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ORIGINAL ARTICLE

Case Control Study

Alterations of serum metabolic profile in major depressive disorder: A case-control study in the Chinese population

Bing Cao, Yuan-Li Liu, Na Wang, Yan Huang, Chen-Xuan Lu, Qian-Ying Li, Hong-Yu Zou

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Abstract

BACKGROUND

Major depressive disorder (MDD) is characterized by persistent depressed mood and cognitive symptoms. This study aimed to discover biomarkers for MDD, explore its pathological mechanisms, and examine the associations of the identified biomarkers with clinical and psychological variables.

AIM

To discover candidate biomarkers for MDD identification and provide insight into the pathological mechanism of MDD.

METHODS

The current study adopted a single-center cross-sectional case-control design. Serum samples were obtained from 100 individuals diagnosed with MDD and 97 healthy controls (HCs) aged between 18 to 60 years. Metabolomics was performed on an Ultimate 3000 UHPLC system coupled with Q-Exactive MS (Thermo Scientific). The online software Metaboanalyst 6.0 was used to process and analyze the acquired raw data of peak intensities from the instrument.

RESULTS

The study included 100 MDD patients and 97 HCs. Metabolomic profiling identified 35 significantly different metabolites (*e.g.*, cortisol, sebacic acid, and L-

glutamic acid). Receiver operating characteristic curve analysis highlighted 8-HETE, 10-HDoHE, cortisol, 12-HHTrE, and 10-hydroxydecanoic acid as top diagnostic biomarkers for MDD. Significant correlations were found between metabolites (*e.g.*, some lipids, steroids, and amino acids) and clinical and psychological variables.

CONCLUSION

Our study reported metabolites (some lipids, steroids, amino acids, carnitines, and alkaloids) responsible for discriminating MDD patients and HCs. This metabolite profile may enable the development of a laboratory-based diagnostic test for MDD. The mechanisms underlying the association between psychological or clinical variables and differential metabolites deserve further exploration.

Key Words: Metabolites; Serum metabolic profiling; Major depressive disorder; Psychological variables; Clinical variables

Core Tip: Our study reported metabolites (some lipids, steroids, amino acids, carnitines, and alkaloids) responsible for discriminating major depressive disorder (MDD) patients and healthy controls. This metabolite signature may facilitate the development of a laboratory-based diagnostic test for MDD. The mechanisms underlying the association between psychological or clinical variables and differential metabolites deserve further exploration.

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INTRODUCTION

Major depressive disorder (MDD) is characterized by persistent depressed mood, loss of interest or pleasure in previously enjoyable activities, recurrent thoughts of death, and physical and cognitive symptoms[1], which is highly prevalent and disabling. The Global Burden of Disease Study (GBD 2021) estimated that approximately 4.7% of people worldwide had a depressive episode in the past 12 months. Currently, the diagnosis of MDD still relies on the subjective identification of symptom clusters rather than empirical laboratory tests. The current diagnostic modality results in a considerable error rate. Thus, the diagnosis of MDD is still difficult[2]. A meta-analysis in 2022 indicated that the extremely low detection of depression by primary care clinicians poses a serious threat to scaling up mental healthcare in low and middle-income countries[3]. Consequently, the identification of high-quality depression biomarkers and the development of precise and accessible early diagnostic tools are imperative[4]. However, research in this field has thus far[2] not lived up to its potential[2].

The scientific community concurs that several biological, psychological, and social environmental variables collectively contribute to the pathogenesis of MDD[5]. The biogenic amine (monoamine) hypothesis, neuroendocrine dysregulation, cytokine theory, and hereditary variables[6], are several pathophysiological mechanisms of MDD that are generally agreed upon[7]. Specific to the field of metabolomics, there have been some comparisons between MDD and healthy controls (HCs) in previous studies. A comprehensive meta-analysis revealed 23 differentially expressed metabolites between patients with MDD and controls across 46 studies, encompassing amino acids (L-glutamine, L-serine, L-methionine, and L-tryptophan), lipids [phosphatidylcholine (32:1), linoleic acid, palmitoleic acid, oleic acid, dodecanoic acid, and palmitic acid], carnitines (L-acetylcarnitine), and various other metabolites[8]. Paige *et al*[9] reported that several fatty acids, glycerol, and γ-aminobutyric acid (GABA) were altered in currently depressed patients when compared with controls. Zheng *et al*[10] found 17 differentially expressed peripheral blood mononuclear cell metabolites to discriminate patients with MDD from HCs, including amino acids (GABA, homoserine, isoleucine, and valine), lipids (octanoic acid, lanosterol, and γ-tocopherol), and some other metabolites. Ali-Sisto *et al*[11] indicated that serum concentrations of inosine and guanosine diminished, while the levels of xanthine and adenosine were elevated in participants with MDD compared to non-depressed controls. Despite advancements in metabolomics research concerning MDD, the majority of these studies have produced inconsistent findings, hence limiting their clinical applicability. Previous studies have also demonstrated that psychological variables [including the Snaith-Hamilton Pleasure Scale (SHAPS), the 5-item World Health Organization Well-Being Index (WHO-5), the Hamilton Depression Rating Scale-24 items (HAMD-24), and the Generalized Anxiety Disorder 7-item scale (GAD-7)] and clinical variables [body mass index (BMI)] play roles in regulating differential metabolites. Irregularities in reward processing are significant indicators of MDD and schizophrenia[12]. Specifically, these variables may influence metabolic pathways through mechanisms such as neuroendocrine regulation, inflammation, and oxidative stress, thereby contributing to the metabolic alterations observed in psychiatric disorders. Anhedonia may also affect metabolite production and regulation through neuroendocrine pathways[13]. The WHO-5 is one of the most commonly used questionnaires for evaluating subjective psychological well-being[14]. A systematic study indicated a potential beneficial correlation between the neurotransmitter serotonin and well-being (*i.e.*,

hedonic well-being). The evidence on the role of additional small molecules, including metabolites, remains inconclusive [15]. A recent large-scale metabolomics meta-analysis showed that depression is associated with a signature in circulating metabolites[16], suggesting that changes in HAMD-24 scores may indirectly reflect dynamic changes in metabolites. GAD-7 is used to assess the severity of anxiety symptoms. Metabolite association studies examining anxiety in animal models and clinical cohorts have revealed changed concentrations of several metabolites[17]. The BMI is the best available tool for monitoring progress in the campaign against obesity[18]. An increasing body of evidence indicates that metabolic abnormalities arising from central obesity, which contribute to metabolic disorders, may also account for the heightened prevalence of depression in individuals with obesity[19]. Furthermore, renal function levels may indirectly indicate human metabolism and excretion. Evidence indicates that patients with depression frequently exhibit renal function abnormalities[20].

In this study, liquid chromatography coupled with mass spectrometry (LC-MS) was used to identify the differential metabolites in serum samples from patients with MDD and HCs, with an aim to discover candidate biomarkers for MDD identification and provide insight into the pathological mechanism of MDD. We also attempted to explore the metabolic mechanisms of differential metabolites by examining their association with other clinical variables [BMI, blood urea nitrogen (BUN), creatinine (CREA), and uric acid (URIC)] and psychological variables [disease severity, pleasure deficit (SHAPS), anxiety (GAD-7), and well-being (WHO-5)].

