Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eMethods 1. Stratification and Analysis of Cases

Stratification of MDD cases

The selected PGC datasets included information on DSM MDD symptoms endorsed during the index depressive episode. Items on neuro-vegetative symptoms were disaggregated to code separately for increase and decrease. Stratification of MDD cases in all datasets was based on two single items coding separately for: 1) decrease in appetite and/or weight (MDD3a) and 2) increase in appetite and/or weight (MDD3b) Among the 11,837 cases in the selected analytical sample, endorsement proportions for the two symptoms for appetite/weight were as follows:

MDD3a (decrease in appetite and/or weight)= 51.1% positive, 5.2% missing;

MDD3b (increase in appetite and/or weight)= 21.7% positive, 7.2% missing.

Two subgroups, namely "decreased-appetite/weight" ($MDD_{\downarrow a/w}$, 45.2%) and "increased-appetite/weight" ($MDD_{\uparrow a/w,}$ 15.8%), were defined by the presence of, respectively, decrease or increase in at least one of the two items (with the other item coded as no change or missing). A third group labeled "no-change" were defined by no change in any of the two items with the other coded also as no change or missing). A small proportion of cases, set as missing, could not be classified due to reporting simultaneously both increase and decrease in the two items (5.9%) or due missingness in both items (4.2%). Cross-tabulation below recapitulate the combination of the two items.

			MDD3b		
			missing	0	1
MDD3a	missing		500	22	94
	0		145	3254	1777
	1		205	5142	698

decreased-appetite/weight: 5142+205=5347

increased-appetite/weight: 1777+94=1871

no-change: 3254+22+145=3421

Genomic relationship matrix

The genomic relationship matrix (GRM) was based on 1,169,543 SNPs present in HapMap3 reference and passing post-imputation QC (missingness < 2%, MAF > 0.01 and INFO > 0.6) in at least 2 out of 14 datasets. The GRM was thus based on a different set of SNPs for individuals from each cohort and between each pair of cohorts (eTable 5), in this way providing genome-wide coverage of well described HapMap3 SNPs. The GRM was built using PLINK v1.9.

Genomic profile risk scores

A panel of 2,548,638 SNPs passing post-imputation QC (missingness < 2%, MAF > 0.01 and INFO > 0.6) in all 14 datasets available for the current analyses were initially selected. Summary statistics for BMI were obtained from GIANT Consortium.[1] Since several datasets included in the present analyses were part of GIANT, we re-ran the discovery GWAS for BMI meta-analysis after removal of overlapping datasets (~16K samples).
Summary statistics from discoveries studies for circulating blood concentrations of CRP (~70K samples) were from Dehghan et al.,[2] and for circulating blood concentrations of leptin (LEP) and BMI-adjusted leptin (LEP_{adjBMI}) were from Kilpelainen et al.[3] (~32K samples). Psychiatric traits GPRS were also built, including schizophrenia (SCZ) based on PGC data[4] (~36K cases, ~113K controls), and MDD based on the joint meta-analyses of datasets participating in the main MDD GWAS, including the 15 PGC datasets not included in the present analyses plus data from deCODE, GenScotland, GERA, iPsych and UK Biobank (~50K cases, ~110K controls).[5] Summary statistics of the discovery GWAS (BMI, CRP, LEP, LEP_{adjBMI} MDD, SCZ) were filtered by removing In/Del and strand ambiguous variants, and, when applicable, SNPs with INFO < 0.9, MAF < 0.01. Overlapping SNPs between the ~2.5M initially selected and those retained from the discovery summary statistics were

carried forward. Since GWAS for MDD and SCZ were based on a larger imputation reference panel (1000 Genomes) as compared to the other traits (HapMap), SNPs for MDD and SCZ were additionally filtered retaining only HapMap SNPs. The final selection included a range of ~400-700K SNPs for all traits. GPRS were built according to LDpred method[6] using the dedicated software. 1000 unrelated individuals were selected to calculate LD for reference. The fraction of causal SNPs was set at 5% consistently with the estimate for schizophrenia by Palla and Dudbdrige.[7]

Phenotype validation

Differences in sex, age of onset, number of DSM-IV symptoms and sex-adjusted BMI across the three subgroups of cases ($MDD_{\downarrow a/w}$, no-change and $MDD_{\uparrow a/w}$) were examined. Data were pooled using a multilevel analysis approach with samples clustered within datasets: a random intercept was set at the dataset level in (generalized) linear mixed models to take into account the correlation between measurements within the same dataset. Analyses with continuous outcomes were based on linear mixed models (Proc mixed, SAS v. 9.2, SAS Institute, Inc., Cary, NC). The analysis with sex as outcome was based on logistic mixed models (‘‘lme4’’ package v. 1.1-12 available in R v. 3.3.2, R Project for Statistical Computing). The direct comparison between $MDD_{\downarrow a/w}$ vs $MDD_{\uparrow a/w}$ cases in the abovementioned variables was additionally tested pooling dataset-specific results (logistic regression for sex, linear regression for other variables) with fixed-effect (number of endorsed symptoms) and random-effect (all other variables) meta-analyses using ‘‘rmeta’’ package v. 2.16 available in R.

