Genetic overlap of depression with cardiometabolic diseases and implications for drug repurposing for comorbidities

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Abstract

Depression and cardiometabolic diseases, such as coronary artery disease (CAD) and type 2 diabetes (DM), are commonly considered as risk factors to each other. However, little is known about the mechanism underlying the relationship between depression and cardiometabolic traits. Using a polygenic risk score approach, we investigated the genetic overlap of major depressive disorder (MDD) with various cardiometabolic traits based on summary statistics from large-scale meta-analyses of genome-wide association studies (GWAS). GWAS results for MDD were taken from MDD-CONVERGE which represents a relatively homogenous sample of severe depression. We also identified shared genetic variants and inferred the enriched pathways. In addition, we looked for drugs over-represented among the top shared genes, with an aim to finding repositioning opportunities for both kinds of disorders.

We found significant polygenic sharing between MDD and cardiometabolic traits, including positive associations with CAD, fat percentage, LDL, triglyceride, body mass index (BMI), waist-hip ratio (WHR) and WHR adjusted for BMI, and an inverse association with HDL. We also observed a modest association of MDD with DM but no significant associations with other glycemic traits or leptin. Some of the shared pathways include lipoprotein metabolism, neurotrophin and oxytocin pathways. Using a gene-set analysis approach, we revealed drugs that may be repositioned for both types of disorders, many of which are supported by previous studies, such as statins, bupropion, verapamil and s-adenosylmethionine. Our study highlights shared genetic bases of MDD with cardiometabolic traits, and implicates the potential of repurposing drugs for comorbidities based on overlapping genetic factors.

Introduction

Major depression is a common psychiatric disorder worldwide. More than 300 million people globally suffer from major depressive disorder (MDD)[1] and it is ranked as the leading cause of disability worldwide by the World Health Organization in a latest report[1]. Depression has also been reported to be associated with numerous physical illnesses, including cardiovascular and metabolic diseases[2], as well as cardiovascular risk factors such as obesity[3] and dyslipidemia[4]. A book-length review on this subject is given in Baune and Tully[5]. However, the mechanism underlying the relationship between depression and cardiometabolic traits is not well understood. As common biological pathways may underlie both depression and cardiometabolic traits[5], shared genetic factors have been proposed as one of the mechanisms contributing to the comorbidities. Studies have shown genetic overlap between depression and blood pressure, total cholesterol level, body mass index (BMI), and heart rate variability [6-9]. However, only a limited spectrum of cardiometabolic abnormalities was considered in previous studies. These studies were mainly twin-based or family-based and the aim was to investigate an overall shared genetic basis; as such, they did not identify which genetic variants are most likely shared or the pathways involved. A recent systematic review nicely summarizes the current evidence for susceptibility genes shared between depression and cardiometabolic traits from candidate gene and some genome-wide studies[10]. Nevertheless, the review mainly focused on a qualitative assessment of the evidence and the results of candidate gene studies, which is a main part of the review, may not as reliable as large-scale GWAS.

In this study, we systematically study the genetic overlap of MDD with cardiometabolic abnormalities by a variety of approaches. Firstly, we study whether polygenic risk score (PRS) of depression is associated with cardiometabolic traits and vice versa. Secondly, we identify the genetic variants most likely shared between the disorders, by a statistical approach based on local true discovery rates. Based on the shared genetic markers, we identify the enriched biological pathways and gene ontology terms, and drugs potentially linked to both kinds of disorders. To our knowledge, this is the also first study to make use of human genomic data to guide drug discovery or repositioning for comorbid disorders.

Drug repositioning is gaining increasingly attention in recent years as a cost-effective approach to identify novel therapies[11]. The development of every new drug requires a major investment on drug design, testing and manufacturing standards[12]. In contrast, the repositioned drugs have passed through multiple stages of clinical development, and thus have well-known safety and pharmacokinetic profiles [13]. An example of drug repositioning in this field is pioglitazone, an insulin sensitizer which was studied in a clinical trial and shown to be a safe and effective adjunctive medication in non-diabetic patients with MDD [14].

It is worth noting that depression is widely regarded as a heterogeneous condition[15]. Depression has a lifetime prevalence of up to 17% according to a US study[16] and the diagnosis is entirely based on clinical symptoms with no reliable biomarkers. As such, it is likely that substantial genetic and phenotypic heterogeneity underlie this diagnosis.

Indeed, recent studies have shown that *severe* depression exhibited a stronger association with MDD polygenic scores, implying a heavier genetic loading[17]. A previous meta-analysis on the association of depression with cardiovascular disease risks also remarked on the high level of heterogeneity among studies[18], which could be partially attributed to the heterogeneity of depression itself. A recent twins study on the genetic overlap of depression with type 2 diabetes mellitus (DM) suggested that the genetic factors underlying the comorbidity might be different in males and females[19]. In this study we focus on a relatively homogenous group of severe depressive patients from the MDD-CONVERGE study[20]. This sample is composed of Chinese women with mainly hospital-ascertained cases of severe depression (85% of them had melancholic symptoms). This study was also the first GWAS to reveal genome-wide significant loci for MDD, reflecting its good power[20]. Besides, since we will employ the PRS approach to study shared genetic bases, the absence of sample overlap between MDD-CONVERGE and other GWAS studies also avoids the possibility of false positive associations due to overlap issues.