MATERIALS AND METHODS

Ethical approval

This study was approved by the Ethics Committee of Chongqing Ninth People's Hospital (Approval No. IRB-2021-016), and performed conforming to the Declaration of Helsinki. Before sample collection, written informed consent was obtained from all participants.

Study design and participants

A cross-sectional patient-control design was employed to compare patients with MDD aged 18 to 60 years to age- and region-matched controls who had never experienced depression, in order to delineate the metabolic profile of MDD patients[2,21]. A total of 197 participants were enrolled in this study, including 100 patients diagnosed with MDD and 97 HCs. All participants were voluntarily recruited from Chongqing Ninth People's Hospital in Chongqing, China between January 2022 and December 2024. The DSM-V diagnostic criteria and the HAMD-24 were evaluated for a singular depressive episode and the severity of patients with MDD, respectively. Only depressive patients with an HAMD-24 score of 20 or above were included. Participants with depression who had confounding variables, including additional mental diseases, a history of mental illness, illicit substance use, and significant physical disabilities, were excluded from this study. The study included individuals with MDD who were experiencing their initial episode, or drug-treated but had not previously taken antidepressants or antipsychotics within the past month. The HCs were typical cohorts from the physical examination center, free from the previously described interference factors.

Demographic and clinical information collection

Demographic information from all participants was collected by trained healthcare workers. Information was collected on gender, age, body mass index, education level, smoking, and alcohol consumption. The HAMD-24 was used to assess the severity of mental symptoms, whilst the SHAPS is regarded as the optimal instrument for evaluating the sense of pleasure. The GAD-7 was used to assess different types of anxiety disorders in the general population. Standard clinical tests for renal function include BUN, CREA, and URIC. BMI was employed to measure an individual's degree of obesity.

Sample preparation and detection

Approximately 8.5 mL of blood samples were collected after a 12-hour fasting period in the morning (between 7-9 a.m.). Serum was separated by centrifugation at 3000 × *g* for 4 min at 4 °C, and then aliquoted into labeled 1.5-mL Eppendorf vials and stored at -80 °C until analysis. Metabolites were extracted from the serum samples using liquid-liquid extraction. In brief, 100 μL of serum was extracted by fourfold volume of cold chloroform:methanol (v/v = 2:1). The mixture was centrifuged at 13000 × *g* for 15 min, and then the upper and lower phases were separately collected and evaporated under vacuum. The dried samples were stored at -80 °C until LC-MS analysis. For LC-MS analysis, the aqueous phase was dissolved in 50 μL water. The organic phase was dissolved in 100 μL chloroform/methanol (1:1), and diluted with 300 μL isopropanol/acetonitrile/water (2:1:1). After centrifugation at 12000 rpm for 15 min, 6 μL of supernatant was injected for LC-MS analysis.

Metabolomics was performed on an Ultimate 3000 UHPLC system coupled with Q-Exactive MS (Thermo Scientific). An Xbridge amide column (100 × 4.6 mm, inner diameter, 3.5 μm; Waters) was used to separate compounds in the water phase (metabolomics) at 30 °C. The mobile phase A consisted of 5 mmol/L ammonium acetate in water with 5% acetonitrile, and mobile phase B was acetonitrile. The flow rate was 0.5 mL/min with the following linear gradient: 0 min, 90% B; 3 min, 90% B; 15 min, 35% B; 18 min, 35% B; 19 min, 90% B; and 24 min, 90% B.

Data-dependent acquisition (DDA) was performed using the Q-Exactive HF MS (Thermo Fisher Scientific, Waltham, MA, United States) as previously described. Each acquisition cycle consisted of one survey scan (MS1) at 60000 resolution from 60 to 900 m/z for hydrophilic metabolites, followed by 10 MS/MS scans in HCD mode at 15000 resolution using step-NCE of 15, 30, and 45. The dynamic exclusion was set to 10 s. Acquisition was performed in positive and negative

ion modes separately. The automatic gain control target was set to 5e6 and 2e5 for the MS1 and MS/MS scans, respectively. The HESI ion source parameters were: Spray voltage 3.3 kV (ESI+) and 3.0 kV (ESI-); sheath gas 40; aux gas 10; probe heater temperature 300 °C; capillary temperature 320 °C; S-lens RF level 55. Samples (n = 196 in total) were analyzed in random order to minimize batch effects. Quality control (QC) samples (n = 20) were prepared by pooling equal volumes of all serum samples and analyzed after every 10 experimental samples during the metabolomic analysis. The QC samples were used to monitor system stability and data reproducibility. Key QC metrics, including retention time stability [cross-validation (CV) < 2%] and peak intensity variability (CV < 15% for > 90% of detected features), demonstrated the high reproducibility of the analytical method. Any features with a CV > 20% in the QC samples were excluded from further analysis to ensure data reliability. Additionally, batch effects were corrected using QC-based normalization, and the overall data quality was assessed using principal component analysis (PCA) of the QC samples, which showed tight clustering and minimal drift over the course of the analysis.

Data processing

Raw data obtained from the DDA-MS were processed with MS-DIAL software v3.6 according to the user guide as previously described[22]. Briefly, the raw MS data was converted into the standardized .abf file format using the Reifycs ABF converter (http://www.reifycs.com/AbfConverter/index.html). Next, MS-DIAL software was employed to perform feature detection, spectra deconvolution, metabolite identification, and peak alignment. Briefly, the MS1 and MS2 spectra-based metabolite identification was performed in MSDIAL by searching the acquired spectra against the MassBank database provided by MSDIAL software, containing information about metabolites. The tolerance for MS1 and MS/MS search was set to 0.01 Da and 0.05 Da, separately. The threshold for the identification score was established at 70%. The remaining parameters used in MS-DIAL were set as default.

Statistical analysis

Basic information was analyzed using SPSS 28.0 software. Numerical data are presented as the mean ± SD, or median and interquartile range, while categorical variables are summarized using frequencies and proportions [n (%)]. An independent sample t-test was applied to data obeying a normal distribution, and the Mann-Whitney U test was used to compare differences between two groups for continuous data characterized by an abnormal distribution. The χ^2 test was used for comparing the frequency distribution of categorical data between the two groups.

