Metabolic Biomarkers of MDD Phenotype Heterogeneity

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INTRODUCTION

Major depressive disorder (MDD) affects one in six adults and can present serious life and health risks in any individual.[1] The lack of a single, concrete mechanistic foundation to depression has continued to complicate research in the field and clinical decision for treatment. This also contributes to MDD's heterogeneity, which arises from a combination of genetic, environmental and psychological factors.[2]

Stratification by phenotype may offer a refined perspective on MDD and enable personalized treatment approaches for remission, moving beyond the current trial-and-error methods.[3] The population-based UK Biobank (UKBB) study has been widely recognized for its extensive phenotyping and has enabled researchers like Cai et al. to develop several definitions of MDD that range in their depth of phenotyping.[4,5,6] In increasing order of granularity/severity, these categories include the no-MDD definition (GPNoDep); two broad definitions that include individuals who sought medical help for depression from either a general practitioner (GPpsy) or a psychiatrist/specialist (Psypsy); a symptom-based definition (DepAll); a self-reported definition (SelfRepDep); a medical-record-based definition based on electronic health records that included individuals who were clinically documented as showing symptomatic depression (ICD10Dep); and two Composite International Diagnostic Interview (CIDI)-based clinical diagnoses (LifetimeMDD, MDDRecur).[6] The first five MDD definitions are classified as minimally phenotyped while the latter two capture clinical diagnostic thresholds. Moreover, it has been found through GWAS that these different phenotypes have distinct genetic architectures,[9] with minimal phenotypes showing broader, nonspecific genetic influences while strictly defined MDD phenotypes exhibit higher SNP-based heritability and more MDD-specific genetic signals.

Importantly, MDD is often a recurrent disorder and it has been estimated that 85% of MDD patients in remission still experience at least one-depressive episode within the next 15 years, underscoring the need for early detection methods to identify individuals at heightened risk.[7,8] Recently, metabolomic biomarkers have been used to identify individuals at risk of developing MDD.[9] For instance, C-reactive protein has been reported to be elevated in MDD patients and even more so in those with treatment-resistant depression.[10] Other metabolites have mixed reported associations with MDD or general depressive symptoms, such as 3-Hydroxybutyrate, citrate, creatinine,[11] glycoprotein acetyls, isoleucine, very-low-density lipoproteins (VLDL) cholesterol, saturated fatty acid,[12] histidine, triglycerides,[13] etc. Generally, the association of specific metabolites with MDD has not been reliably replicated across independent studies, likely due to the broad range of metabolites and covariates, such as environmental factors, that indirectly influence metabolic levels.[14,15] Moreover, existing studies often treat depression as a binary category, failing to account for the spectrum of MDD presentations and nuanced

phenotyping. A recent metabolomics study examined the causal association between lifetime MDD and fatty acids but did not explore how these associations vary across different MDD phenotypes.[16] Addressing these challenges requires investigating whether metabolite associations differ systematically across phenotypes of varying severity, offering a potential pathway to enhance our understanding of MDD and refine approaches for phenotype-specific classification and risk assessment.[11]

By aligning metabolomic data with the stratified MDD phenotypes developed by Cai et al., this study aims to determine whether metabolite levels systematically change in correlation with depth of depression phenotypes. Using multivariable logistic regression models, this study examines whether individual metabolic markers and covariates show systematic differences across MDD phenotypes, reflecting variations in severity and specificity. Additionally, the study examines whether residualization, which isolates non-genetic components of metabolite variation, can reveal how non-genetic influences contribute to metabolic variability across MDD phenotypes. By investigating the interplay between metabolic and phenotypic specificity, this research seeks to move beyond the generalized “one size fits all” approach to MDD, establishing a foundation for personalized and phenotype-specific assessments.

METHODS

Metabolic, Phenotypic, and Covariate Data

Plasma nuclear magnetic resonance (NMR) metabolic biomarkers were generated by Nightingale Health between 2019 and 2020 using eight spectrometers from approximately 280,000 participants in the UK Biobank.[17,18,19] The biomarker profiling included 251 measures of fatty acids, lipoprotein subclasses, and small molecules (amino acids, ketones, glycolysis metabolites, etc.). NMR metabolomic variables were z-score normalized to follow a normal distribution, and allow for comparability across subjects and features. Depression phenotypes were ascertained based on prior work, which stratified depression from minimally-defined to strictly defined phenotypes. Specifically, this included 9 phenotypes, ranging in depth from GPNoDep (UKBB fields 2090-20126), GPpsy (UKBB field 2090), Psypsy (UKBB field 2100), DepAll (UKBB field 20126), SelfRepDep (UKBB field 20002), ICD10Dep (UKBB field 41202 & 41204), LifetimeMDD (UKBB field 20440), and MDDRecur (UKBB field 20442).[6] Briefly, minimal phenotyping includes help-seeking definitions such as GPNoDep (no cardinal symptoms), GPpsy (seen by a GP), and Psypsy (seen by a psychiatrist). Symptom-based definitions include DepAll (reporting low mood or anhedonia for two weeks) and SelfRepDep (self-reported non-cancer illness code). The EMR-based definition, ICD10Dep, utilizes diagnostic ICD-10 codes for depression. Strictly defined phenotypes LifetimeMDD and MDDRecur rely on the CIDI framework, which includes cardinal symptoms, functional impairment, and recurrence of depressive episodes.[6] Covariates included age (UKBB field 21022), sex (UKBB field 31), assessment center (UKBB field 54),[21] BMI (UKBB field 21001), waist circumference (UKBB field 48), hip circumference (UKBB field 49), and diabetes diagnosis (UKBB field 2443).[21,22]

Mutual Information Metrics for Feature Selection

The `infotheo` R package was utilized to calculate the mutual information metrics between pairs of metabolites for each phenotype; with 251 metabolite biomarkers, mutual information was computed for 31,375 unique metabolite pairs. After the metabolic data was discretized, an empirical entropy estimator method was used for the calculations. To minimize redundancy or noise among metabolite pairs, various quantile cutoffs (95%, 99%, 99.5%, 99.9%) were evaluated to determine the optimal threshold that eliminated noise while preserving meaningful metabolite differences across phenotypes. The `igraph` package was used to perform Louvain clustering on the significant edges, enabling the selection of representative features from each cluster. These representative features were then subjected to consensus feature selection, where feature selection was first performed individually for each phenotype and then compared across all phenotypes. Only features consistently selected across all phenotypes were retained in the final feature set. This approach ensured uniformity in feature selection and mitigated phenotype-specific biases in feature associations.