METHODS

Polygenic sharing of depression with cardiometabolic disorders or traits

We studied polygenic sharing of MDD [21] with a panel of cardiometabolic traits, including body mass index (BMI) [22], waist-hip ratio (WHR) [21], fasting glucose (FG)[23], fasting insulin (INS)[23], Insulin resistance (HOMA-IR)[24], fat-percentage [25], high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides (TG), total cholesterol (TC) [26], leptin[25], coronary artery disease (CAD) [27] and type 2 DM[28]. GWAS summary statistics were downloaded from the Psychiatric Genomics Consortium website (https://www.med.unc.edu/pgc) and LD hub (http://ldsc.broadinstitute.org/). Details of each study may be found in the references listed above.

Polygenic risk score (PRS) is a weighted sum of allelic counts, with the weights given by log odds ratios of individual SNPs. The PRS for an individual *i*, or $r_{i,}$ can be computed by $\sum_i w_j x_{ij}$, where x_{ij} is the centered allelic count for the *j*th SNP for the *i*th individual, w_j is the weight given to the *j*th SNP, given by the log odds ratio or regression coefficient in a linear regression. In this study we performed analyses using the summary statistics of each pair of traits, as raw genotype data are not available. Association testing was carried out by the method "gtx" described by Johnson [29]. This method was also described and elaborated in a number of papers e.g. [30-32]. Briefly, we tested for the association of the PRS derived from the first trait with a second trait y_i (with values centered) by regression:

$$y_i = \alpha r_i$$

Then it can be shown that the regression coefficient α can be estimated by

$$\tilde{\alpha} = \frac{\sum_i w_j \hat{\beta}_j s_j^{-2}}{\sum_i w_j^2 s_j^{-2}}$$

and the standard error cam be estimated by

$$SE(\tilde{\alpha}) = \frac{1}{\sqrt{\sum_i w_j^2 s_j^{-2}}}$$

where $\hat{\beta}_j$ is the regression coefficient when the second trait y_i is regressed onto the *j*th SNP and s_j is corresponding standard error of $\hat{\beta}_j$. This method was implemented in the R program PRsice[33]. We performed LD-clumping with an R^2 threshold of 0.05 prior to association analyses, following the suggestions given in the PRsice vignette. A series of ten *p*-value thresholds (0.001, 0.005, 0.01, 0.03, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5) was considered. Multiple testing was corrected by the false discovery rate (FDR) approach, which controls the expected proportion of false positives among the results declared to be significant. FDR-adjusted *p*-value (*q*-value) was calculated by the R program p.adjust using the Benjamini-Hochberg procedure[34]. Results with *q*-value below 0.05 are regarded as significant, and those with *q*-value below 0.1 are regarded as suggestive associations.

Discovery of genetic variants associated to both MDD and cardiometabolic traits

The SNPs shared by MDD and cardiometabolic traits were identified by an approach based on the concept of local false discovery rates[35]. For each SNP, the probability of being associated with *both* traits (denoted by tdr_{11}) was calculated based on the observed z-statistics. The approach is closely related to the conditional false discovery rate[36] but here we focused on the chance of *shared* associations instead of probability of association conditioned on the other trait. We adopted the same statistical formulation proposed by Chung et al.[37], although we worked with the z-statistics instead of *p*-values. Briefly, we assumed a four-group mixture model of *z*-statistics:

$$f(z_A, z_B) = p_{00} f_{00}(z_A, z_B) + p_{10} f_{10}(z_A, z_B) + p_{01} f_{01}(z_A, z_B) + p_{11} f_{11}(z_A, z_B) \quad \text{----(1)}$$

where z_A and z_B refer to the *z*-statistics of trait A and trait B respectively. There are four possibilities for each SNP when two traits are considered: 1) the SNP is associated with none of the traits; (2) the SNP is associated with the first trait only; (3) the SNP is associated with the second trait only; and (4) the SNP is associated with both traits. Each of these four possibilities are represented in the above mixture model. For instance, p_{11} denotes the proportion of markers that has association with both traits, and f_{11} denotes the probability density function of the z-statistics of this group of markers. From equation (1) we can derive the probability that a SNP is associated with both traits (denoted by tdr_{11}), using an expectation-maximization (EM) algorithm. Further details of the method are given in Supplementary Information.

Pathway and Gene Ontology (GO) enrichment analysis by ConsensusPathDB

Shared SNPs with $tdr_{11} > 0.5$ were selected and mapped to related genes using the Bioconductor package BioMart. However, some SNPs were mapped to multiple genes, which may lead to the enrichment of certain pathways that consist of genes from the same (or a few) SNPs. We adopted the following method to correct for this potential bias. We first extracted variant consequences (using sequence ontology [SO] terms) of variants via BioMart, and each SNP was mapped to the gene corresponding to the highest impact rating (as listed in http://asia.ensembl.org/info/genome/variation/predicted_data.html#consequences). ConsensusPathDB was used to infer the biological pathways and gene ontology (GO) (level 5) terms enriched among the top shared genes. ConsesusPathDB is a comprehensive resource that integrates multiple databases for pathway analyses[38]. Over-representation of pathways or GO terms was assessed by hypergeometric tests with a *p*-value cutoff of 0.01 with at least two genes in each pathway, following the default settings.