The online software Metaboanalyst 6.0 (https://www.metaboanalyst.ca/) was used to process and analyze the obtained raw data of peak intensities from the instrument[16]. Briefly, the raw data were pre-processed by eliminating features with > 15% missing values, and the remaining missing values were substituted with limit of detection, which was set at 1/5 of the minimum positive value of each variable. Subsequently, the data were processed by normalization using the median, log transformation (base 10), and auto scaling (mean-centered and divided by the standard deviation of each variable). Next, the Metaboanalyst 6.0 online software was used for univariate and multivariate analyses. For univariate analysis, significance was determined by one-way ANOVA or independent samples t-test, and a false discovery rate (FDR) adjusted P value < 0.05 indicated significance. The multivariate analysis included fold change representation, volcano plot, PCA, and partial least squares discriminant analysis (PLS-DA) to assess clustering, trends, or outliers among samples. The supervised PLS-DA was performed to achieve enhanced group differentiation and gain deeper insights into the variables that contribute to categorization. Further volcano plot analysis with fold-change (FC) ≥ 1.2 or ≤ 0.83, variable importance in projection (VIP) ≥ 1.5 of PLS-DA, and FDR adjusted P value < 0.05 by the two-sample t-tests was used to identify significantly differential metabolites. Univariate and multivariate receiver operating characteristic (ROC) curve analysis were conducted to assess the diagnostic value of differential metabolites. The threshold of area under the ROC curve (AUC) was set at 0.5, with 0.8-0.9 indicating very good accuracy, and more than 0.9 indicating excellent accuracy. AUC values approaching 1 signify superior test performance[19]. The top 5, 10, 15, 25, 50, and 100 critical features were then used to build classification models. Spearman's correlation was used to analyze the correlations between clinical indices and metabolites in the MDD cohort as a heatmap.

RESULTS

Demographic and clinical characteristics of study participants

A total of 100 adults diagnosed with MDD, consisting of 44 males and 56 females, were included in the study. Additionally, 97 HCs were recruited, including 28 males and 69 females. No significant differences were seen in age, education level, smoking status, or drinkers between the two participant groups (all P > 0.05). However, it is worth noting that the sex distribution in the MDD group was more varied compared to the HC group. The mean BMI of HCs was significantly higher than that of MDD patients (22.21 ± 4.25 *vs* 23.91 ± 2.14, P < 0.001). Table 1 displays the clinical and demographic features of the participants. The SHAPS, GAD-7, and HAMD-24 scores of HCs were significantly lower than those of MDD patients (all P < 0.001).

Metabolomic profiles of individuals with MDD and HCs

Upon concluding data processing, a total of 197 features were incorporated into the data analysis to identify differences in metabolomic profiles between the MDD group and HC group. The PCA scatter plot (Supplementary Figure 1A) shows a significant separation of groups. The screen plot indicates that the top five PCs accounted for 39.9% of the accumulated variance (Supplementary Figure 1B). The PLS-DA graph reflects remarkable separations of MDD and HCs in Figure 1.

Table 1 Basic information of included participants

Variable	MDD patients (*n* = 100)	HCs (*n* = 97)	*P* value
Age (years), mean ± SD	39.07 ± 15.23	40.33 ± 6.61	0.238
Sex, *n* (%)			0.027
Male	44 (44.0)	28 (28.9)	
Female	56 (56.0)	69 (71.1)	
Education level, *n* (%)			0.751
Primary school	19 (19.0)	22 (22.7)	
Secondary school	48 (48.0)	41 (42.3)	
High school	23 (23.0)	21 (21.6)	
Undergraduate or above	10 (10.0)	13 (13.4)	
Drinker, *n* (%)	11 (11.0)	16 (16.5)	0.262
Smoker, *n* (%)	8 (8.0)	15 (15.5)	0.103
BMI (kg/m^2), mean ± SD	22.21 ± 4.25	23.91 ± 2.14	0.001
HAMD-24, mean ± SD	27.14 ± 6.10	2.08 ± 1.63	< 0.001
SHAPS, mean ± SD	37.71 ± 4.97	18.33 ± 3.51	< 0.001
GAD-7, mean ± SD	19.76 ± 3.28	7.54 ± 0.93	< 0.001

HCs: Healthy controls; MDD: Major depressive disorder; BMI: Body mass index; HAMD-24: Hamilton Depression Rating Scale-24 items; SHAPS: Snaith-Hamilton Pleasure Scale; GAD-7: Generalized Anxiety Disorder 7-item scale.

Differential metabolites between the HC and MDD groups were selected based on VIP > 1.5, FDR adjusted $P < 0.05$, and FC > 1.2 or < 0.83. A total of 35 identified metabolites were considered significantly different in serum (Table 2). Compared to HCs, 22 metabolites were raised and 13 were decreased in the MDD group. A heatmap was created to visually depict the relative changes in these metabolites (Figure 1C). For the untargeted metabolomic profiling, a total of 20 positive-mode features were identified, including 2 kinds each of lipids, steroids, amino acids, carnitines, and alkaloids, and 5 kinds of other metabolites. Additionally, 15 negative-mode features were identified, consisting of 13 kinds of lipids, 2 kinds of steroids, and 2 kinds of other metabolites. The majority of the discovered differential metabolites consisted of lipids and steroids, while there were also amino acids, carnitines, and alkaloids. The comprehensive information regarding these metabolites can be found in Table 2. The log2 transformed FC for the 35 metabolites that showed differential expression between individuals with MDD and HCs (Figure 2). The volcano plot demonstrates the significant differences of metabolites between the MDD and HC samples (Supplementary Figure 2). The heatmap of the top 25 features obtained by the *t*-test is shown in Supplementary Figure 3. R-SVM showed that the error rate of the first six features was only 19.8% (Supplementary Figure 4). Pathway analysis of potential mechanisms of candidate metabolic biomarkers for MDD is shown in Supplementary Figure 5.

ROC analysis identifies potential metabolite biomarkers for MDD

ROC analyses were performed on each plasma metabolite to evaluate the diagnostic significance of the dysregulated metabolites. 8-HETE, 10-HDoHE, 10-hydroxydecanoic acid, 12-HHTrE, and cortisol were identified as the top 5 efficient diagnostic biomarkers for MDD from HCs, with an AUC of 0.923, 0.910, 0.880, 0.883, and 0.890, respectively. ROC analysis demonstrated the following performance metrics: For 8-HETE, the sensitivity, specificity, positive predictive value, and negative predictive value were 90%, 10%, 50.76%, and 49.24%, respectively; for 10-HDoHE, these values were 90%, 20%, 53.7%, and 65.9%; for 10-hydroxydecanoic acid, they were 80%, 10%, 47.8%, and 32.7%; and for both 12-HHTrE and cortisol, the corresponding values were 80%, 20%, 50.76%, and 49.24%. Figure 3A-E displays the relative concentrations of these metabolite biomarkers for depression. Multiple ROC curves constructed with 5, 15, 25, 50, and 100 lipids are shown in Figure 3F. The top five curves attained an AUC of 0.954, and the 100 lipids achieved an AUC of 0.995. Figure 3G and H illustrates the predictive accuracy of each PLS-DA model developed with different numbers of features.