SNP-heritability and genetic correlations

The total variance in liability to MDD sub-groups explained by the joint effect of all SNPs (SNP-heritability, h^2_{SNP}) was estimated using genomic-relationship-matrix restricted maximum likelihood (GREML) analyses[8] implemented in GCTA (Genome-wide Complex Trait Analyses) v.1.24.1. h^2_{SNP} is estimated in a linear mixed model in which the measure of genetic similarity (based on the GRM) is included as a random effect to predict the phenotype. Linear transformation of the estimates on the liability scale was based on lifetime risk (K) of 0.15 for MDD; in main analyses Ks for subgroups were empirically derived based on subgroups proportions among cases ($MDD_{\downarrow a/w}$: 45% of cases, K=0.0675; no-change: 30% of cases, K= 0.045; $MDD_{\uparrow a/w}$ 16% of cases, K=0.024).

Genetic correlations (rg) across MDD subgroups and with BMI were estimated via bivariate-GREML,[9] allowing estimation of the genetic covariance between two traits. For all analyses, unrelated individuals were selected from the GRM applying a relatedness cut-off of <0.05. Initial analyses on MDD sub-groups were adjusted for sex, 10 ancestry-informative principal components (PCs) and 13 dummy-variables indexing datasets. In analyses estimating pairwise rg between sub-groups, controls in each dataset were randomly split in two equal groups maintaining the same sex ratio.

MDD subgroup SNP-heritability estimates obtained via univariate GREML analyses were substantially in line with those obtained from concurrent techniques. Cross-product Haseman-Elston regression[10] analyses (adjusted by calculating the residuals of linear regression of MDD subgroups on covariates) provided the following $h^2_{SNP:}$ $MDD_{\downarrow a/w}$, est=0.09 (se=0.02); $MDD_{\uparrow a/w}$, est=0.08 (se=0.03); no-change, est=0.05 (se=0.02).

Furthermore, h^2_{SNP} for $MDD_{\downarrow a/w}$ obtained applying LDscore-regression[11] (LDSR) to summary statistics of the GWAS (see related paragraph at pag.7) contrasting $MDD_{\downarrow a/w}$ against controls

was 0.13 (se=0.03); h^2_{SNP} could not be reliably estimated via LDSR for $MDD_{\uparrow a/w}$ due to small sample size in the related GWAS.

GREML analyses including BMI were based on 9 datasets and were adjusted for sex, 10 PCs and 8 dataset dummy-variables.

Analyses including BMI were repeated using 7 datasets with BMI (excluding GenRED1 and GenRED2 providing BMI data only in cases) and were adjusted for sex, 10 PCs and 6 dataset dummy-variables. Results were substantially unchanged: rg MDD-BMI= 0.07 (0.09), p=0.46; rg $MDD_{\downarrow a/w}$-BMI= -0.13 (0.13), p=0.30; rg $MDD_{\uparrow a/w}$-BMI= 0.56 (0.13), p=6.3e-4.

Finally, although not part of the specific hypothesis that was tested (whether the smaller resemblance between $MDD_{\downarrow a/w}$ and $MDD_{\uparrow a/w}$ could be attributed to a different underlying liability to obesity), we report for completeness of information the estimated genetic correlation between the appetite/weight no-change MDD sub-group and BMI: rg= -0.01 (0.13), p=0.94

Polygenic risk analyses

The association of $GPRS_{LDpred}$ with MDD (sub-groups) was estimated by binary (reference =controls) logistic mixed models (‘‘lme4’’ package v. 1.1-12 available in R v. 3.3.2, R Project for Statistical Computing) with random intercept at the dataset level to take into account the correlation between measurements within the same dataset. Analyses were adjusted for sex and 5 ancestry-informative PCs. Analyses based on leptin polygenic risk were based on 13 out of 14 dataset available (PsyCoLaus dropped because included in the discovery GWAS[3]). FDR q-values were calculated assuming 12 tests (4 $GPRS_{LDpred}$ * 3 MDD groups; main hypothesis based on obesity-related traits) or 18 tests (6 $GPRS_{LDpred}$ * 3 MDD groups; supplemental analyses additionally including psychiatric traits). The proportion of variance explained by GPRS on the liability scale for MDD (sub-groups) was additionally

estimated using a complementary approach. Pooling all dataset together, binary logistic models were fitted adjusting for sex, 5 PCs and 13 dummy-variables (12 in analyses based on leptin GPRS) indexing datasets. For each model, Nagelkerke's pseudo-R^2 was derived and corrected for the covariates by substituting the null model in Nagelkerke's equation for the model including the covariates. The corrected pseudo-R^2 obtained was then re-scaled to the liability scale according to Lee et al.,[12] obtaining a value directly comparable with heritability and robust against ascertainment bias. Linear transformation on the liability scale was based on the following lifetime risk (K): MDD K=0.15, $MDD_{\downarrow a/w}$ (45% of cases) K=0.0675; no-change (30% of cases) K= 0.045; $MDD_{\uparrow a/w}$ (16% of cases) K=0.024.