Multivariable Logistic Regression & Odds Ratio Analysis

Multivariable logistic regression models were performed for each MDD phenotype, using consensus features derived from the previously stated quantile cutoffs and covariates as previously described (age, sex, BMI, etc.). The binary outcome (case vs. control) was used to assess the associations between Nightingale biomarkers and each MDD phenotype. The odds ratios, 95% confidence intervals ascertained using the profile likelihood method, and false discovery rate (FDR)-adjusted p-values for each feature/biomarker were calculated from each regression model and used for comparative analyses between phenotypes.

To address the low statistical power of comparisons between individual metabolites, metabolites were grouped into 47 categories based on Nightingale's specified sub-groups, such as triglycerides and cholesterol. This grouping allowed for more robust and generalized comparisons across MDD phenotypes. The Kruskal-Wallis test was used to evaluate differences across phenotypes for each metabolite and metabolite group considering the non-normal nature of the data. Post-hoc Dunn tests were performed with the Benjamini-Hochberg method to identify specific phenotype pairs with significant differences in relation to the metabolite or metabolite grouping. The pairwise comparison outputs guided the determination of the optimal quantile cutoff for the consensus features selected for the metabolite and group analyses.

Residualizing Metabolites for Genetic Influences

The machine learning (ML)-predicted genetic scores for 133 of Nightingale's metabolic traits in UKBB subjects were obtained from OmicsPred; they used Bayesian ridge regression models with single nucleotide polymorphisms (SNPs) as predictors to estimate individuals' blood levels of these molecular traits.[23] Metabolites whose genetic scores explain at least 1% of the variance in their levels were kept for analysis. To account for genetically predicted variance in NMR metabolomic biomarkers, a linear regression model was fitted with the z-score normalized actual metabolite levels as the outcome and the genetically imputed metabolomic variables as predictors. The residuals from this model represented metabolite levels adjusted for genetic

predictors, isolating the variation unexplained by genetic contributions to better understand other influencing factors, such as environmental and non-genetic effects.

The multivariable logistic regression was rerun using the residualized data for the 133 features and repeated using the non-residualized data. The features' ORs and significance levels were compared between the residualized and non-residualized data for each phenotype as well as across phenotypes.

RESULTS

Distribution of Post-QC Data

The multivariable logistic regression models with features filtered at different quantile cutoffs were compared to identify the threshold that maximizes biologically relevant metabolite variability while minimizing noise. The number of significant pairwise comparisons from each method was evaluated (Supplementary Figure 1) to determine the optimal balance between retaining variability and reducing redundancy. While the full dataset yielded a high number of significant comparisons, this likely included a substantial amount of noise as there were 56 less significant pairwise comparisons in the 99.9% cutoff. The 99.5% cutoff resulted in a sharper drop of 73 significant comparisons, indicating a notable loss of meaningful metabolite variability. Interestingly, increasing the quantile cutoff resulted in an increased number of features included, as larger clusters were formed potentially due to overclustering, capturing additional features that might have been excluded at lower cutoffs. Therefore, the 99.9% cutoff was chosen as it effectively retains the biologically relevant features while reducing unnecessary noise and overlap among metabolites.

To identify the metabolites removed by applying the 99.9% cutoff, a network plot was generated (**Figure 1**). Data from all MDD phenotypes were aggregated to create a consensus network. This network comprised 54 unique metabolite features organized into 22 clusters using Louvain clustering, with cluster sizes ranging from 2 to 4 features. Representative features from each cluster were selected based on their average mutual information within the cluster, leaving 218 metabolite features from the original 251. Clusters included highly correlated metabolites such as Total Cholesterol and Total Esterified Cholesterol, as well as Total Lipids in Very Large HDL and Phospholipids in Very Large HDL. These results highlight the removal of redundant and noise-inducing metabolites, enabling a more focused and robust analysis. Interestingly, six features were kept in the phenotype-specific networks but did not overlap with the consensus set, which may be suggestive of potential phenotype-specific metabolic signals (Supplementary Table 1).