Correlations of metabolites with clinical and psychological variables

Lipids (*e.g.*, 12-hydroxydodecanoic acid and hexanedioic acid), steroids (*e.g.*, cortisol and dehydroisoandrosterone sulfate), and some other metabolites (*e.g.*, phytosphingosine and 2-hydroxyisocaproic acid) were found to be positively correlated with psychological variables (*e.g.*, SHAPS, WHO-5, HAMD-24, and GAD-7). Lipids (*e.g.*, sebacic acid and methylsuccinic acid), amino acids [*e.g.*, cyclo(Leu-Pro) and L-glutamic acid], and some other metabolites [*e.g.*, d-(+)-malic acid, viridiflorine, and 2-hydroxyisocaproic acid] were found to be positively correlated with clinical variables (*e.g.*, BMI, BUN, CREA, and URIC). Spearman correlations of metabolites and variables are shown in Figure 4. The results of supple-

Table 2 Differential metabolites between major depressive disorder and healthy control groups identified from metabolomic data

Adduct type	Metabolite	Reference m/z	FC	log2 (FC)	FDR	VIP	Ontology	Trend
POS	Phytosphingosine	318.30	2.33	2.43	3.34E-16	2.42	1,3-aminoalcohols	↑
	Cortisol	363.22	2.14	-1.45	1.00E+00	3.23	21-hydroxysteroids	↑
	Estriol	289.18	1.97	1.89	2.38E-18	2.55	Estrogens and derivatives	↑
	D-pantothenic acid	220.12	1.72	2.50	4.40E-06	1.50	Secondary alcohols	↑
	Niacinamide	123.06	1.54	1.66	3.13E-07	1.64	Nicotinamides	↑
	Palmitoylcarnitine	400.34	1.51	0.40	1.74E-10	1.98	Acyl carnitines	↑
	Oleoyl-L-carnitine	426.36	1.50	-0.28	7.24E-07	1.60	Acyl carnitines	↑
	L-glutamic acid	146.05	1.41	-2.15	3.19E-11	2.05	Glutamic acid and derivatives	↑
	S1P (d18:1)	380.26	1.35	-0.46	2.32E-16	2.43	Phosphosphingolipids	↑
	Viridiflorine	286.20	0.65	1.95	4.77E-18	2.53	Pyrrolizidines	↓
	Cyclo(Leu-Pro)	211.14	0.58	2.76	6.45E-09	1.83	Alpha amino acids and derivatives	↓
	Sebacic acid	225.11	0.52	-1.80	9.56E-09	1.81	Medium-chain fatty acids	↓
	Piperine	286.14	0.30	1.10	7.26E-09	1.82	Alkaloids and derivatives	↓
	Theobromine	181.02	0.29	-0.78	3.13E-07	1.64	Xanthines	↓
	3-indoleacetic acid	176.07	0.23	0.22	1.44E-07	1.68	Indole-3-acetic acid derivatives	↓
NEG	8-HETE	279.20	6.77	0.89	1.71E-26	2.96	Long-chain fatty acids	↑
	12-HHTrE	319.23	5.67	1.45	8.90E-22	2.74	Hydroxyeicosatetraenoic acids	↑
	10-HDoHE	343.23	5.38	0.78	3.68E-21	2.71	Very long-chain fatty acids	↑
	5,12-DiHETE	335.22	3.86	0.98	5.46E-16	2.40	Leukotrienes	↑
	12-HEPE	317.21	3.70	-1.20	7.26E-09	1.83	Hydroxyeicosapentaenoic acids	↑
	Hexanedioic acid	145.05	3.21	-1.27	3.54E-08	1.75	Medium-chain fatty acids	↑
	12-hydroxydodecanoic acid	215.17	3.17	-1.32	3.13E-07	1.64	Medium-chain hydroxy acids and derivatives	↑
	Dodecanedioic acid	229.14	2.73	1.68	7.04E-15	2.33	Medium-chain fatty acids	↑
	Methylsuccinic acid	131.03	2.59	0.49	6.38E-11	2.02	Methyl-branched fatty acids	↑
	Pregnenolone sulfate	395.19	2.06	1.37	3.07E-08	1.76	Sulfated steroids	↑
	Dehydroisoandrosterone sulfate	367.16	1.85	0.63	6.90E-08	1.72	Sulfated steroids	↑
	D-(+)-malic acid	133.01	1.54	0.59	1.02E-12	2.17	Beta hydroxy acids and derivatives	↑
	2-hydroxyisocaproic acid	131.07	1.32	0.60	5.57E-14	2.27	Hydroxy fatty acids	↑
	3-hydroxyanthranilic acid	152.03	0.82	1.22	1.63E-18	2.57	Hydroxybenzoic acid derivatives	↓
	4-nitrophenol	138.02	0.73	-1.74	1.57E-09	1.90	Nitrophenols	↓
	FA 18:1 + 2O	313.24	0.43	1.04	2.34E-11	2.06	Long-chain fatty acids	↓
	FA 18:1 + 3O	329.23	0.42	-0.95	1.38E-07	1.68	Long-chain fatty acids	↓
	FA 18:3 + 1O	297.24	0.40	0.43	6.45E-09	1.83	Lineolic acids and derivatives	↓
	10-hydroxydecanoic acid	187.14	0.37	-1.77	1.93E-09	1.89	Medium-chain hydroxy acids and derivatives	↓
	CMPF	239.09	0.29	-0.62	1.67E-08	1.79	Furanoid fatty acids	↓

FC: Fold change; FDR: False discovery rate; VIP: Variable importance projection; CMPF: 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid; FA: Fatty acid; S1P: Sphingosine-1-phosphate.