In post-hoc analyses we tested whether the associations found between $MDD_{\uparrow a/w}$ and $GPRS_{LDpred}$ of immuno-metabolic traits were consistent across sex. In the previous logistic mixed models, already including the main terms for sex and $GPRS_{LDpred}$, we included a $GPRS_{LDpred}$-by-sex interaction term. All the interactions terms were non-significant: $GPRS_{LDpred}$-BMI-by-sex p=0.33; $GPRS_{LDpred}$-CRP-by-sex p=0.76; $GPRS_{LDpred}$-LEP-by-sex p=0.44; $GPRS_{LDpred}$- LEP_{adjBMI}-by-sex p=0.80).

Finally, although not part of the specific hypothesis tested (whether the smaller resemblance between $MDD_{\downarrow a/w}$ and $MDD_{\uparrow a/w}$ could be attributed to a different underlying liability to obesity) we reported in eTable 4 - for completeness of information - the association between the appetite/weight no-change MDD sub-group and $GPRS_{LDpred.}$

GWAS

The association of $MDD_{\downarrow a/w}$ and $MDD_{\uparrow a/w}$ with single genetic variants was estimated in three GWAS meta-analyses: 1) $MDD_{\downarrow a/w}$ vs controls, 2) $MDD_{\uparrow a/w}$ vs controls and 3) $MDD_{\downarrow a/w}$ vs $MDD_{\uparrow a/w}$. Analyses were performed following the same procedural pipeline established for the largest GWAS of PGC-MDD2 using the PGC "ricopili" pipeline.[4] Briefly, in each cohort,

logistic regression association tests were conducted for imputed marker dosages adjusting for sex and 5 PCs. The results were combined across samples using an inverse-weighted fixed effects model. In order to discard possible spurious signals, only SNPs with INFO ≥ 0.6, MAF (controls) ≥ 0.01 and present at least in 1000 samples were retained. Due to small sample size the GWAS were expected to be underpowered, with the largest one ($MDD_{\downarrow a/w}$ vs controls, N=20,138, effective N=14,806) reaching 80% statistical power to detect a genome-wide statistically significant association only assuming an effect size > 1.35 for a SNP with MAF=0.05 (Quanto v 1.2.4).

Gene-based test was performed using MAGMA (Multi-marker Analysis of GenoMic Annotation).[13] Analyzed SNPs were mapped to 18,565 genes (35kb upstream and 10kb downstream window to include regulatory elements) according to genome reference NCBI37. P-values obtained in the GWAS were used to perform a gene-based test using EUR population data from 1000 Genomes as reference. Genome-wide significant threshold was set at 2.65e-6 (0.05/18,565).

As expected, due to small sample size the three GWAs performed were substantially underpowered to detect significant association with single genetic variants (λ_{GC1000}=1.00-1.03). In analyses comparing cases sub-groups versus controls no genome-wide statistically significant associations was found in both SNP-based and gene-based tests. When comparing $MDD_{\downarrow a/w}$ vs $MDD_{\uparrow a/w}$ one SNP reached genome-wide statistically significance (rs7598414, OR=1.42, p=4.7e-08), harbored in a locus on chromosome 2 (2.p22.1) overlapping several genes including SOS1, CDKL4 and MAP4K3 (eFigures 3-5); CDKL4 emerged as statistically significant in gene-based test analyses (p=8.3e-07).

Genetic variants at this locus were not previously associated with other traits (GWAS Catalog). Gene Ontology (GO) annotations related to CDKL4 (Cyclin Dependent Kinase

Like 4) gene include cyclin-dependent protein serine/threonine kinase activity, ATP binding, protein phosphorylation and regulation of cell cycle.

eMethods 2. URLs of Software Used in the Analyses

PLINK https://www.cog-genomics.org/plink/1.9/

LDpred https://github.com/bvilhjal/ldpred

GCTA http://cnsgenomics.com/software/gcta/

LDSR https://github.com/bulik/ldsc

Ricopili https://github.com/Nealelab/ricopili/

MAGMA https://ctg.cncr.nl/software/magma

GWAS Catalog https://www.ebi.ac.uk/gwas/

GO http://www.geneontology.org/

BMI GWAS summary statistics

http://portals.broadinstitute.org/collaboration/giant/index.php/GIANT_consortium_data_files