Drug repositioning by over-representation analyses in WebGestalt

We then looked for drug-related gene-sets that are over-represented among the most significantly shared genes. We used WebGestalt[39] for this analysis. WebGestalt employed a computational approach known as GLAD4U[40] to query the scientific literature to retrieve and prioritize gene lists associated with drugs. The over-represented drugs were identified by hypergeometric tests. We require at least 2 genes in each gene-set and the top 10 significant results were retrieved.

We expected to discover drugs associated with the overlapping genes, and therefore identify known drugs that have genetic associations to non-target disorders. This may provide us hints for new indications of known drugs; for example, drugs known to treat psychiatric disorder can be used as a therapy for cardiometabolic diseases, or vice versa. We may also find repositioning candidates with undiscovered beneficial effects on both depressive and cardiometabolic diseases.

Results

Polygenic associations between MDD and cardiometabolic traits

Polygenic associations between MDD and cardiometabolic traits are shown in Table 1. Firstly, PRSs were constructed from MDD, and metabolic traits are regarded as target (i.e. dependent) phenotypes. Polygenic score of MDD was positively and significantly associated with CAD (q = 2.28E-04), BMI (q = 5.87E-04), WHR (q = 5.92E-06), and WHR adjusted for BMI (q = 1.23E-03). Statistically significant associations were also observed for traits of lipid metabolism, including fat percentage (q = 7.77E-03), HDL (q = 2.97E-04), and TG (q = 3.44E-04). The direction of association was positive for fat percentage and TG, and negative for HDL. MDD polygenic score also predicted DM at a suggestive level of significance (q = 5.18E-02).

When cardiometabolic traits were used to construct PRS and MDD was regarded as the outcome, polygenic score of HDL was negatively associated with MDD (q = 3.91E-04), while the scores of BMI (q = 1.19E-06) and WHR (q = 3.38E-04) both showed positive associations. After controlled for BMI, the association between WHR and MDD was slightly attenuated (q = 6.65E-02). Other suggestive associations included FG and leptin (adjusted for BMI), both in the positive direction. Polygenic scores of CAD (q = 1.65E-01) and fat percentage (q = 4.01E-01) were not significant predictors for MDD.

Shared SNPs and Pathway and GO term over-representation analysis

The top SNPs shared by MDD and cardiometabolic traits are shown in Tables 2 and 3. To facilitate interpretation, we have performed LD-clumping (with an R-squared threshold of 0.1 and a window-size of 250 kb) on the shared SNPs using PLINK[41], and extracted the top five SNPs for presentation.

To explore whether the genes shared by MDD and cardiometabolic traits share specific canonical pathways and functional features, we performed pathway and GO enrichment analysis using ConsensusPathDB. For CAD and HDL, many overrepresented pathways and GO terms were related to lipid and lipoprotein metabolism (Table 4 & Supplementary Tables 1-2), including the statin pathway. We also found enrichment of pathways related to neurotrophins [*e.g.* brain-derived neurotrophic factor (BDNF) and nerve growth factor (NGF)] and oxytocin in the genes shared between MDD and BMI, fat percentage, and WHR (Table 4-5 and Supplementary Tables 1-2). Some other enriched pathways included insulin signaling (for TG and WHR), epidermal growth factor receptor (EGFR) and fibroblast growth factor (FGF) receptor pathways (for BMI).

Drug enrichment analysis

Results of drug enrichment analysis were listed in Table 6. Consistent with the finding in the pathway enrichment analysis, the top drugs overrepresented in candidate genes shared by MDD and CAD, HDL, TG, TC, and fat percentage included drugs used for reducing cholesterol level, including statins. Some other interesting hits included the antidepressant bupropion (for BMI), the calcium channel blocker verapamil (for fat percentage), the lipid-lowering agent fenofibrate (for TG) and s-adenosylmethionine (SAMe) (for TC).

Discussion

In this study we discovered significant polygenic sharing between MDD and multiple cardiometabolic traits, and inferred pathways that are enriched among the shared genes. These findings provide further support to common pathophysiology shared between the two types of disorders. We also explored drugs with the potential of being repositioned for the comorbid disorders. The results of each part of analyses are discussed below.

Polygenic associations of MDD with cardiometabolic traits

When polygenic score of MDD is treated as predictor, it showed strong associations with CAD; on the other hand, the association was insignificant when polygenic score of CAD was used to predict MDD (Table 1). One possibility is that the genetic variants may not (only) exert pleiotropic effects (the variants affecting each trait separately); instead, the variants that influence MDD risk may promote the development of CAD through a causal effect of MDD on CAD. It is obviously possible for the co-existence of both pleiotropic and causal effects. A number of meta-analyses have found significant associations of depression with CAD, although there is substantial heterogeneity among these studies[42]. To the best of our knowledge, this is the first study revealing a polygenic association between MDD and CAD.

With regards to type 2 DM, when using MDD PRS as a predictor, we observed a suggestive association (p = 5.18E-03; q = 5.18E-02) with type 2 DM although no significant association was found for fasting glucose, fasting insulin or HOMA-IR (Table 1). The association between depression and type 2 DM is supported by a number of studies. A meta-analysis showed an association between depression and incident DM that could not be completely explained by either use of antidepressant drugs or being overweight [43]. Another meta-analysis reported that DM is also associated with increased risk for depressive symptoms, with slightly lower adjusted and unadjusted risk ratios[44]. As for the evidence of genetic overlap, a recent twins study revealed shared genetic factors between depression and type 2 DM in two samples[19]. Interestingly, in the Swedish sample, the relationship between the two disorders was driven mainly by genetic factors in females but in males the association was mostly explained by environmental factors. In the other Danish sample, genetic effects account for most of the covariance in both sexes. This study also suggests that different genetic risk factors contribute to the comorbidity in males and females[19]. The findings highlight the heterogeneity of depression and its association with other diseases, and supports our use of a more homogenous sample of severe depression in women to delineate shared genetic effects.