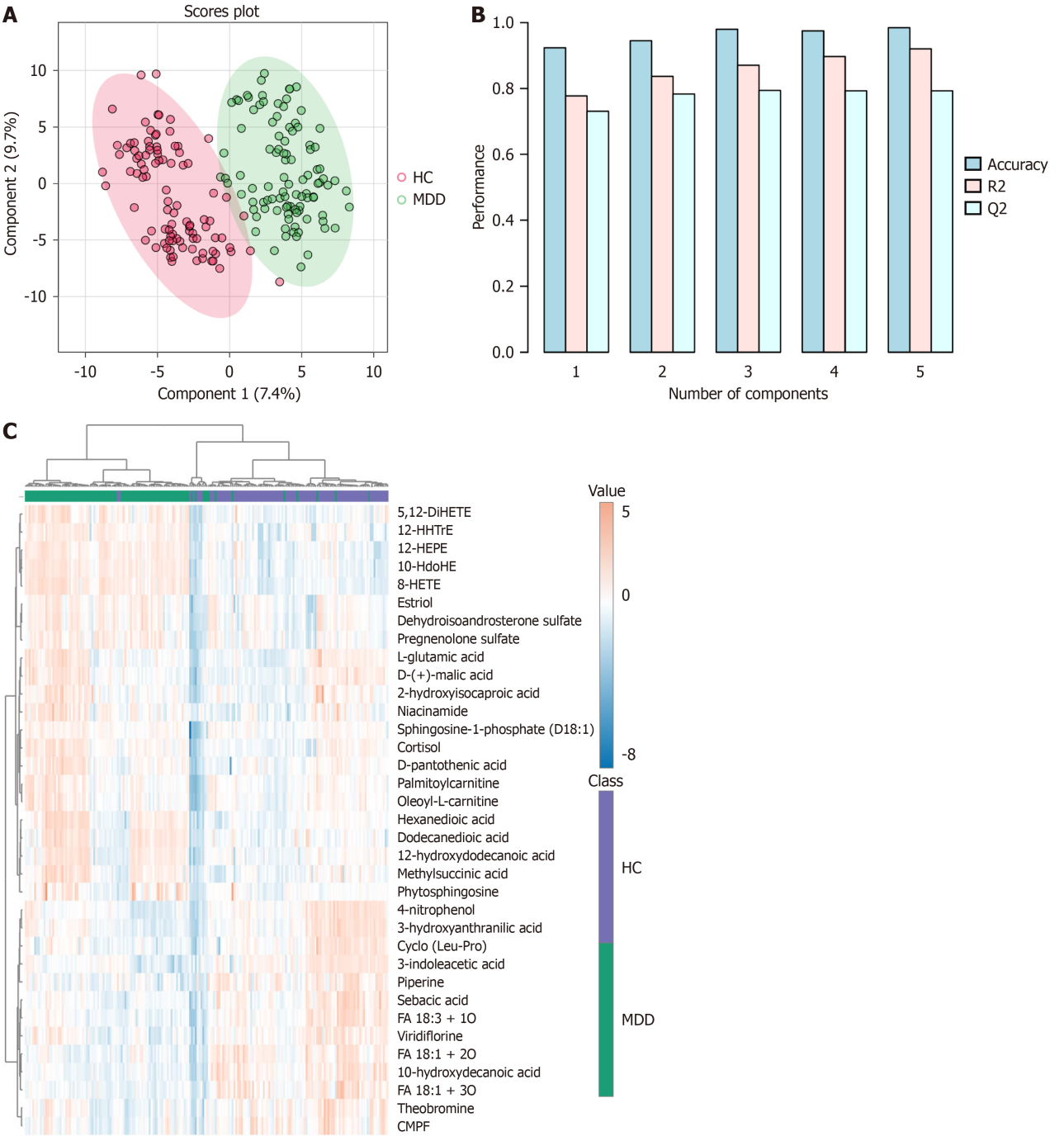

Figure 1 Metabolomic analysis of serum samples from major depressive disorder and healthy control groups. A: 2D partial least squares discriminant analysis scores plot of top 2 components; B: Overview of the performance of the top 5 components; C: The heatmap of representative metabolites to distinguish major depressive disorder and healthy control. [1]The model with three components has the highest Q2 value, thus demonstrating the best prediction performance. HC: Healthy control; MDD: Major depressive disorder; FA: Fatty acid; CMPF: 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid.

mentary regression analysis are shown in the supplementary table[23,24].

DISCUSSION

The present study employed GC-MS-based metabolomics to investigate the metabolomic profile of patients with MDD and identify potential diagnostic biomarkers. The primary findings are as follows: (1) 35 differential metabolites responsible for discriminating MDD patients and HCs were identified. We found that MDD patients showed a decrease in 13 types of differential metabolites (mainly belongs to lipids and alkaloids) in patients with depression and an increase in 22 types (mainly belongs to lipids, steroids, carnitines, and amino acids); (2) The AUC values of 14 metabolites are above 0.8. Additionally, a combination of five metabolites for the diagnosis of MDD patients was established, demonstrating the ability to distinguish MDD patients from HCs with an AUC of 0.954; and (3) The concentrations of

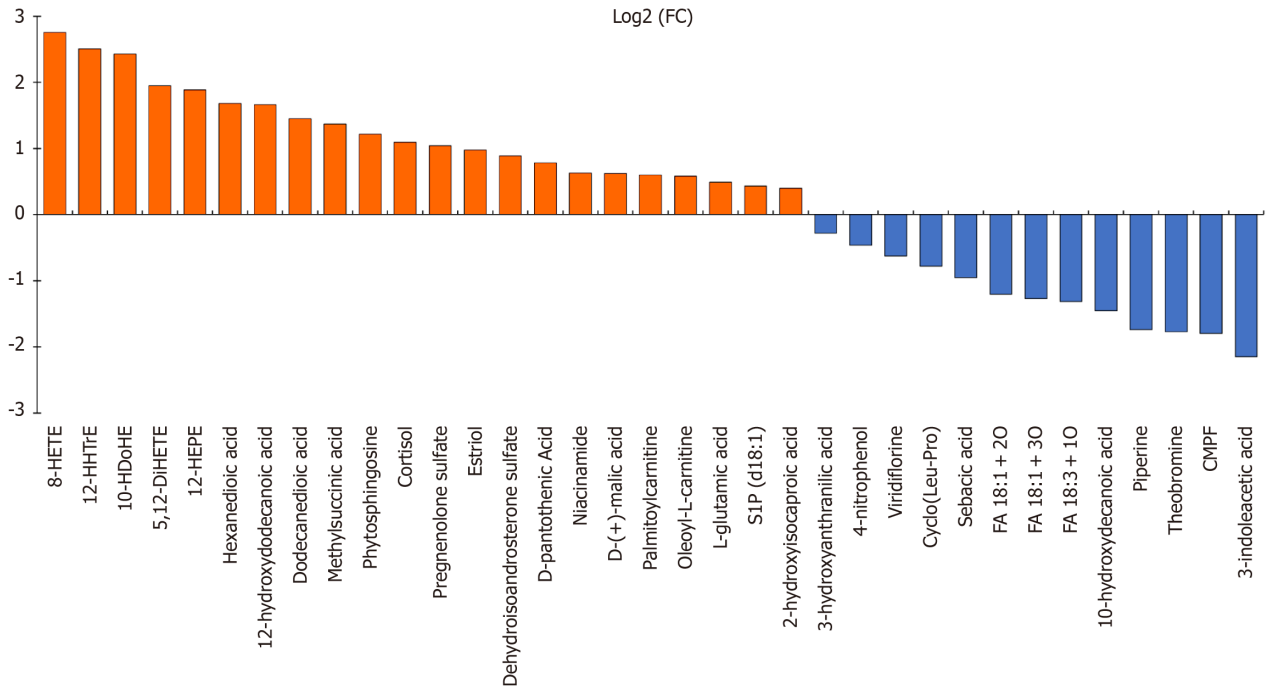

Figure 2 Total 35 differential metabolites between major depressive disorder and healthy control groups. The abscissa represents each feature, and the ordinate represents the fold change after the log2 transformation. Red: Major depressive disorder (MDD) > healthy control (HC); Blue: MDD < HC. FC: Fold change; CMPF: 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid.

some lipids and steroids (*e.g.*, 12-hydroxydodecanoic acid and cortisol) were positively correlated with a number of metabolic markers reflecting BMI and renal functions (*i.e.*, CREA, URIC, and BUN). Some lipids and amino acids [*e.g.*, sebacic acid and cyclo(Leu-Pro)] were positively correlated with psychological variables (*e.g.*, SHAPS, WHO-5, HAMD-24, and GAD-7).