Leptin GWAS summary statistics https://walker05.u.hpc.mssm.edu/

eResults. Association of BMI With MDD Subgroup and Status

From the NESDA/NTR dataset, MDD cases classified (according to symptoms endorsed in worst lifetime episode) as $MDD_{\downarrow a/w}$ (N=548), no-change (N=415) and $MDD_{\uparrow a/w}$ (N=349) were selected (Table 1). These samples were part of the Netherlands Study of Depression and Anxiety (NESDA), an ongoing cohort study into the long-term course and consequences of depressive and anxiety disorders.[14] For these samples, we retrieved data on BMI and presence of an MDD diagnosed in the last 6 months at NESDA baseline and 2-year follow-up. The relationship of BMI with MDD sub-group and status was analyzed in a linear mixed model (Proc mixed, SAS v. 9.2, SAS Institute, Inc., Cary, NC) with a random intercept at sample level, taking into account within-person correlations when examining multiple observations per subject. BMI across the two assessments was regressed on MDD sub-groups classification, time-varying MDD status (non-active/active), sex, age, age^2, education (years) and assessment (baseline/2-year follow-up); the model additionally included MDD sub-group-by-status interaction terms. Estimated BMI means according to sub-group and status derived from the model are depicted in eFigure 6. Participants classified as $MDD_{\uparrow a/w}$ had significantly higher BMI as compared to other subgroups when the disorder was non-active ($MDD_{\uparrow a/w}$ vs no-change: β=2.01,se=0.36,p<0.0001; $MDD_{\uparrow a/w}$ vs $MDD_{\downarrow a/w}$:β=2.96,se=0.33, p<0.0001). This difference was enhanced when the disorder became active ($MDD_{\uparrow a/w}$ vs no-change: β=2.52,se=0.36,p<0.0001; $MDD_{\uparrow a/w}$ vs $MDD_{\downarrow a/w}$:β=3.79,se=0.34, p<0.0001). This was mainly due by the fact that $MDD_{\uparrow a/w}$ cases increased their BMI when entering an active episode (β=0.37,se=0.16,p=0.02), while $MDD_{\downarrow a/w}$ cases decreased their BMI (β=-0.46,se=0.14,p=0.001). The sub-group of cases with no-change in appetite/weight did not show any significant variation in BMI transitioning to the active status of the disorder (β=-0.13,se=0.15,p=0.39). A sub-group-by-status-by-assessment interaction term subsequently included in the same model (including all the nested interaction terms) was not significant

(p=0.51), suggesting that the interactive effect of MDD sub-group and status on BMI was constant over time.

eTable 1. Additional Phenotypes Collected

		Additional phenotypes											
		age of onset		N symtpoms[a]		BMI[b]		BMI cases		BMI controls	
dataset		n	*(% cases)*	n	*(% cases)*	n	*(% cases)*	n	*(% cases)*	n	*(% controls)*
BOMA		568	*96.9*	548	*93.5*	69	*4.2*	69	*11.8*	0	
PsyCoLaus		507	*100.0*	500	*98.6*	1951	*99.9*	507	*100.0*	1444	*99.9*
GenRED1		1019	*100.0*	1011	*99.2*	990	*41.9*	990	*97.2*	0	
GenRED2		824	*99.3*	821	*98.9*	799	*61.3*	799	*96.3*	0	
GSK/MPIP		880	*100.0*	837	*95.1*	0		0		0	
NESDA/NTR		1364	*91.3*	1417	*98.9*	3018	*97.5*	1493	*99.9*	1525	*95.2*
QIMR-qi3c		557	*64.5*	816	*94.4*	1421	*98.5*	850	*98.4*	571	*98.6*
QIMR-qi6c		283	*56.7*	467	*93.6*	1075	*98.7*	491	*98.4*	584	*99.0*
QIMR-qio2		318	*56.3*	533	*94.3*	1084	*99.4*	561	*99.3*	523	*99.4*
RADIANT-UK		1639	*87.6*	1703	*91.0*	593	*18.1*	477	*25.5*	116	*8.3*
RADIANT-GER		291	*90.4*	306	*95.0*	85	*15.5*	85	*26.4*	0	
SHIP0		365	*99.7*	326	*89.1*	1201	*82.7*	286	*78.1*	915	*84.2*
STAR*D		926	*98.9*	907	*96.9*	0		0		0	
TwinGene		911	*83.0*	799	*72.8*	3698	*98.4*	1079	*98.4*	2619	*98.3*
		10452	*88.3*	10991	*92.9*	15984	*64.9*	7687	*64.9*	8297	*56.1*

[a] 520 samples with number of endorsed symptoms < 5 were set as missing

[b] 17 samples with BMI > 2 SDs (62.5 kg/m^2) were set as missing

eTable 2. Number of Overlapping SNPs Across Datasets Selected to Build the Genomic Relationship Matrix

N SNPs	BOMA	PsyCoLaus	GenRED1	GenRED2	GSK/MPIP	NESDA/NTR	QIMR-qi3c	QIMR-qi6c	QIMR-qi6c	RADIANT-UK	RADIANT-GER	SHIP0	STAR*D	TwinGene
BOMA	1016914													
PsyCoLaus	656688	713298												
GenRED1	883250	702617	994774											
GenRED2	947548	671950	912539	1054828										
GSK/MPIP	995893	659569	887414	953635	1024098									
NESDA/NTR	832523	679906	907328	854782	835416	924787								
QIMR-qi3c	808024	569746	738015	778213	808395	702250	821974							
QIMR-qi6c	975883	650579	872638	934468	974866	822954	803446	1000512						
QIMR-qio2	729558	561538	715586	749377	732470	683496	635209	724195	772317					
RADIANT-UK	998254	662498	892877	958195	998681	840621	811506	983793	736767	1028921				
RADIANT-GER	985682	648553	868939	931514	977600	819377	797638	959899	719980	985451	997974			
SHIP0	883121	697857	966696	909675	886747	907329	737015	871372	713690	890930	868610	991885		
STAR*D	595205	614004	636746	606933	597117	618852	521836	590777	513034	600058	588086	633176	642633	
TwinGene	969428	681568	932246	1026955	974281	874894	793697	955079	764002	979649	951796	932029	617593	1078923