As for the other traits related to glucose metabolism (FG, fasting insulin, HOMA-IR), most did not show significant associations with MDD, although we observed a suggestive association of FG with MDD (q = 5.58E-02) using FG PRS as a predictor. It is worth noting that the genetic bases of the glucose levels and DM might not completely overlap. For example, Merino et al. reported that the polygenic score of 12 variants having strong associations with FG did not significantly predict the risk of type 2 DM [45]. It has also been reported that some SNPs may have differential effects on quantitative glycemic traits and the risk of frank diabetes[46, 47]. A more detailed review was given by Marullo et al.[48].

MDD PRS was also associated with BMI, WHR (with and without adjustment for BMI) and components related to

lipid metabolism (fat percentage, HDL and TG), and vice versa in most cases. High body fat percentage, BMI, WHR and TG as well as low HDL obesity have all been reported as risk factors for DM and cardiovascular diseases in numerous studies[49, 50].

Shared genetic variants and pathways

We will briefly discuss some interesting pathways shared between MDD and cardiometabolic traits inferred from shared genetic markers. Our analyses demonstrated that many lipid-related pathways and GO terms were overrepresented among genes shared by MDD with CAD and HDL. Particularly, the statin pathway was enriched in both sets of shared genes (Table 4). Statins were also ranked highly in drug enrichment tests of CAD and HDL (Table 6). Consistent with our results, statins have been found to exert many pleiotropic beneficial effects on cardiovascular diseases, including anti-inflammatory actions, beyond their LDL cholesterol-lowering effects [51]. Recently, some researchers started to study its therapeutic potential on depression, as previous studies postulated that inflammation also played a role in depression [52, 53]. A Swedish national cohort study reported that statin possibly reduced risk of depression in individuals over the age of 40 [54]. It was suggested that concomitant treatment with selective serotonin reuptake inhibitor (SSRI) and statin might have superior antidepressant effect than SSRI treatment alone [55]. A Korean group also successfully showed an anti-depressant action of statin in patients with acute coronary syndrome (ACS) [56]. Taken together, our result provides additional evidence for the use of statins as a novel therapy for depression, especially for patients with comorbid cardiovascular diseases.

Other pathways that were enriched included the neurotrophin and oxytocin signaling pathways which have been implicated in the pathophysiology of depression. Depression may be associated with impaired neuronal plasticity, and decreased BDNF and NGF level have been proposed as biomarkers for major depression [57, 58]. Oxytocin is also postulated to attenuate activity of the hypothalamic-pituitary adrenal (HPA) axis [59, 60] and was suggested to have therapeutic effects on depression[61].

These signaling pathways were enriched for the shared genes between BMI, fat percentage and WHR with depression, suggesting an association with obesity traits. In addition, we observed enrichment of GO terms related to neuronal or synaptic functions for several cardiometabolic traits, particularly BMI (Table 5). Although the exact relationship between neurotrophins and metabolic disorders has yet to be elucidated, NGF and BDNF were suggested to play important roles in cardiometabolic functioning; for example, both exert insulinotropic effect and suppress food intake [62]. More detailed reviews on this topic are available elsewhere[63, 64]. On the other hand, oxytocin can ameliorate weight gain in diet-induced obese rats by enhancing adipose tissue lipolysis and fatty acid β-oxidation via the production of oleoylethanolamide, a peroxisome proliferator-activated receptor alpha (PPARα) activator [65, 66]. It is worthwhile to further investigate the molecular mechanisms by which neurotrophin and oxytocin signaling pathways

are involved in the comorbidity of MDD and cardiometabolic abnormalities.

Drug enrichment analyses

As already discussed above, statins were ranked highly in our drug enrichment tests and previous studies supported its therapeutic effects for both cardiovascular and depressive disorders. We will discuss other repositioning hits backed up by prior clinical or pre-clinical studies. Bupropion is the top-ranked drug candidate when we considered the shared genes between BMI and MDD. Interestingly, bupropion has been shown in a meta-analysis to be the only antidepressant that produces weight loss both at the acute phase and over longer period of treatment[67]. Bupropion provides an important example supporting the validity of our approach in identifying repositioning opportunities for comorbid disorders.

Fenofibrate is a well-known lipid-lowering agent. However, an animal study also revealed antidepressant-like effects of fenofibrate by PPARα stimulation in the mesolimbic dopamine system[68]. Verapamil is a calcium channel blocker mainly used for hypertension, angina and arrhythmias. Studies have also suggested this drug might also have broader beneficial effects on cardiometabolic abnormalities. For example, verapamil has been shown to correct autophagic defects related to obesity[69]. The administration of this drug to obese mice reduced the accumulation of hepatic lipid droplets, and ameliorated pathologies of fatty liver such as inflammation and insulin resistance[69]. Regarding the effects on mood disorders, calcium channel blocker has been proposed as a novel therapeutic option for bipolar disorder and depression, although the evidence was mixed[70]. Verapamil has been reported to demonstrate antidepressant-like effects in animal models[71-73]. Interestingly, we found verapamil among the top repositioning hits for MDD with fat percentage, broadly consistent with literature findings.