Mechanisms of candidate metabolic biomarkers in MDD patients

Lipids: Fatty acids (FAs), constituting the majority of lipids in human physiology and dietary sources, are essential for numerous physiological and pathological processes[25,26]. Dietary FAs can be classified into saturated FAs (SFAs), monounsaturated FAs (MUFAs), and polyunsaturated FAs (PUFAs) based on the amount and type of double bonds, as well as chain length[27]. In the present study, the levels of most SFAs (hexanedioic acid, 12-hydroxydodecanoic acid, dodecanedioic acid, and methylsuccinic acid) increased while some (sebacic acid and 10-hydroxydecanoic acid) decreased in patients with MDD compared with HCs. A human cross-sectional investigation indicated a significant positive connection between depressed symptoms and SFAs[28]. A comparative cross-sectional investigation indicated that elevated intakes of saturated fat was a risk factor for depressive symptoms in women[29]. Prior research has demonstrated that the consumption of a high-fat diet can elicit depression-like behavior in rodents[30]. Mechanically, numerous studies suggest that dietary SFAs can affect the neurochemistry and functionality of the brain[29]. Of note, SFAs have been demonstrated to disrupt several brain circuits associated with mood regulation, including neuroinflammation and eating behavior[31]. For example, evidence indicates that SFAs can provoke neuroinflammation by promoting the release of pro-inflammatory cytokines and inducing death of astrocytes, the supportive cells of the central nervous system[32]. Although our findings suggested an increase in most SFAs, the reason for the decreased sebacic acid and 10-hydroxydecanoic acid needs further exploration. The concentrations of MUFAs (FA 18:1 + 2O, FA 18:1 + 3O) were reduced in the MDD group compared to the HC group. A population-based study indicated that the intake of MUFAs correlated with decreased odds ratios for depressive symptoms. The negative correlation between MUFA consumption and depression symptoms was stronger in women[33]. Importantly, a clinical investigation indicated that a diet that is more prosperous with MUFAs in humans decreases the risk of depression[34]. In contrast to the effects of SFAs, preclinical data indicate that consuming MUFAs may enhance brain function, including preserving dopamine system integrity and facilitating neurotransmitter signal transduction[35,36]. MUFAs are thought to function by reducing inflammation, modulating neurotransmitters (including the augmentation of serotonin availability), and promoting the expression of neuroprotective proteins such as brain-derived neurotrophic factor (BDNF)[37-39]. Notably, A high MUFA:SFA ratio has been demonstrated to enhance brain membrane fluidity[36], facilitating neurotransmitter signal transduction and improving mental health.

The levels of ω-6 PUFAs (8-HETE, 12-HHTrE, and 5,12-DiHETE) increased while those of ω-3 PUFAS (10-HDoHE and 12-HEPE) decreased in patients with MDD compared with the HC group. Previous studies mainly focused on ω-3 and ω-6 PUFAs in samples of patients with MDD. Several small clinical studies noted that ω-6 levels were elevated in the tissues of depressed patients relative to controls, and the severity of depression correlated with ω-6 levels[40]. A study presents compelling evidence that a diet high in ω-6 may increase the risk of depression in the general population. ω-6 FAs are believed to have a possibly positive correlation with depression, particularly due to their pro-inflammatory effects[34].

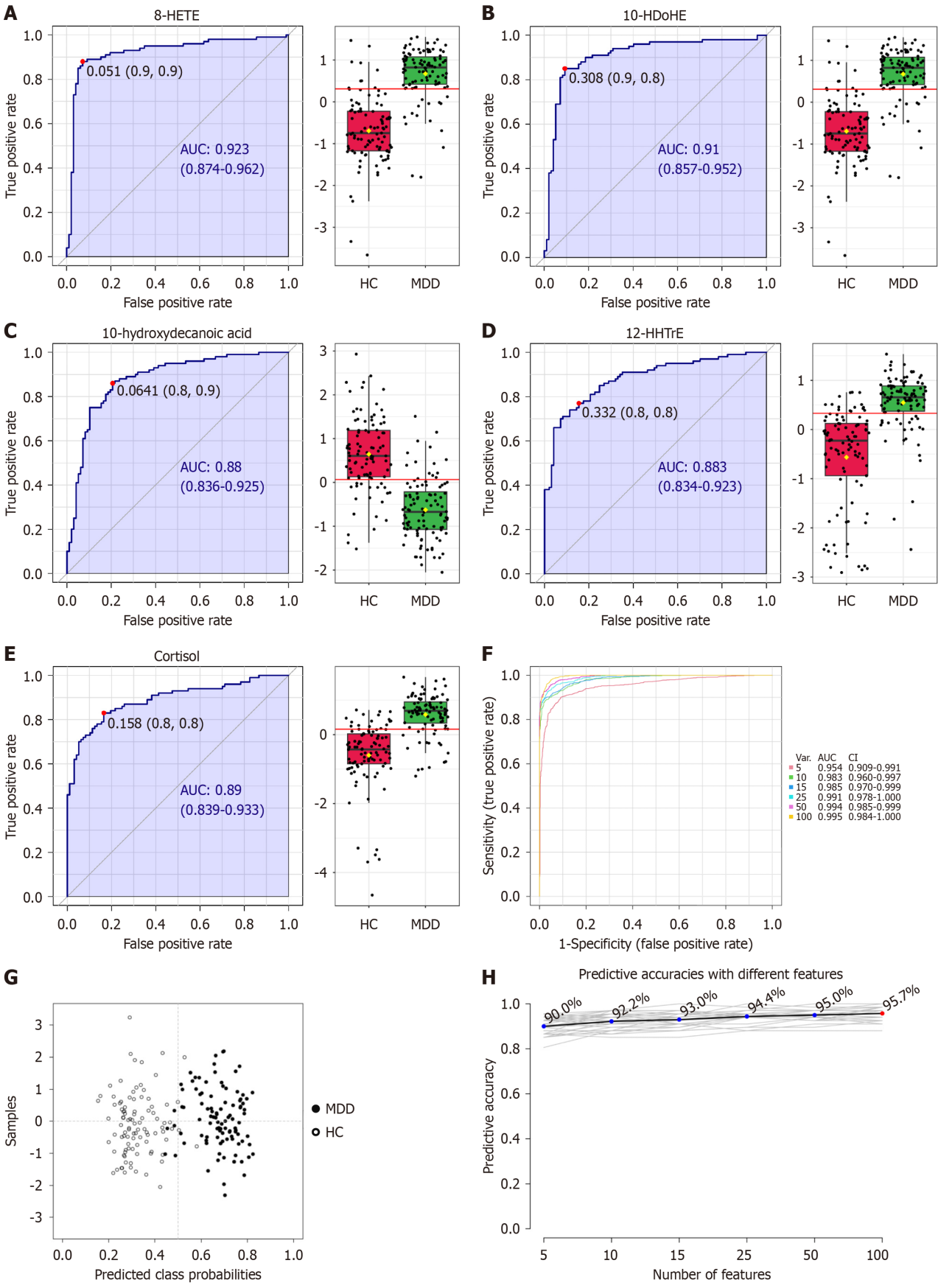

Figure 3 Receiver operating characteristic analysis revealing candidate metabolomic biomarkers for major depressive disorder diagnosis. A-E: Receiver operating characteristic (ROC) curves of 8-HETE, 10-HDoHE, cortisol, 12-HHTrE, and 10-hydroxydecanoic acid. The left panel of each picture represents the ROC for differentiating the major depressive disorder (MDD) group from the healthy control (HC) group, and the boxplots on the right side are the feature intensities of the two groups. The y-axis refers to the relative value after normalization of the peak intensities; F: Multivariate ROC curves constructed with 2-

100 metabolites based on the cross-validation performance. Each curve represents the potential of the top 5, 10, 15, 25, 50, and 100 features in differentiating the MDD group from the HC group; G: Predicted class probabilities (average of the cross-validations) for each sample using the 5-feature model of metabolites; H: Corresponding predictive accuracy of each partial least squares discriminant analysis model constructed with different numbers of features. The predictive accuracy of 5 to 100 features is from 90% to 95.7%, respectively. HC: Healthy control; MDD: Major depressive disorder; AUC: Area under the receiver operating characteristic curve.