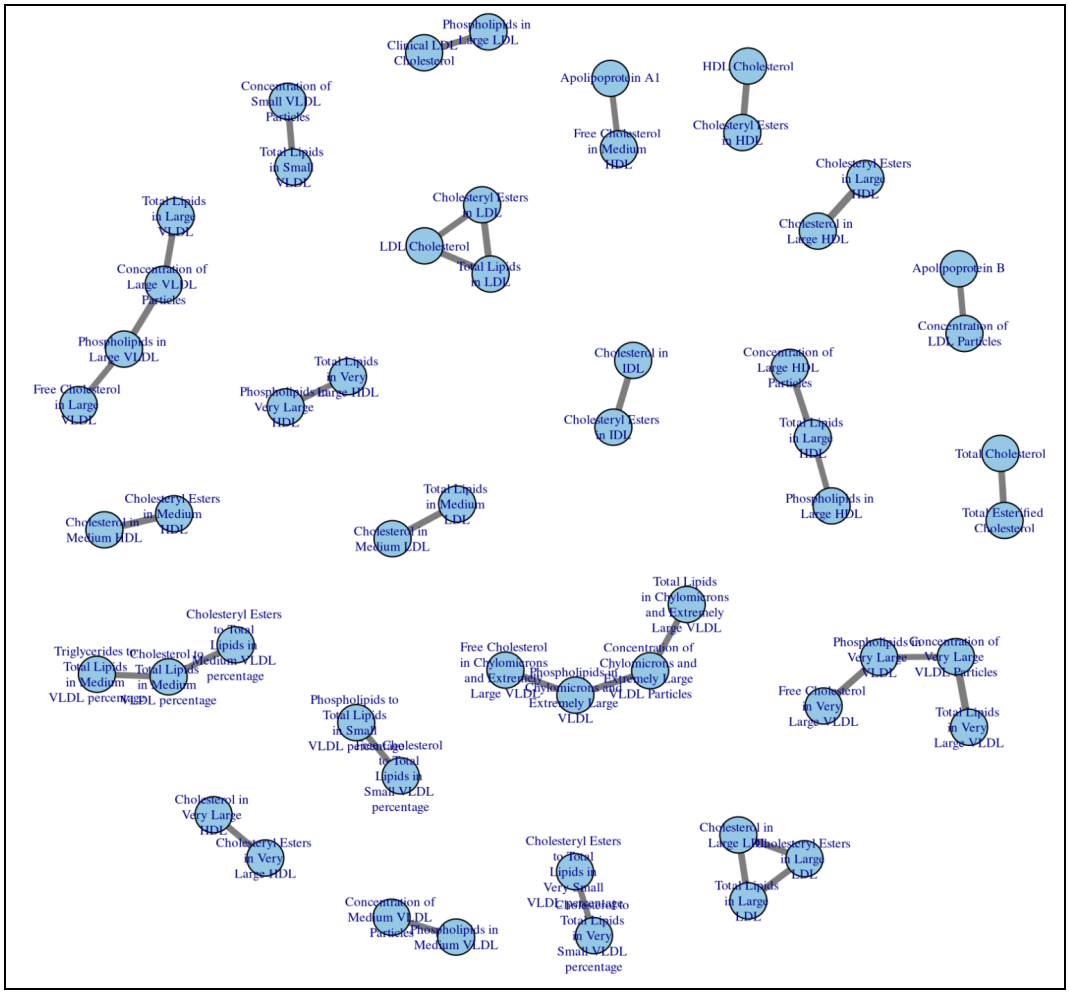

Figure 1. Consensus Mutual Information Network Plot for MDD Phenotypes.
Nodes represent metabolites, and edges indicate significant mutual information relationships. Clusters were identified using Louvain clustering.

Metabolic Variability Across MDD Phenotypes

The distributions of metabolite odds ratios (ORs) were analyzed across MDD phenotypes (**Figure 2**). Most phenotypes exhibited ORs centered around 1.0, indicating minimal variation in metabolite associations. However, the SelfRepDep phenotype displayed a slightly higher mean OR closer to 1.05, suggesting stronger associations with specific metabolites. Additionally, the ICD10Dep phenotype showed a broader distribution of ORs, potentially reflecting greater heterogeneity within this group. The case and control counts for each phenotype (Supplementary Figure 2) revealed notably low case-to-control ratios for SelfRepDep and ICD10Dep, which may contribute to the variability in their OR distributions.

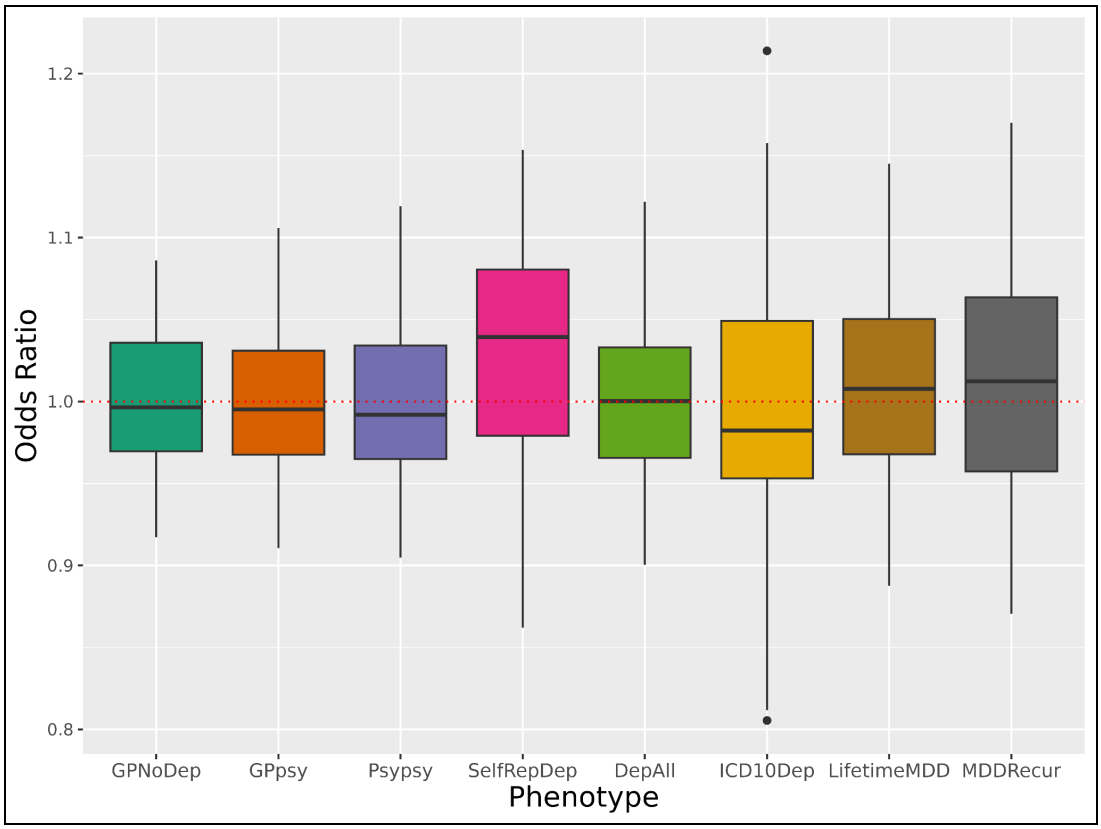

Figure 2. Distribution of Odds Ratios by MDD Phenotype

Significant Metabolite Group-Level Differences

To evaluate both individual and group-level metabolic differences across MDD phenotypes, Kruskal-Wallis tests were conducted on the individual metabolites and the Nightingale-defined metabolite groupings. While no individual metabolites had statistical significance between phenotypes, 14 metabolite groups demonstrated significance. These groups include branched amino acids; very small, small, medium, large, and very large very-low-density lipoproteins (VLDL); chylomicrons and extremely large VLDL; triglycerides; small and medium low-density lipoproteins (LDL); intermediate-density lipoproteins (IDL); ketone bodies; very large high-density lipoprotein (HDL); and cholesterol (**Table 1**). Post-hoc Dunn tests were conducted to see the exact phenotypes these groups have observed differences in. There were 150 reported significant pairwise comparisons between phenotypes across these groups (Supplementary Table 2).