Another drug worthy of mentioning is s-adenosylmethionine (SAMe), which has been shown to have antidepressant properties in clinical studies[74, 75], although the results are mixed and there is no conclusive evidence yet for clinical use[76]. On the other hand, SAMe is also related to lipid metabolism; for example, depletion of SAMe may lead to accumulation of lipid droplets in human skin fibroblasts[77]. It has been suggested SAMe supplementation may be useful in patients with non-alcoholic fatty liver disease in limiting the progression to steatohepatitis, although it requires further verification in clinical trials[78].

There are a few limitations to our study. Firstly, as we relied on summary statistics in our polygenic score analysis, we could not easily control for covariates of interest. For example, a number of datasets (e.g. GWAS on lipids) do not provide results adjusted for BMI or WHR, hence we are unable to conclude if the association between MDD and cardiometabolic abnormalities is independent of overweight or obesity status. Future studies using raw genotype data will enable more flexible analyses including covariate adjustment. Also in this study we have focused on a relatively

homogenous sample of severe depression in Chinese women[20]. This approach alleviates the issue of heterogeneity among depressive patients; however, as most other GWAS samples are composed of Caucasians, the polygenic associations between MDD and cardiometabolic phenotypes may be attenuated. Nevertheless, there is evidence that GWAS results from Europeans are highly replicable in East Asians and the effect sizes are also highly correlated[79]. Further studies are required to confirm whether our results can be generalized to other ethnic groups, male subjects, or individuals with different severity or subtypes of MDD. In addition, the sample size of MDD-CONVERGE is relatively moderate (N = 10640)[20] when compared to other GWAS studies. Further studies, preferably with larger sample sizes, are warranted to validate our findings and to detect weaker polygenic associations.

As for the drug enrichment analyses, we have employed a relatively straightforward approach by testing for over-representation of shared genes among known drugs. Also, the significance of each gene is determined by the most significant variant and we did not take into account of LD structure and size of each gene or the significance of all SNPs in the gene. Due to the relatively moderate sample size of MDD-CONVERGE, for some traits there are no markers with tdr_{11}>0.5 and hence are not included in the pathway or drug enrichment analyses. Here we tested for over-representation of drug-related gene sets but the directions of drug effects are not explicitly considered. Further methodological developments are warranted in view of these limitations. While we have presented a computational framework for drug repositioning for comorbidities, the approach should be considered exploratory rather than confirmatory, and further validation in preclinical and clinical studies are crucial before applications in the clinic.

Conclusions

Our study highlights a significantly shared genetic basis of MDD with CAD, lipid and obesity-related traits, and a modest association with type 2 DM. The various enrichment analyses of shared SNP reveal the importance of several pathways, e.g. lipid metabolism, NGF, BDNF, and oxytocin signaling pathways in the comorbidity of depressive and cardiometabolic traits. Using a gene-set analysis approach, we also revealed drugs that may be repositioned for both types of disorders, some of which are supported by prior preclinical and clinical studies. Increased awareness and further investigation into the the complex relationship between depressive and cardiometabolic diseases are warranted to reduce the morbidities and mortalities in patients with either or both kinds of health problems.

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The authors declare no competing interests.

Table 1. Polygenic risk score (PRS) analysis between MDD and cardiometabolic traits

	MDD-CONVERGE as Target				**MDD-CONVERGE as Base**			
	best_p	pval	coef	qvalue	best_p	pval	coef	qvalue
BMI	0.03	1.64E-07	1.42E-01	**1.19E-06**	0.05	5.87E-05	1.72E-03	**5.87E-04**
CAD	0.4	3.88E-02	1.31E-02	1.65E-01	0.5	5.98E-05	2.89E-03	**2.28E-04**
DM	0.05	1.65E-01	-4.25E-03	3.98E-01	0.03	5.18E-03	5.70E-03	*5.18E-02*
Fat-percentage	0.001	6.59E-02	3.06E-02	4.01E-01	0.3	2.27E-03	1.50E-03	**7.77E-03**
FG-adj-BMI	0.01	1.06E-01	1.90E-02	5.03E-01	0.01	1.29E-01	8.49E-04	9.69E-01
FG	0.3	2.77E-02	1.67E-02	*5.58E-02*	0.01	3.67E-02	1.14E-03	3.67E-01
HDL	0.4	4.79E-05	-4.91E-02	**3.91E-04**	0.5	4.29E-05	-1.69E-03	**2.97E-04**
HOMA-IR	0.2	6.96E-02	-2.52E-02	3.89E-01	0.01	3.34E-02	1.49E-03	2.25E-01
Insulin	0.005	2.68E-01	2.02E-02	6.77E-01	0.01	5.80E-02	1.05E-03	2.60E-01
INS-adj-BMI	0.1	1.78E-01	-1.16E-02	6.48E-01	0.005	3.68E-01	-5.23E-04	9.70E-01
LDL	0.001	5.27E-01	2.35E-02	9.83E-01	0.001	1.10E-01	-2.93E-03	5.62E-01
Leptin	0.05	1.67E-02	2.78E-02	1.20E-01	0.01	1.99E-02	2.59E-03	1.14E-01
Leptin-adjBMI	0.005	9.00E-03	7.44E-02	*9.00E-02*	0.001	8.65E-02	3.05E-03	5.37E-01
TC	0.01	1.49E-01	-3.47E-02	5.94E-01	0.001	8.10E-02	-3.11E-03	7.63E-01
TG	0.4	9.19E-04	4.07E-02	**4.86E-03**	0.3	6.77E-05	1.64E-03	**3.44E-04**
WHR	0.01	3.38E-05	1.26E-01	**3.38E-04**	0.5	8.59E-07	1.79E-03	**5.92E-06**
WHR-adj-BMI	0.01	6.65E-03	8.33E-02	**6.65E-02**	0.5	2.02E-04	1.37E-03	**1.23E-03**