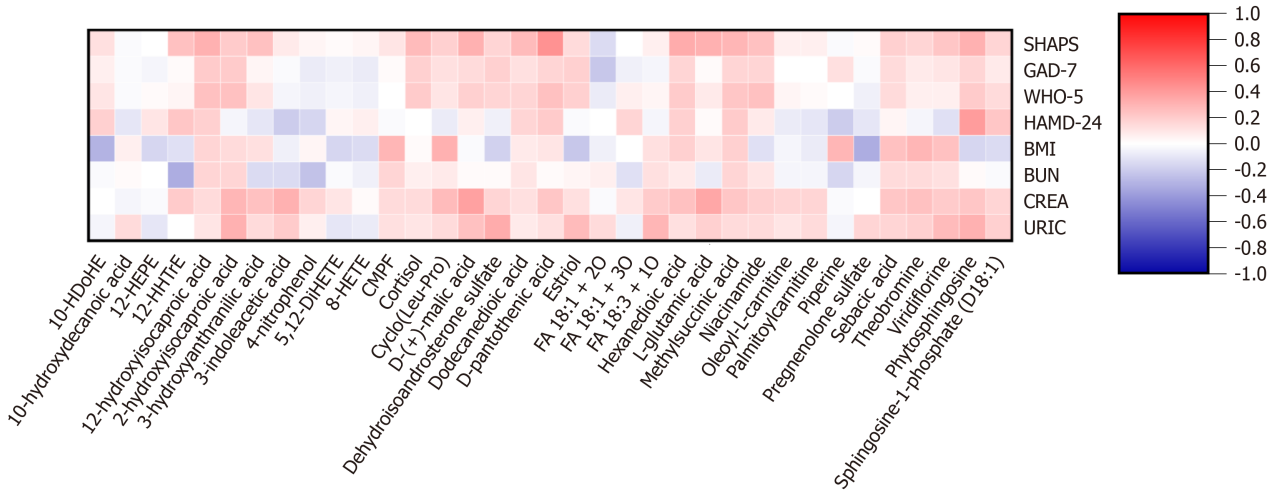

Figure 4 Spearman correlations of metabolites and clinical variables in patients with major depressive disorder and healthy controls. The red background represents the positive correlations between the two compared variables, while the blue background represents the negative correlations. FA: Fatty acid; SHAPS: Snaith-Hamilton Pleasure Scale; GAD-7: Generalized Anxiety Disorder 7-item scale; WHO-5: 5-item World Health Organization Well-Being Index; HAMD-24: Hamilton Depression Rating Scale-24 items; BMI: Body mass index; BUN: Blood urea nitrogen; CREA: Creatinine; URIC: Uric acid; CMPF: 3-Carboxy-4-methyl-5-propyl-2-furanpropanoic acid.

Notably, some investigations have identified a reduction in ω-3 levels in patients with MDD. For instance, ω-3 levels were significantly diminished in patients with depression[41], and reduced total ω-3 levels and elevated ω-6/ω-3 ratio were also observed in individuals with prenatal depression[42]. Conversely, ω-3 dietary supplementation during pregnancy or postpartum alleviates depressive symptoms, and ω-3 adjunctive treatment offers a viable option for managing depression and anxiety symptoms in individuals with recent onset psychosis[43,44]. The antidepressant effects of ω-3 PUFAs are associated with their capacity to reduce inflammatory responses[45]. A further study demonstrated that ω-3 PUFAs can mitigate hippocampal neuroinflammation in mice by modulating TLR4 expression, hence enhancing depression-like behavior[46]. Moreover, hippocampus atrophy is a significant indicator in individuals with depression, and ω-3 PUFAs facilitate hippocampal neurogenesis[47]. In summary, PUFAs are crucial for brain function and neurological disorders, influencing neurotransmission, neuroinflammation, mood, and cognition[48]. PUFAs constitute the fundamental components of the brain and are essential for the optimal functioning of neurons, synapses, and neural transmission. The lack of a crucial element, ω-3 FAs, in preference to ω-6 FAs, might worsen mental disease and serve as a potential catalyst for neurodegenerative alterations[47]. One study confirms that major depression is associated with a high ω-6/ω-3 ratio and elevation in the cytokine IL-6[49]. Research indicates that an imbalanced diet of PUFAs, characterized by elevated ω-6 FAs at the expense of ω-3, resulted in atherosclerosis and diminished cognitive performance[50].

Steroids: Steroids are present in all eukaryotic species and exhibit a wide range of biological functions[51]. The current study found elevated levels of cortisol, estriol, dehydroisoandrosterone sulphate, and pregnenolone sulphate in patients with MDD compared to HCs. Cortisol plays a multifaceted role in MDD. A review suggests that higher levels of cortisol are a risk for subsequent depression. Diurnal rhythms are disrupted, there is heightened resistance to the feedback mechanism of glucocorticoids, excessive cortisol may precipitate MDD, baseline cortisol levels may be elevated, and the post-awakening cortisol surge is intensified in individuals predisposed to MDD[52]. Evidence has amassed in favour of a contemporary paradigm suggesting that cortisol exhibits immune-enhancing capabilities, potentially leading to the heightened inflammation observed in depression[53]. For example, Munhoz *et al*[54] indicated that, in contrast to the anti-inflammatory effects of glucocorticoids through NF-kB inhibition, rats subjected to chronic unpredictable stress exhibited heightened glucocorticoid levels, leading to increased NF-kB activation and proinflammatory gene expression triggered by acute stress exposure. Furthermore, pre-treatment with a GR antagonist weakened this effect, thus suggesting the putative immune potentiating properties of glucocorticoids. Estrogen, an important steroid hormone secreted by the ovaries in the female body, exists in three forms, including estrone (E1), estradiol (E2), and estriol (E3)[55]. Some researchers suggest that the E3 to progesterone ratio may affect depression symptoms in predicting premature birth[56]. Estrogen has been demonstrated to affect neurotransmitters, including glutamate, GABA, serotonin, and dopamine, highlighting the complex role of this hormone in the aetiology of depression[57-59] as it inhibits GABA and input[60], and the serotonergic and dopaminergic systems can also be regulated by estrogen[61-63]. Significant variations in

estrogen levels due to stress exposure can increase the risk of depression, anxiety, and post-traumatic stress disorder[55]. Dehydroepiandrosterone (DHEA) and its sulfate (DHEA-S) are neurosteroids produced in the body either from cholesterol or from steroid hormone precursors, which are prevalent in the brain[64]. Certain data indicate that alterations in DHEA-S levels correlate with the state of remission following antidepressant therapy[65]. A study indicated that plasma DHEA-S levels in patients were markedly elevated compared to those in HCs[66]. DHEA and DHEA-S modulate neuronal activity *via* receptors located on the neuronal cell membrane. DHEA and DHEA-S function as antagonists of the GABA-A receptor[67,68] and sigma-1 receptor agonists[69]. In addition, DHEA and DHEA-S have been proposed to possess antidepressant and anxiolytic properties[66]. The function of the prevalent adrenal steroid DHEA has been examined, with some indication that it may exert an antiglucocorticoid impact[70].