Table 1. Significant Metabolite Groups From Kruskal-Wallis Tests

Group	Kruskal Statistic	p-value
Branched-Chain Amino Acids	29.06	0.00014
Very small VLDL	27.85	0.00023
Chylomicrons and extremely large VLDL	26.61	0.00039
Small VLDL	26.34	0.00044
Triglycerides	25.78	0.00055
Small LDL	25.05	0.00074
Large VLDL	23.77	0.00125
Medium VLDL	23.61	0.00133
Very large VLDL	21.86	0.00268
Medium LDL	19.92	0.00574
IDL	19.68	0.00630
Ketone Bodies	17.69	0.01343
Very large HDL	14.56	0.04210
Cholesterol	14.20	0.04778

Comparing Metabolite Groups Across Phenotypes

To further investigate these group-level differences, a heatmap of mean ORs by metabolite group and phenotype was created (**Figure 3**). The detailed OR distributions for individual metabolites across MDD phenotypes (Supplementary Figure 3) highlight subtle variations that are not as discernible as those at the group-level. With this, the heatmap provides a more qualitative comparative approach that consolidates these granular patterns for phenotype-specific comparisons.

The data generally highlights the relative homogeneity of odds ratios (ORs) across MDD phenotypes, with a few notable deviations. Among these, ICD10Dep stands out for its significantly higher ORs in the inflammation-related metabolite group, which may be attributed to the broader distribution of ORs previously observed for this phenotype, potentially reflecting greater heterogeneity within this group. Similarly, SelfRepDep exhibited higher ORs in several metabolite groups, which may be attributed to its broad and ambiguous phenotype definition, capturing individuals with varying levels of depressive symptoms and comorbidities. In contrast,

GPNoDep appeared distinct within lipid-related groups, particularly those involving very large VLDL ratios, likely due to its classification as a non-depressed phenotype.

Additionally, a pattern emerges for lipid-related metabolite groups such as triglycerides, small VLDL, and large VLDL, where ORs appear to increase progressively with the depth of MDD phenotypes.

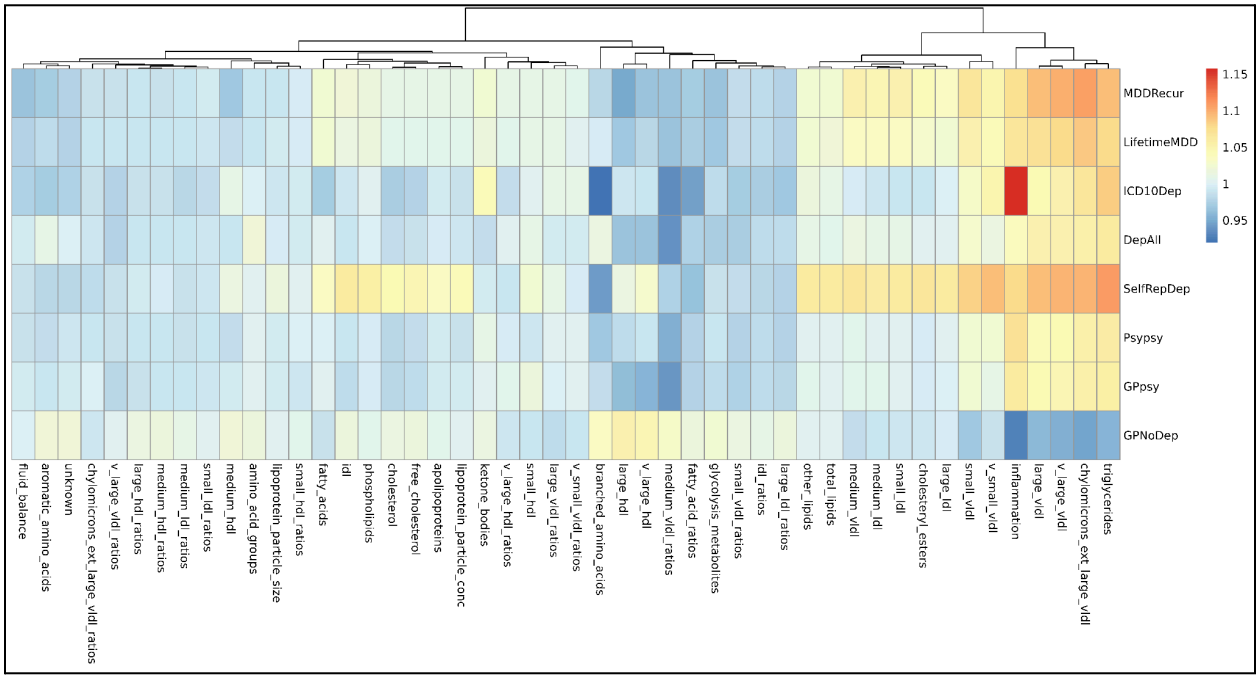

Figure 3. Heatmap of Mean Odds Ratios by Metabolite Group and MDD Phenotype

From both the Kruskal-Wallis test and heatmap results, the metabolite groups with significant differences were examined in greater detail to better understand the variability these groups exhibit between MDD phenotypes (Supplementary Figure 4). Across phenotypes, the overall range and direction of metabolite odds ratios were largely consistent. Notably, a pattern for specific lipid metabolites commonly associated with MDD was identified where odds ratios tended to be higher (though non-significantly) with increasing phenotype specificity (**Figure 4**). While ORs remain relatively similar across phenotypes, the observed trends suggest that these lipid metabolites may reflect varying degrees of depressive symptomatology, depending on the nature of their association with MDD. This pattern is most prominent in lipid groups, including phospholipids in large VLDL, triglycerides in very small, small, and very large VLDL, and HDL cholesterol.