eTable 3. SNP-Heritability Estimates for MDD Subgroups According to Varying Lifetime Risk

h^{2SNP}		*% cases*	*5*	*10*	*15*	*20*	*25*	*30*	*35*	*40*	*45*	*50*	*55*
est ***(se)***		*Ks*	*0.0075*	*0.015*	*0.0225*	*0.03*	*0.0375*	*0.045*	*0.0525*	*0.06*	*0.0675*	*0.075*	*0.0825*
MDD	**↓a/w**								0.10 *(0.02)*	0.11 *(0.02)*	0.11 *(0.02)*	0.12 *(0.02)*	0.12 *(0.02)*
	no change					0.07 *(0.02)*	0.07 *(0.02)*	0.08 *(0.02)*	0.08 *(0.02)*	0.08 *(0.02)*			
	↑a/w		0.08 *(0.03)*	0.09 *(0.03)*	0.10 *(0.03)*	0.11 *(0.03)*	0.11 *(0.03)*						

eTable 4. Associations of Polygenic Risk for Obesity-Related and Psychiatric Traits With MDD and Subgroups With Increased or Decreased Appetite/Weight

part I: MDD

		MDD						
$GPRS_{LDpred}$		**OR**	**95%CIs**	**p**	**fdr-q^1**	**fdr-q^2**		**h^2_{liab} *(%)***
BMI		1.01	0.99-1.04	0.313	0.469	0.402		0.01
CRP		1.03	1.01-1.06	0.012	0.034	0.021		0.03
LEP [a]		1.01	0.99-1.04	0.361	0.451	0.433		0.00
LEP_{adjBMI} [a]		1.01	0.98-1.03	0.610	0.666	0.646		0.00
MDD		1.23	1.19-1.26	9.0E-54		2.8E-51		1.13
SCZ		1.21	1.18-1.25	1.2E-45		1.3E-45		0.95

part II: MDD sub-groups

	MDD ↓a/w						MDD ↑a/w					
$GPRS_{LDpred}$	OR	95%CIs	p	fdr-q^1	fdr-q^2	h^2_{liab} *(%)*	OR	95%CIs	p	fdr-q^1	fdr-q^2	h^2_{liab} *(%)*
BMI	0.96	0.93-0.99	0.014	0.034	0.023	0.03	1.18	1.12-1.25	1.6E-10	2.0E-09	4.2E-10	0.56
CRP	1.02	0.99-1.06	0.163	0.279	0.225	0.01	1.08	1.02-1.13	7.3E-03	0.029	0.01	0.09
LEP [a]	0.99	0.96-1.02	0.521	0.625	0.586	0.00	1.09	1.06-1.12	1.7E-03	0.010	3.8E-03	0.14
LEP_{adjBMI} [a]	1.00	0.97-1.04	0.795	0.795	0.795	0.00	1.06	1.01-1.12	0.021	0.042	0.032	0.07
MDD	1.25	1.21-1.29	1.3E-38		5.1E-38	1.05	1.23	1.17-1.30	1.1E-15		3.1E-15	0.87
SCZ	1.24	1.20-1.29	1.7E-34		1.8E-33	0.96	1.24	1.18-1.32	4.7E-15		2.9E-15	0.84

Results (Odds Ratios and 95% Confidence Intervals) from binary (reference=controls) logistic mixed models adjusted for sex and five ancestry-informative principal components

fdr-q^1: 12 tests (4 $GPRS_{LDpred}$ * 3 MDD groups; main hypothesis based on obesity-related traits)

fdr-q^2: 18 tests (6 $GPRS_{LDpred}$ * 3 MDD groups; supplemental analyses additionally including psychiatric traits)

h^2_{liab}: linear transformation of Nagelkerke's pseudo-R^2 derived from binary logistic regressions (reference=controls) adjusted for sex, 5 PCs and 13 dummy-variables (12 in analyses based on leptin GPRS) indexing datasets

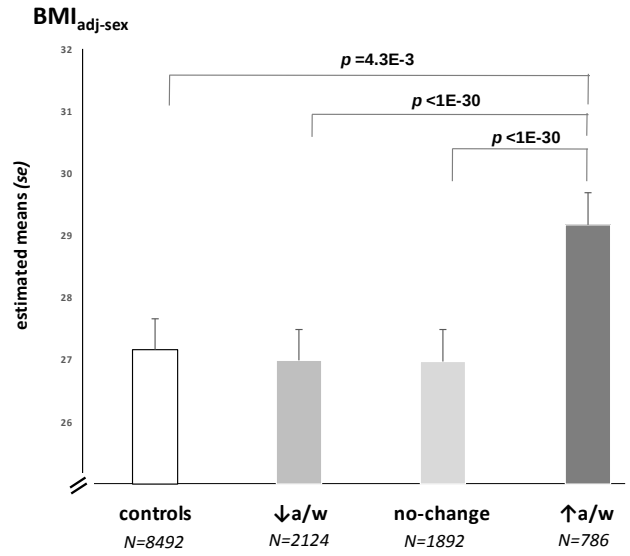
eTable 5. Associations of Polygenic Risk for Obesity-Related and Psychiatric Traits With MDD With No Change in Appetite/Weight