Best_p, best *p*-value threshold for polygenic score association; coef, regression coefficient.

BMI, body mass index; CAD, coronary artery disease; DM, type 2 diabetes mellitus; Fat-percentage, total fat percentage; FG-adj-BMI, fasting glucose adjusted for BMI; FG, fasting glucose; HDL, high-density lipoprotein; HOMA-IR, Insulin resistance; INS-adj-BMI, fasting insulin adjusted for BMI; Insulin, fasting insulin; LDL, low-density lipoprotein; leptin-adjBMI, leptin adjusted for BMI; leptin, leptin; TG, triglycerides; TC, total cholesterol; WHR, waist-hip ratio; WHR-adj-BMI, waist-hip ratio adjusted for BMI.

Results with *q*-value <0.05 are in bold and those with *q*-value between 0.05 and 0.1 (suggestive associations) are in italics.

Table 2 Top 5 SNPs shared by MDD with CAD and lipid traits

Trait	Chr	SNP	Tdr_{11}	*Gene*
	2	rs10168194	0.862	*SPHKAP*
	10	rs1492705	0.847	
CAD	10	rs2639468	0.842	
	9	rs7028268	0.841	*CDKN2B-AS1*
	12	rs11172113	0.838	*LRP1; STAT6*
	12	rs10876041	0.555	*DIP2B*
	19	rs7252981	0.503	*PBX4*
LDL	1	rs12239399	0.499	
	11	rs888246	0.463	*SIK3; APOA1-AS*
	19	rs17347726	0.462	*ZNF229*
	12	rs838913	0.857	*SCARB1*
	3	rs9881942	0.811	*ADCY5*
HDL	16	rs176060	0.808	
	11	rs1900198	0.799	*SIK3*
	3	rs9831938	0.769	*ETV5*
	7	rs10261412	0.761	*CNTNAP2; RANP2*
	7	rs10261412	0.761	
TC	11	rs2080586	0.738	*SIK3*
	12	rs10876041	0.730	*DIP2B*
	19	rs7252981	0.680	*PBX4*
	11	rs2080586	0.712	*SIK3*
	11	rs1900198	0.709	*SIK3*
TG	17	rs12449442	0.692	*BPTF*
	19	rs7252981	0.646	*PBX4*
	6	rs1265093	0.645	*PSORS1C1; CCHCR1; PSORS1C2; POLR2LP1*

Please refer to the legends of Table 1 for abbreviations.

Table 3 Top 5 SNPs shared by MDD with obesity-related (left column) and glycemic traits (right column)

Trait	Chr	SNP	Tdr_{11}	*Gene*	Trait	Chr	SNP	Tdr_{11}	*Gene*
	3	rs12638263	0.922	*ETV5-AS1; ETV5*		10	rs10998853	0.404	
	1	rs11119409	0.897	*SYT14*		2	rs243085	0.401	
BMI	11	rs10742752	0.846		**DM**	12	rs3764002	0.382	*WSCD2*
	3	rs2332510	0.811	*ADCY5*		4	rs4834481	0.369	
	19	rs287104	0.809	*KCTD15*		2	rs243054	0.340	*MIR4432HG*
	15	rs12898654	0.823	*SKOR1; RNU6-1*		3	rs9865576	0.676	*ADCY5*
	8	rs7009799	0.800	*LINC00536*		11	rs7942309	0.597	
Fatpercent	3	rs2332510	0.794	*ADCY5*	**FG**	3	rs13097625	0.524	*PCNP*
	16	rs1477196	0.774	*FTO*		2	rs17265240	0.501	
	2	rs2943657	0.769			7	rs10260512	0.493	*DGKB*
	2	rs12617139	0.445	*STAM2*		2	rs17265240	0.382	
	12	rs11168547	0.408	*OR5BJ1P*		3	rs13097625	0.318	*PCNP*
Leptin	2	rs12468450	0.401		**FG -adjBMI**	11	rs377432	0.313	*PDE2A*
	14	rs10129827	0.399	*GPHN*		3	rs9865576	0.279	*ADCY5*
	14	rs6573663	0.398			7	rs10260512	0.278	*DGKB*
	18	rs1348017	0.253			12	rs1078869	0.389	
	14	rs8013247	0.223	*GPHN*		1	rs12043275	0.338	
Leptin -adjBMI	1	rs12144426	0.217		**INS2012**	19	rs4804833	0.316	*MAP2K7;LRRC8E*
	3	rs3863070	0.198	*KALRN*		7	rs38171	0.283	
	2	rs4832117	0.179	*TRABD2A*		11	rs6589846	0.263	*GRIK4*
	12	rs3764002	0.752	*WSCD2*		12	rs1078869	0.297	
	17	rs12449442	0.751	*BPTF*		7	rs38171	0.236	
WHR	3	rs2332510	0.686	*ADCY5*	**INS -adjBMI**	13	rs7339054	0.208	
	20	rs6090583	0.651	*EYA2*		19	rs4804833	0.196	*MAP2K7;LRRC8E*
	2	rs11695471	0.650	*DNMT3A*		1	rs10802828	0.172	*FMN2; RPS7P5*
	2	rs12991495	0.251	*DNMT3A*		10	rs10997875	0.498	*SIRT1; HERC4*
	7	rs12700794	0.237			11	rs6589846	0.409	*GRIK4*
WHR-adjBMI	12	rs3764002	0.203	*WSCD2*	**HOMA-IR**	18	rs10871708	0.386	
	20	rs1412957	0.159	*EYA2*		12	rs1078869	0.374	
	9	rs4149261	0.155	*ABCA1*		7	rs1915973	0.356	