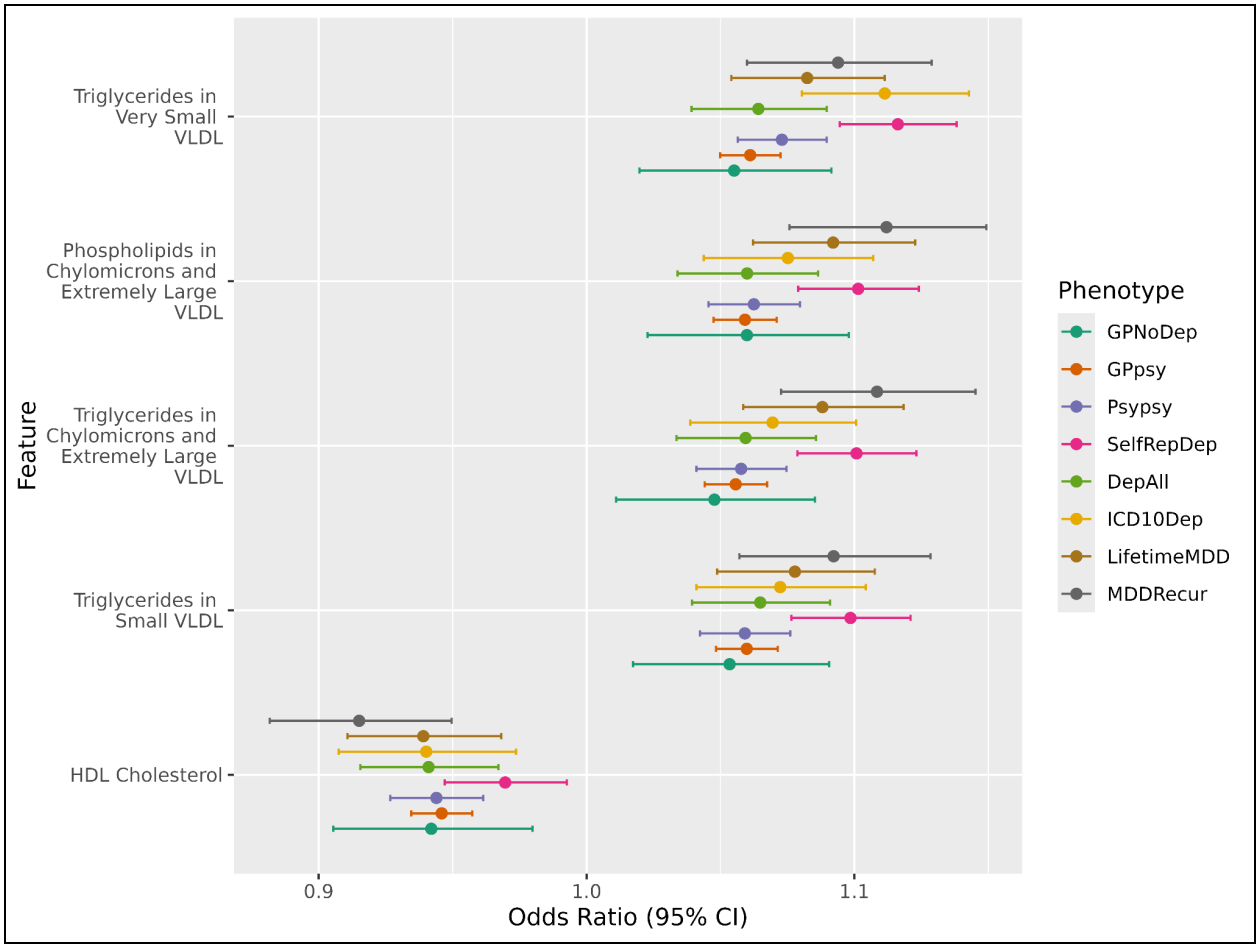

Figure 4. MDD-Severity and Odds Ratios Gradient Distribution Across Phenotypes

*Full opacity indicate significant results, lower intensity indicate insignificant results

Residualization Effectiveness Analysis

Residuals were calculated for 133 metabolites with ML-predicted genetic scores to isolate the non-genetic components of metabolite variation. Residualization had minimal impact on the number of significant features across phenotypes (**Figure 5**) and on the odds ratio distributions (**Figure 6**). In some cases, fewer significant features were observed after residualization, likely due to the removal of genetic variance that contributed to associations in the non-residualized data. These results suggest that residualization, under the current analysis conditions, did not substantially enhance the detection of additional metabolite associations potentially driven by non-genetic factors.

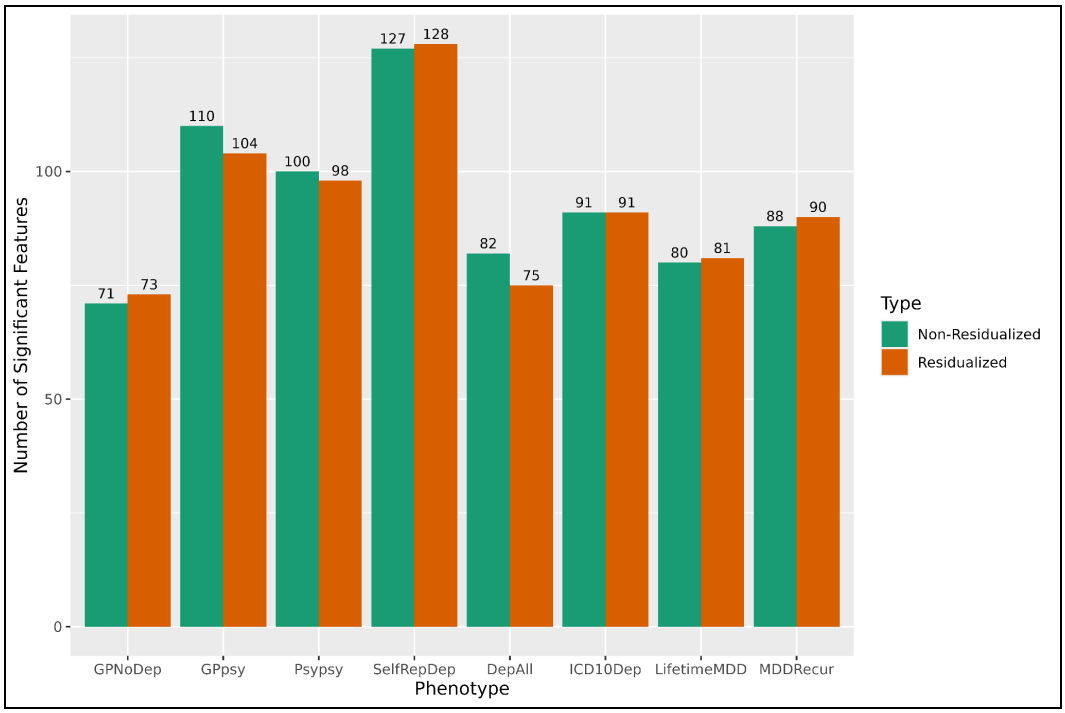

Figure 5. Changes in Number of Significant Features From Residualization Across MDD Phenotypes