		MDD no-change appetite/weight		
$GPRS_{LDpred}$		OR	95%CIs	p
BMI		1.00	0.96-1.04	0.89
CRP		1.03	0.99-1.07	0.21
LEP [a]		1.02	0.98-1.06	0.40
LEP_{adjBMI} [a]		1.00	0.96-1.04	0.94
MDD		1.20	1.15-1.25	9.9E-19
SCZ		1.16	1.12-1.21	5.4E-13

Results (Odds Ratios and 95% Confidence Intervals) from binary (reference=controls) logistic mixed models adjusted for sex and five ancestry-informative principal components

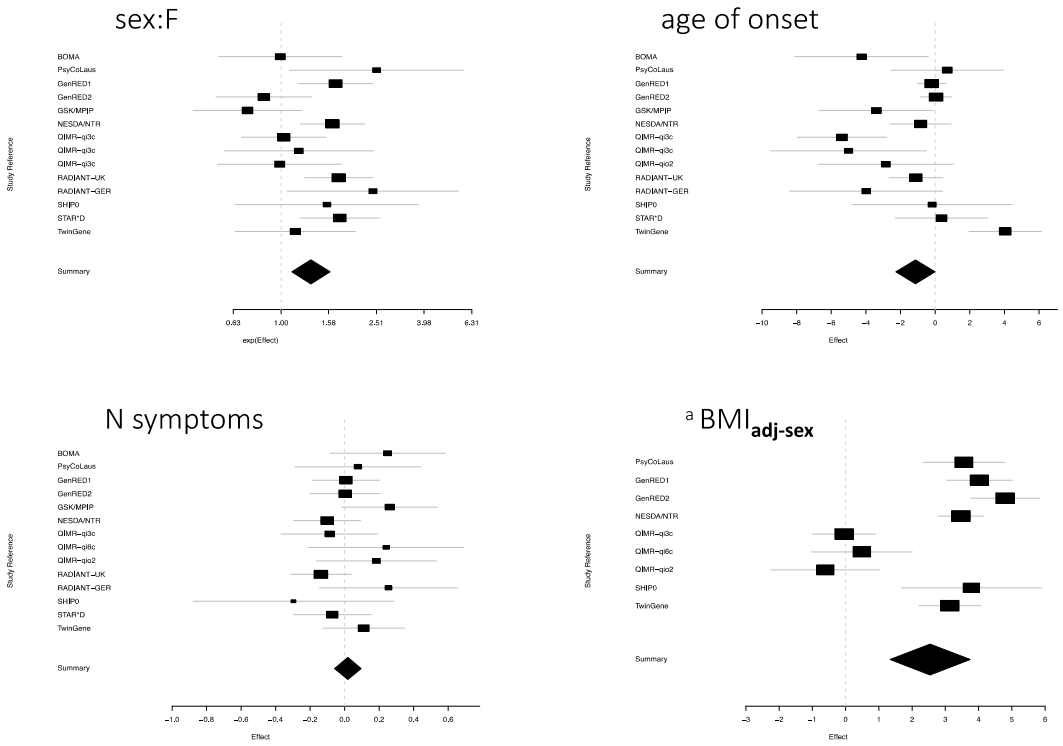
[a] Analyses based on 13 out of 14 target datasets available not included in the discovery GWAS

eFigure 1. Phenotype Validation: BMI



Differences in sex-adjusted BMI across subgroups of MDD cases and controls.
Analyses based on 7 out of 14 datasets providing BMI data for > ~80% of the samples. Results from linear mixed models.
Sex-adjusted BMI *(kg/m^2)*, estimated means (standard error): controls 27.1 (0.5), ↓a/w 27.0 (0.5), no-change 27.0 (0.5), ↑a/w 29.2 (0.5).

eFigure 2. Phenotype Validation: Comparison Between MDD Cases With Increased vs Those With Decreased Appetite/Weight



Forest plots of differences in sex, age of onset, number of DSM-IV symptoms and sex-adjusted BMI in MDD↓a/w versus MDD↑a/w cases.

Results from fixed-effect (number of symptoms) and random-effect (all other variables) meta-analyses; MDD↓a/w = reference category.

[a] Sex-adjusted BMI analyses based on 9 out of 14 datasets providing BMI data for >~80% of cases.