Please refer to the legends of Table 1 for abbreviations.

Table 4. Top pathways enriched in genes shared by MDD with CAD and lipid-associated traits

	Pathway	*p*-value	*q*-value
CAD with MDD			
1.	Retinoid metabolism and transport	8.15E-05	1.03E-02
2.	Statin Pathway, Pharmacodynamics	3.41E-04	1.17E-02
3.	LDL-mediated lipid transport	4.46E-04	1.17E-02
4.	SREBP signalling	5.33E-04	1.17E-02
5.	Lipoprotein metabolism	5.90E-04	1.17E-02
6.	srebp control of lipid synthesis	6.22E-04	1.17E-02
7.	Statin Pathway	6.51E-04	1.17E-02
8.	Abacavir transport and metabolism	1.32E-03	1.98E-02
9.	Purine metabolism	1.42E-03	1.98E-02
10.	Visual phototransduction	1.94E-03	2.04E-02
Fat percentage with MDD			
1.	BDNF signaling pathway	3.66E-04	1.87E-02
2.	Pancreatic secretion - Homo sapiens (human)	1.54E-03	3.92E-02
3.	Neurotrophin signaling pathway - Homo sapiens (human)	2.91E-03	4.95E-02
4.	Oxytocin signaling pathway - Homo sapiens (human)	6.29E-03	7.84E-02
5.	Antiarrhythmic Pathway, Pharmacodynamics	7.69E-03	7.84E-02
HDL with MDD			
1.	Olfactory Signaling Pathway	4.15E-12	1.20E-09
2.	Olfactory transduction - Homo sapiens (human)	1.32E-10	1.91E-08
3.	Signaling by GPCR	1.21E-08	1.16E-06
4.	GPCR downstream signaling	1.42E-07	1.03E-05
5.	Signal Transduction	1.38E-05	7.97E-04
6.	Glycerophospholipid metabolism	7.50E-05	3.61E-03
7.	Glycerolipid metabolism - Homo sapiens (human)	1.02E-03	4.22E-02
8.	Cation-coupled Chloride cotransporters	1.17E-03	4.22E-02
9.	Lipoprotein metabolism	1.48E-03	4.58E-02
10.	Statin Pathway	1.63E-03	4.58E-02
TC with MDD			
1.	Regulation of Androgen receptor activity	4.84E-03	7.80E-02
2.	Constitutive Signaling by Aberrant PI3K in Cancer	6.86E-03	7.80E-02
3.	Vesicle-mediated transport	7.13E-03	7.80E-02
4.	RMTs methylate histone arginines	9.46E-03	7.80E-02

TG with MDD

1.	Neuronal System	7.31E-05	1.83E-03
2.	Transcriptional regulation of white adipocyte differentiation	2.53E-04	3.16E-03
3.	Uptake and actions of bacterial toxins	7.17E-04	5.97E-03
4.	Voltage gated Potassium channels	2.22E-03	1.39E-02
5.	Transmission across Chemical Synapses	4.31E-03	1.68E-02
6.	Amphetamine addiction - Homo sapiens (human)	5.22E-03	1.68E-02
7.	Endoderm Differentiation	5.37E-03	1.68E-02
8.	PPAR signaling pathway - Homo sapiens (human)	5.37E-03	1.68E-02
9.	Insulin secretion - Homo sapiens (human)	8.24E-03	2.13E-02
10.	GABAergic synapse - Homo sapiens (human)	8.80E-03	2.13E-02

Up to 10 most significantly enriched pathways with p-value <0.01 are listed. Cardiometabolic traits with no shared genetic variants having tdr_{11}>=0.5 are not included for analyses.