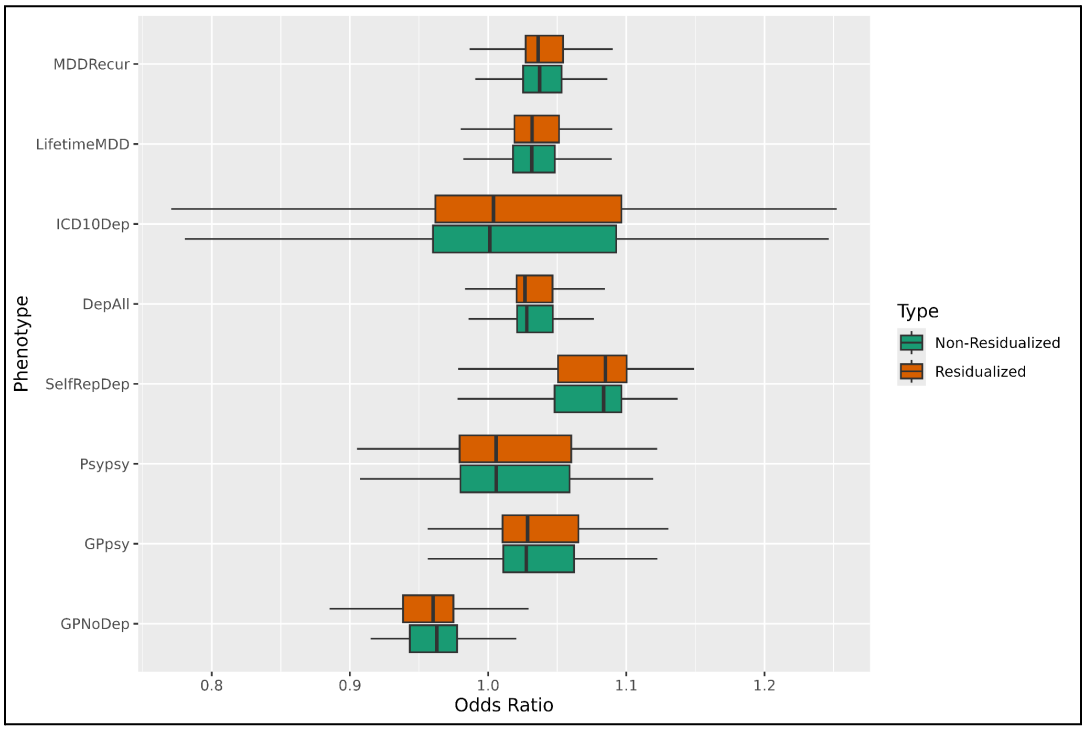

Figure 6. Changes in MDD Phenotype Odds Ratios Distributions from Residualization

DISCUSSION

This study expands on existing research linking metabolites to depression[23,24,25,26,27] by extending the analysis to stratified phenotypes of MDD of varying specificities. Through this approach, differences in lipid-related metabolites were observed across phenotypes, such as triglycerides, phospholipids, HDL cholesterol, and VLDL subclasses. These findings are consistent with previous studies reporting elevated triglyceride levels,[28] reduced HDL cholesterol levels,[29] and increased remnant cholesterol, including VLDL subclasses[30] in individuals with MDD. This is the first reported instance of these lipid metabolites being used to reflect phenotypic heterogeneity within MDD. Additionally, this study marks the first analysis of residualization on these metabolites in MDD, highlighting that residualization had minimal impact on metabolic variability across stratified phenotypes.

The observed patterns in lipid-related metabolites align with the findings of Cai et al., where strictly defined MDD phenotypes have stronger genetic contributions and more specific genetic markers compared to broader, minimal definitions. This progression likely reflects increasing clinical and genetic specificity, driving the metabolic dysregulation observed in severe MDD phenotypes. By incorporating stratified phenotypes, this study reinforces the role of lipid dysregulation in MDD and highlights its potential to reflect varying levels of severity across phenotypes. While this stratified approach identified metabolite associations across phenotypes, it did not replicate the fatty acid causal relationship recently reported in the literature,[16] potentially due to differences in MDD phenotype definitions and the absence of causal inference modeling in this analysis.

However, the variability in metabolite associations for minimal phenotypes like SelfRepDep and ICD10Dep suggests limitations in their specificity. SelfRepDep, in particular, frequently deviated from the observed gradient across phenotypes, likely due to its broad and ambiguous definition, which captures individuals with varying levels of depressive symptoms and comorbidities. These minimal phenotyping groups, characterized by lower SNP-based heritability and broader genetic influences, may include signals overlapping with traits such as neuroticism or general distress, diluting their metabolic associations. Additionally, residualization had limited impact on significant features and odds ratio distributions. The consideration of non-genetic factors did not reveal additional significant associations, likely due to the strong genetic contributions already captured in the analysis. Moreover, the predominantly European composition of the dataset further limits the generalizability of these findings, especially considering how metabolite associations may differ across diverse populations.

Future validation studies are needed to confirm which metabolites or metabolite groups are most reflective of MDD severity. Additionally, refined phenotyping methods are necessary to better define the boundaries of MDD phenotypes and ensure that their physiological and psychological dimensions are accurately captured. These efforts could pave the way for developing blood-based biomarkers that enable more precise stratification and identification of MDD phenotypes. Such biomarkers could facilitate the early detection of initial MDD phenotypes, enabling preventive interventions before the progression to more severe forms of the disorder.