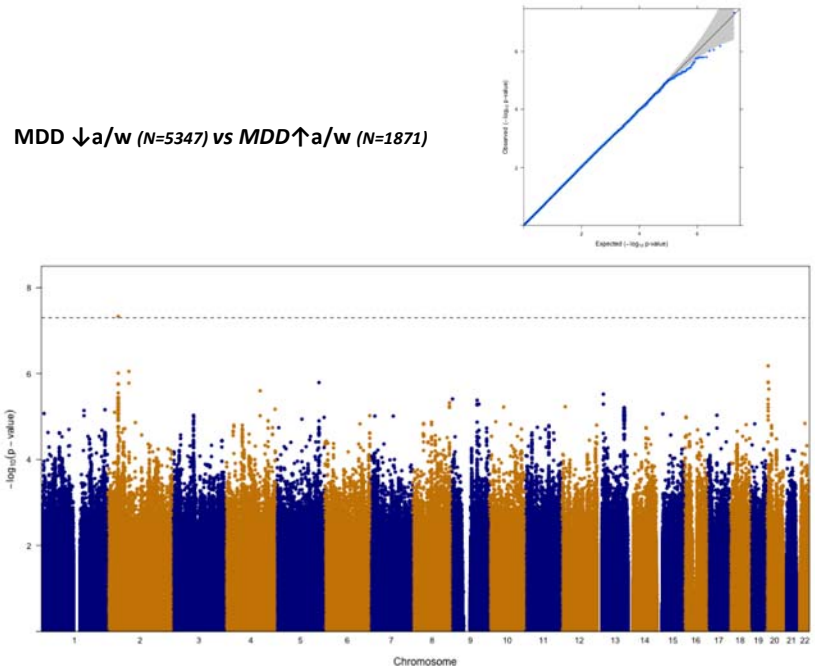
Sex: heterogeneity p=0.03, I^2=48%; summary effect, OR=1.33, 95%CIs=1.11,1.60.

Age of onset: heterogeneity p=3.5e-06, I^2=74%; summary effect, estimate=-1.14, 95%CIs=-2.27,-0.005.

Number of DSM-IV symptoms: heterogeneity p=0.29, I^2=15%; summary effect, estimate=0.02, 95%CIs=-0.06,0.08.

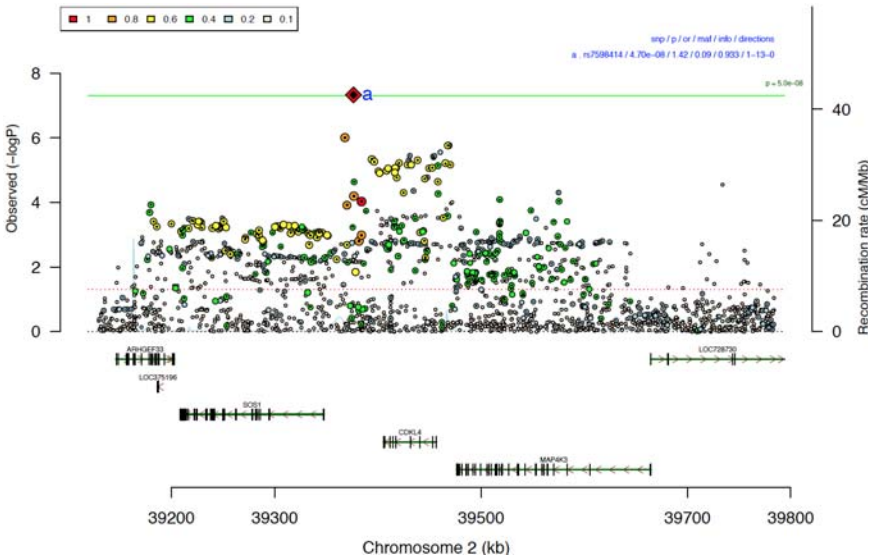
Sex-adjusted BMI: heterogeneity p=3.6e-16, I^2=91%; summary effect, estimate=2.54, 95%CIs=1.34,3.75.

eFigure 3. Quantile-Quantile and Manhattan Plot of the Associations in the GWAS Meta-analysis Comparing Decreased A/W vs Increased A/W Cases



