studies will be needed to elucidate the potential causal role of the related pathways. Finally, although we specifically focused on A/W symptoms, future studies should consider other axes of variation in the association between MDD and genetic and biological factors, including other symptoms such as sleep disturbances or interaction with environmental factors.

The present findings may have important translational implications, providing molecular ground to the observed heterogeneity of response observed in intervention studies. For instance, anti-inflammatory agents have been proposed for depression treatment, and a recent meta-analysis⁵² of randomized placebo-controlled trials indicated substantial heterogeneity in their antidepressant effects. Of interest, post hoc analyses of a previous trial showed that anti-inflammatory agents exerted antidepressant effects only in patients with high baseline CRP levels.⁵³ These data underline the need to iden-

tify subgroups of patients who may benefit most from a specific treatment according to a personalized medicine approach. In the present study, increased A/W symptoms identified a subgroup of approximately 15% of patients with MDD with a higher genetic risk for immunometabolic dysregulations. Future clinical trials should plan to test treatment efficacy across patients with depression stratified according to

this criterion, especially for treatments targeting immunometabolic pathways (eg, anti-inflammatory agents⁵ or weight reduction pharmacologic or behavioral interventions with or without recombinant leptin⁷). Development of tailored treatments effectively targeting immunometabolic dysregulations may benefit this specific subgroup of patients with MDD and obesity, both of which are associated with disability.

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