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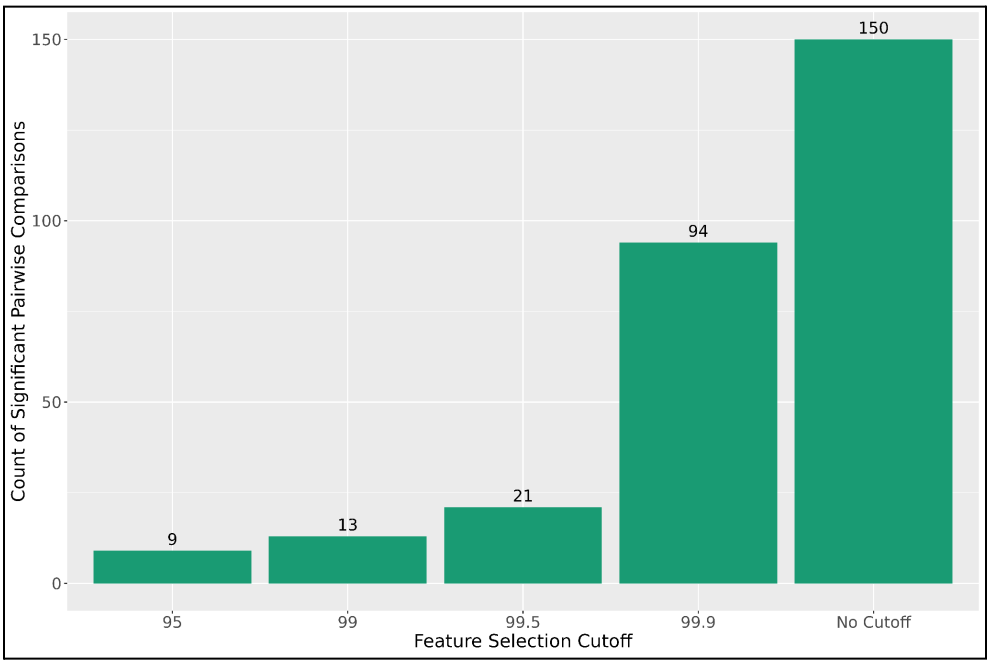
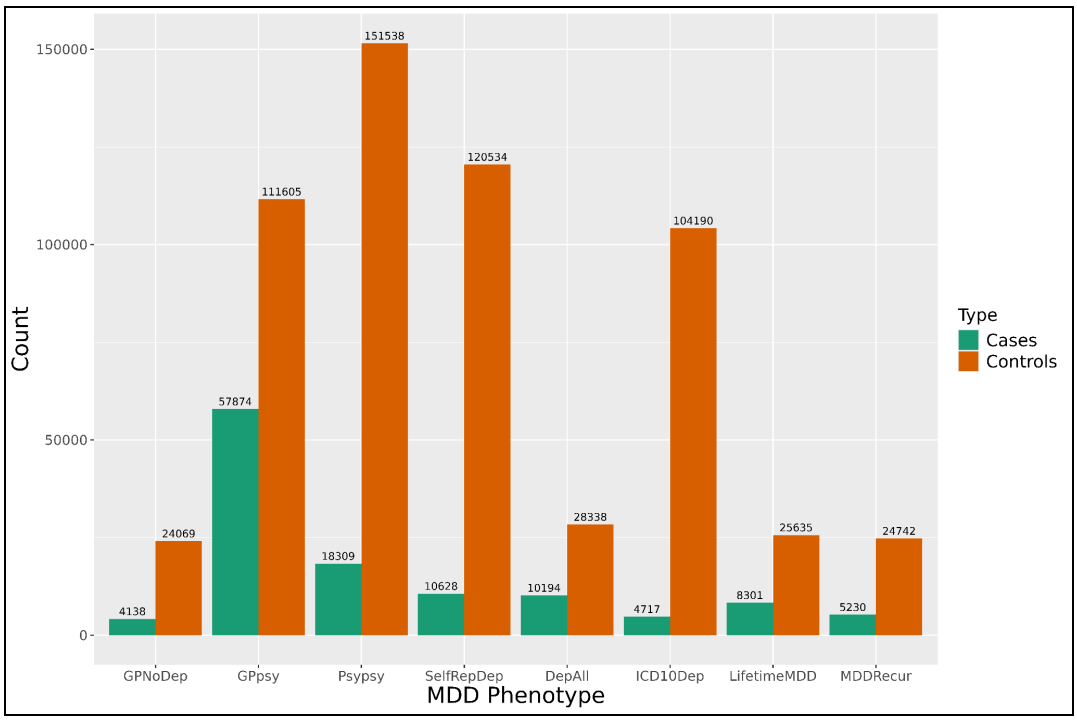
SUPPLEMENTARY FIGURES



Supplementary Figure 1: Change in Number of Significant Pairwise Comparisons at Different Feature Selection Quantile Cutoffs



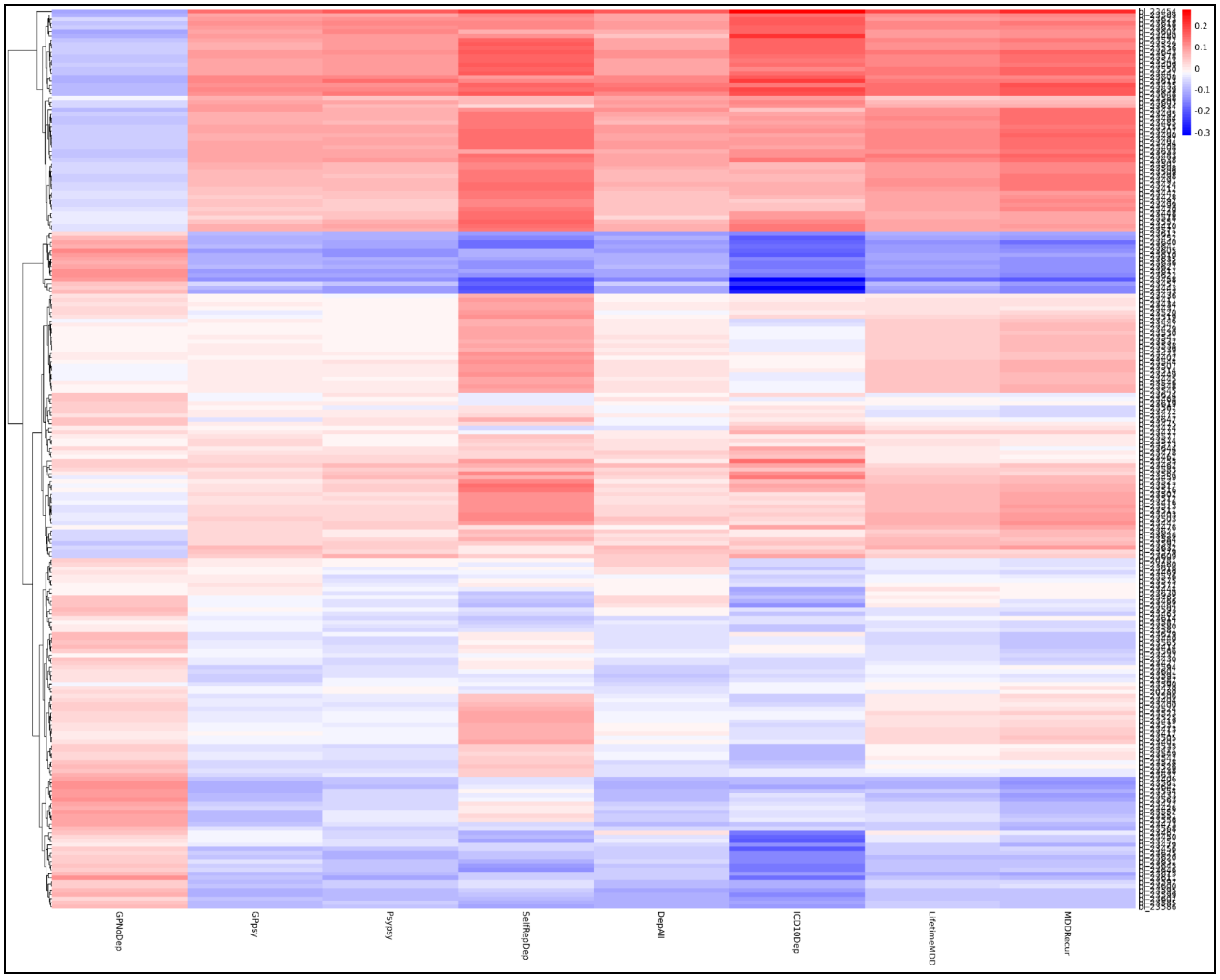
Supplementary Figure 2: Counts of Cases and Controls by MDD Phenotype