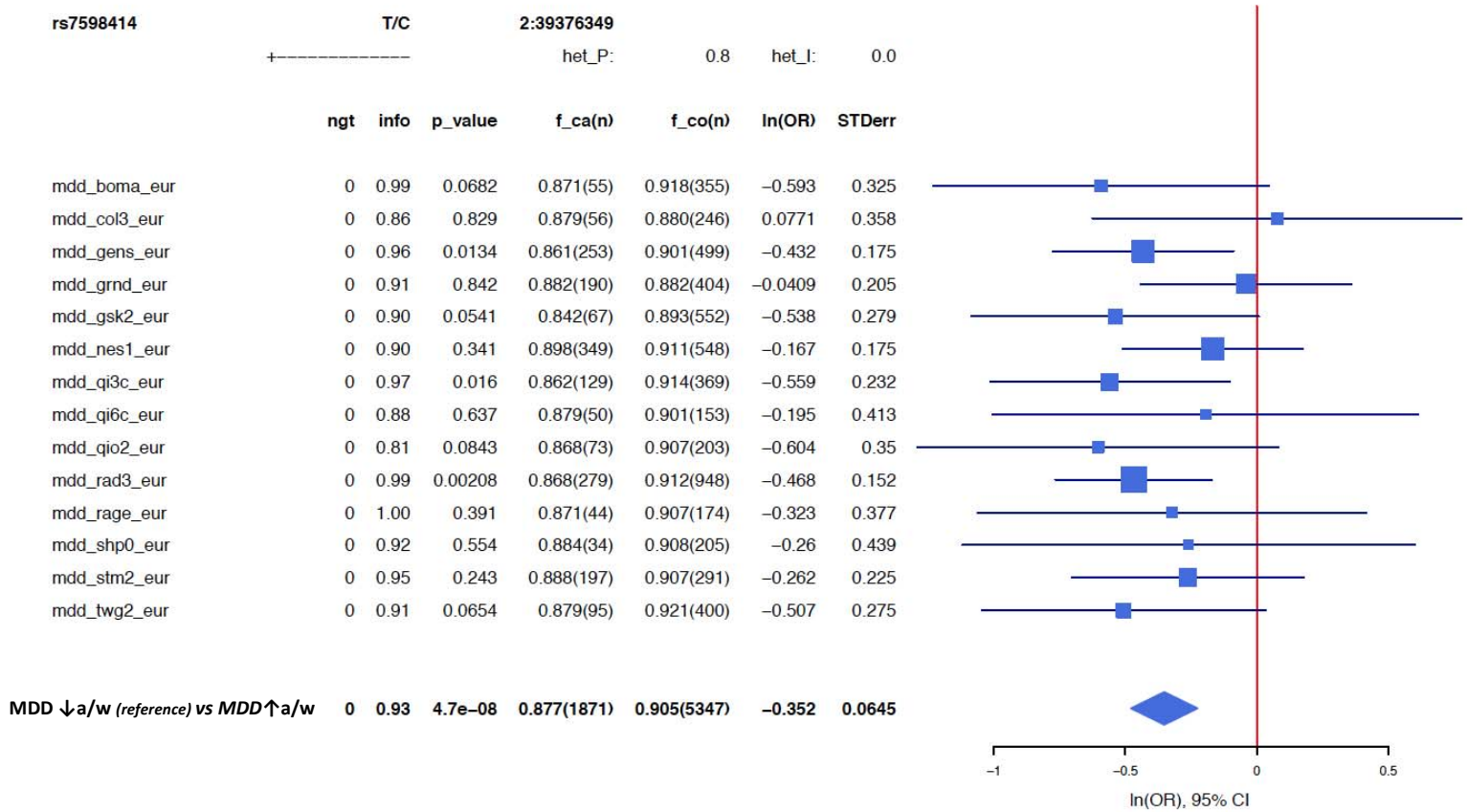
Genomic positions in Manhattan plot are given in NCBI Build 37/UCSC hg19. The dashed line shows the genome-wide significance threshold ($p=5x10^{-8}$)

eFigure 4. Regional Plot of the Associations in the Locus Harboring rs7598414 in the GWAS Meta-analysis Comparing Decreased A/W vs Increased A/W Cases

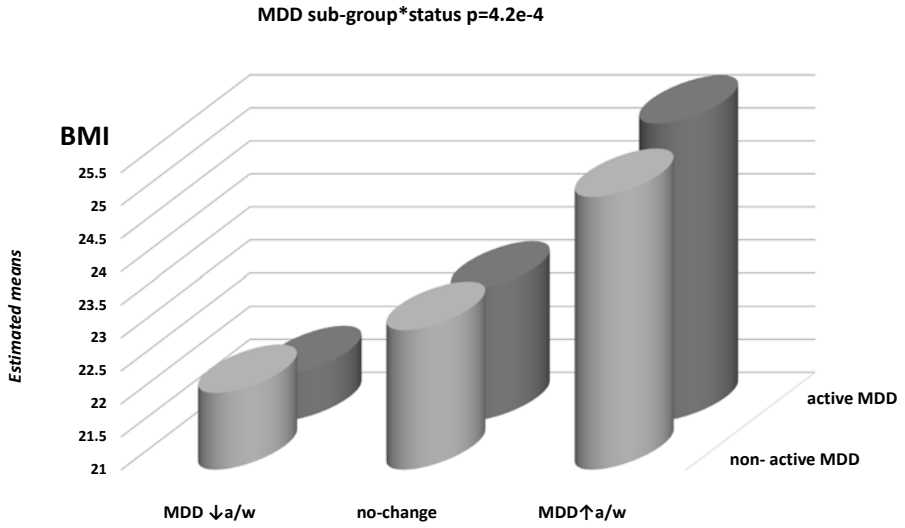


Genomic positions are given in NCBI Build 37/UCSC hg19.
[a] Top SNP: rs7598414, chr 2, bp 39376349

eFigure 5. Forest Plot of the Associations of rs7598414 Across Datasets



eFigure 6. Association of BMI With MDD Subgroup and Status in 1312 Cases From the Netherlands Study of Depression and Anxiety



Results from linear mixed model adjusted for sex, age, age^2, education (years) and assessment wave.
BMI *(kg/m^2)*, estimated means (standard error):

- non active MDD: ↓a/w 22.2 (1.4), no-change 23.1 (1.4), ↑a/w 25.1 (1.5);
- active MDD: ↓a/w 21.7 (1.4), no-change 22.9 (1.4), ↑a/w 25.5 (1.5).

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