Table 5. Top pathways enriched in genes shared by MDD and obesity-related traits

	Pathway	*p*-value	*q*-value
BMI with MDD			
1.	Signaling by EGFR	3.61E-04	2.19E-02
2.	Oxytocin signaling pathway - Homo sapiens (human)	3.82E-04	2.19E-02
3.	NGF signalling via TRKA from the plasma membrane	5.39E-04	2.19E-02
4.	Downstream signaling of activated FGFR2	1.11E-03	2.19E-02
5.	Downstream signaling of activated FGFR1	1.11E-03	2.19E-02
6.	Downstream signaling of activated FGFR3	1.11E-03	2.19E-02
7.	Downstream signaling of activated FGFR4	1.11E-03	2.19E-02
8.	IL2	1.15E-03	2.19E-02
9.	Signaling by FGFR3	1.19E-03	2.19E-02
10.	Signaling by FGFR4	1.19E-03	2.19E-02
WHR with MDD			
1.	Insulin Signaling	1.52E-04	4.41E-03
2.	NGF signalling via TRKA from the plasma membrane	1.05E-03	9.53E-03
3.	Validated targets of C-MYC transcriptional repression	1.18E-03	9.53E-03
4.	Signaling Pathways in Glioblastoma	1.48E-03	9.53E-03
5.	Gap junction - Homo sapiens (human)	1.70E-03	9.53E-03
6.	Signalling by NGF	1.97E-03	9.53E-03
7.	Neurotrophin signaling pathway - Homo sapiens (human)	3.06E-03	1.27E-02
8.	BDNF signaling pathway	4.37E-03	1.58E-02
9.	Oxytocin signaling pathway - Homo sapiens (human)	5.24E-03	1.69E-02
10.	Chemokine signaling pathway - Homo sapiens (human)	7.35E-03	2.01E-02

The 10 most significantly enriched pathways with p-value <0.01 are listed. Cardiometabolic traits with no shared genetic variants having tdr_{11}>=0.5 are not included for analyses.

Table 6. Drugs enriched among the top shared genes between MDD and cardiometabolic traits

Drug	***p*-value**	***q*-value**	**Overlapped genes**
BMI with MDD			
bupropion	3.00E-04	4.50E-03	ERC2_CSMD1_SALL4_PCDH15
tamoxifen	1.40E-03	1.05E-02	ETS2_FOXO3_ERBB4
CAD with MDD			
atorvastatin	9.15E-05	1.70E-03	LPL_LPA_LDLR_SREBF1
lipase	2.00E-04	1.90E-03	LPL_LPA_LDLR_LRP1
rosuvastatin	4.00E-04	2.50E-03	LPL_CELSR2_LPA_LDLR
pravastatin	1.00E-03	3.80E-03	LPA_LDLR_SREBF1
fluvastatin	9.00E-04	3.80E-03	LDLR_SREBF1
lovastatin	1.50E-03	4.10E-03	LPL_LDLR_SREBF1
aminocaproic acid	1.30E-03	4.10E-03	PPP1R12A_LPA
simvastatin	2.10E-03	5.00E-03	LPL_LDLR_SREBF1
cyclosporine	8.80E-03	1.86E-02	AGT_ILF3
s-adenosylmethionine	1.03E-02	1.96E-02	AS3MT_CARM1
Fat percentage with MDD			
dantrolene	1.00E-04	1.10E-03	RYR2_ATP2A1
verapamil	2.00E-04	1.10E-03	SLC22A3_ATP2A1
isoproterenol	1.10E-03	3.00E-03	RYR2_ADCY5
caffeine	1.00E-03	3.00E-03	RPTOR_RYR2
epinephrine	2.10E-03	4.60E-03	RYR2_SLC22A3
tacrolimus	2.60E-03	4.80E-03	RPTOR_RYR2
atorvastatin	3.40E-03	5.30E-03	COBLL1_ABCA1
simvastatin	3.90E-03	5.40E-03	COBLL1_ABCA1
tobramycin	6.10E-03	7.50E-03	RNU6-1_IGF2BP1
adenosine	9.80E-03	1.08E-02	ATP2A1_BPTF_ABCA1
HDL with MDD			
simvastatin	3.00E-04	2.10E-03	LPL_SCARB1_MVK_ABCA1
fenofibrate	1.00E-04	2.10E-03	LPL_ABCA1_JMJD1C
lovastatin	2.00E-04	2.10E-03	LPL_SCARB1_MVK_ABCA1
glycine	3.00E-04	2.10E-03	LPL_TCAP_GRIN3A_TPM1_GPHN
probucol	6.00E-04	2.80E-03	SCARB1_ABCA1
lipase	5.00E-04	2.80E-03	LPL_SCARB1_ABCA1_ANGPTL4

yohimbine	9.00E-04	3.20E-03	GNAO1_NISCH
rosuvastatin	8.00E-04	3.20E-03	LPL_TCAP_SLC12A4_GNAO1
epinephrine	1.40E-03	4.20E-03	GRIN3A_GNAO1_NISCH
xanthophyll	1.50E-03	4.20E-03	SCARB1_STARD3
TC with MDD			
s-adenosylmethionine	1.60E-03	4.80E-03	EHMT2_CARM1
rosuvastatin	7.60E-03	1.12E-02	SLC12A4_PBX4
adenosine	1.12E-02	1.12E-02	SMARCA4_BPTF_CARM1
TG with MDD			
fenofibrate	1.00E-04	3.00E-04	LPL_JMJD1C
glycine	1.00E-04	3.00E-04	LPL_GPHN_STX1A
lipase	1.60E-03	3.20E-03	LPL_ANGPTL4
rosuvastatin	2.10E-03	3.20E-03	LPL_PBX4
heparin	4.10E-03	4.90E-03	LPL_ANGPTL4
glutathione	1.30E-02	1.30E-02	MPP5_STX1A
WHR with MDD			
tamoxifen	5.00E-04	5.00E-04	FOXO3_XBP1

Up to 10 most significant results with *q*-value <0.05 are shown. Note that we require at least two overlapping genes for each drug.

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