Supplementary Table 1: Features that Made Phenotype-Specific Feature Cutoff But Not Consensus Feature Selection

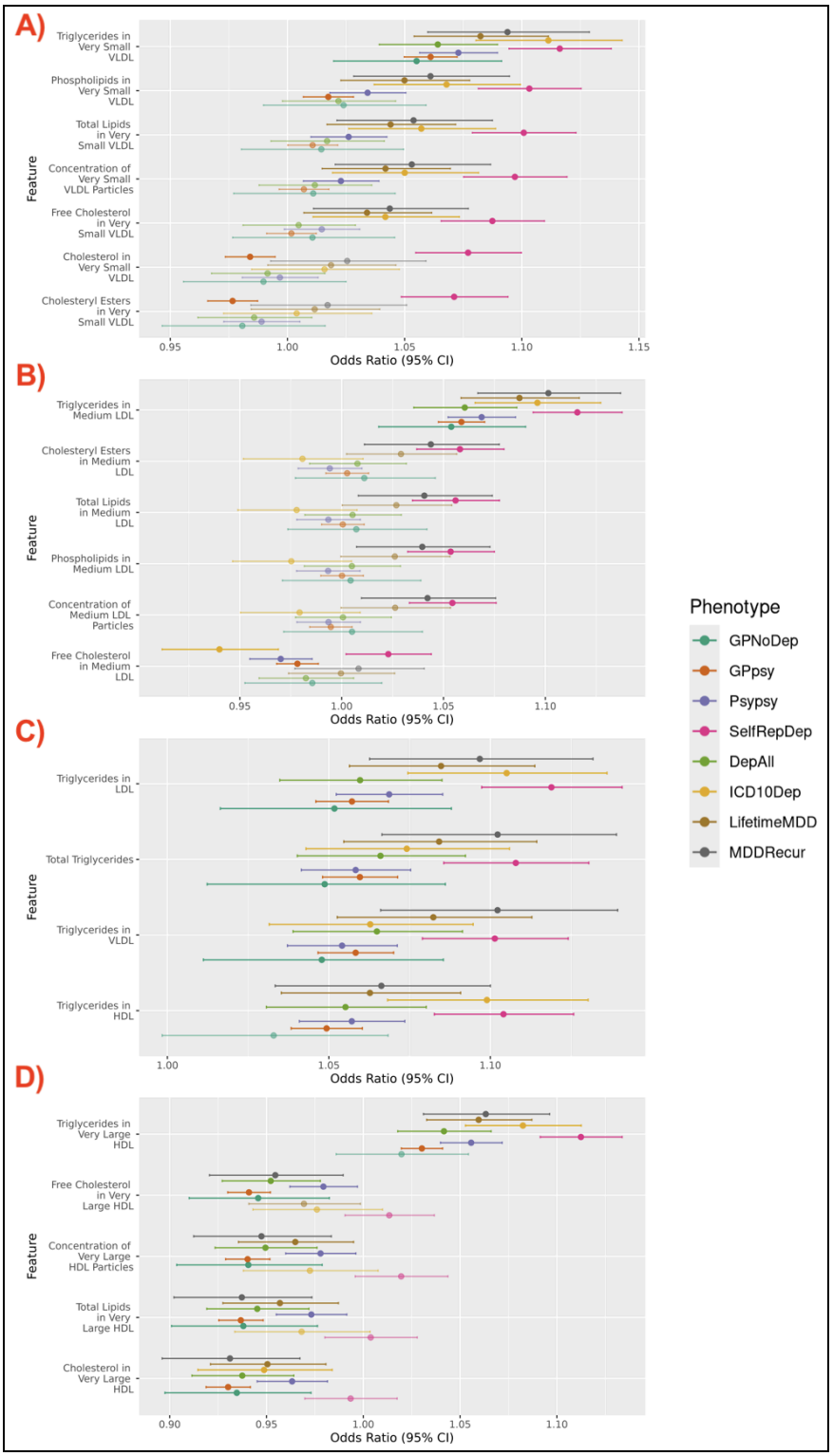
Feature	# of Phenotypes that Met the Cutoff
Apolipoprotein B	6
Total Lipids in Large HDL	6
Free Cholesterol to Total Lipids in Small VLDL percentage	6
Phospholipids in Very Large HDL	2
Concentration of Large HDL Particles	2
Phospholipids in Large HDL	2

Supplementary Table 2: 10 Significant Pairwise Comparisons between Metabolic Groups

Group	Comparison	Z-Value	p-Value
branched_amino_acids	DepAll - GPNoDep	2.675913	0.017389388
v_small_vldl	GPpsy - MDDRecur	-2.441639	0.040938138
chylomicrons_ext_large_vldl	DepAll - LifetimeMDD	-2.110579	0.048731870
small_vldl	DepAll - MDDRecur	-2.598076	0.016405845
triglycerides	GPNoDep - LifetimeMDD	-2.600535	0.021718300
small_ldl	GPpsy - MDDRecur	-2.490799	0.025491212
large_vldl	DepAll - MDDRecur	-2.110579	0.044301700
medium_vldl	GPpsy - MDDRecur	-2.371260	0.031023220
v_large_vldl	GPpsy - MDDRecur	-2.788980	0.018506019
medium_ldl	MDDRecur - Psypsy	2.453739	0.039586314



Supplementary Figure 3: Heatmap of Metabolite Odds Ratios Across MDD Phenotypes



Supplementary Figure 4. Distribution of Odds Ratios Across Phenotypes for A) Very Small VLDL, B) Medium LDL, C) Triglycerides, and D) Very Large HDL*

*Full opacity indicate significant results, lower intensity indicate insignificant results