Research has demonstrated a negative correlation between plasma pregnenolone concentrations and HAMD scores after electroconvulsive therapy[71]. Previous studies indicated that pregnenolone levels were decreased in the cerebrospinal fluid and plasma of patients with depression, returning to normal ranges after antidepressant treatment[72,73]. Our study, however, observed elevated levels of pregnenolone sulfate in the MDD group, which contrasts with these previous findings. This discrepancy may be explained by several potential mechanisms. First, pregnenolone sulfate is known to negatively modulate GABA-A receptors, thereby enhancing excitability in the central nervous system. This unique pharmacological action could lead to increased levels of pregnenolone sulfate as a compensatory response to the neurochemical imbalances associated with depression. Second, differences in study populations, including variations in disease severity, duration of illness, and treatment history, may contribute to the observed differences. Additionally, methodological variations in sample collection, processing, and analytical techniques could also play a role. Further research is needed to elucidate the precise mechanisms underlying these differences and to determine whether elevated pregnenolone sulfate levels represent a distinct subtype of MDD or a specific pathophysiological state within the disorder.

Amino acids: The current study found increased levels of L-glutamic acid and 2-hydroxyisocaproic acid, while cyclo(Leu-Pro) and 3-hydroxyanthranilic acid (3-HAA) were decreased in patients with MDD compared to HCs. Increasing evidence suggests that glutamatergic signaling may be involved in the pathophysiology of MDD. A meta-analysis indicated that blood glutamate concentrations were markedly elevated in patients with MDD compared to controls, exhibiting considerable heterogeneity[74]. L-glutamic acid (glutamate) is recognized as the principal excitatory neurotransmitter in the neurological system. It significantly influences brain development by impacting neuronal migration, differentiation, axon formation, and survival[75]. 3-HAA is involved in the kynurenine-tryptophan metabolic pathway. A study demonstrated the novel neuroprotective activity of the tryptophan metabolite 3-HAA[76]. The kynurenine derivative 3-HAA is recognized for its role in modulating the immune system and demonstrating anti-inflammatory properties by suppressing T-cell cytokine release and affecting macrophage activity[77]. Our results suggest that cyclo(Leu-Pro) and 2-hydroxyisocaproic acid may be related to the metabolic disorders in the early metabolic stage or subsequent metabolic steps, and further targeted exploration is needed.

Others: Regarding carnitines, in the present study, the levels of palmitoylcarnitine and oleoyl-L-carnitine increased in patients with MDD compared with HCs. Acylcarnitine is an acylated derivative of carnitine that efficiently facilitates FA oxidation to produce energy for essential functions. It has been documented to mitigate the symptoms of depression. A study revealed that palmitoylcarnitine and carnitine levels were markedly decreased in the serum of individuals with depression[78]. However, Moaddel *et al*[79] found a reduction in acylcarnitine concentrations after ketamine treatment compared to placebo. Additional comprehensive research is required to clarify the relationship between carnitines and depression. The observed differences in carnitine levels across studies may reflect varying degrees of mitochondrial impairment or compensatory mechanisms in different patient populations or treatment contexts. Concerning alkaloids, in the present study, the levels of piperine and viridiflorine decreased in patients with MDD compared with HCs. Piperine is the primary chemical component in pepper, exhibiting antioxidant effects and immunological modulation, while also facilitating the reversal of HPA axis dysfunction caused by chronic stress[80]. Research indicates that the co-treatment approach employing piperine may serve as an effective alternative therapy for mitigating chronic stress[81]. Trans-resveratrol and piperine may partially function through the 5-HT-cAMP-PKA-CREB-BDNF signaling pathway. This study also confirmed the above views. There are few studies on the direct relationship between viridiflorine and MDD. However, alkaloids often have a variety of biological activities, including anti-inflammatory, antioxidant, and neuroprotective effects, and these properties may have potential effects on MDD.

There are also other metabolites involved in MDD. For example, theobromine, 3-indoleacetic acid, and 4-nitrophenol decreased, and phytosphingosine, D-pantothenic acid, D-(+)-malic acid, and niacinamide increased in patients with MDD compared with HCs. However, due to the limited number of studies on the relationship between these metabolites and MDD, further research is required.

Relationship between differential metabolites and clinical and psychological variables

In this study, the concentration of lipids, amino acids, and some other metabolites is associated with multiple indicators of kidney function and BMI. A cross-sectional study of a Chinese population revealed a significant correlation between the severity of depression and depressive symptoms and renal function levels, which remained after adjusting for confounding variables, including chronic kidney disease, hypertension, and diabetes. This implies that minor alterations in early renal function may be associated with depression[82]. Microvascular illness in the kidney is thought to mirror conditions in the brain, and there may be a connection between the two organs[83]. However, few studies have explored the association between MDD and renal function from the perspective of metabolomics. This study also examined the reciprocal nature of the relationship between metabolites and BMI. A review explicitly examines shared biological

pathways that may mechanistically elucidate the connection between depression and obesity, encompassing genetics and modifications in systems responsible for homeostatic regulation[84]. Nonetheless, not all patients demonstrate comparable dysregulations in associating biological mechanisms. Consequently, our research encompassed metabolomics to deliver a comprehensive characterization of the biological pathways linking depression.

Regarding psychological variables, the concentration of lipids and steroids is correlated with psychological factors (SHAPS, WHO-5, HAMD-24, and GAD-7). Anhedonia is regarded as a fundamental characteristic of MDD. The neuropharmacology of anhedonia in MDD delineates the neurotransmitters potentially implicated in hedonic capacity[85]. Glutamate plays a crucial part in the reward system. Serotonin may play a regulatory role in the reward mechanism. Acetylcholine and cholecystokinin also regulate glutamate and dopamine release, influencing associated behaviors and emotions[86,87]. Research indicates that oxidative stress, modifications in lipid and energy metabolism (*i.e.*, mitochondrial regulation), glutamine metabolism, and neurotransmission appear to be implicated in anxiety disorders [88]. Overall, many early anxiety metabolomics studies focused on lipids (lipidomics), as there is a known connection between lipids and neuronal signaling and disease[89]. A meta-analysis showed that depression status was related to well-being, and well-being scores were lower in depressed participants[90]; however, little research has been done on the underlying mechanisms[91]. Some investigations indicated that the metabolic phenotypes in the plasma of patients with varying severities of MDD were different[92]. Therefore, we explored the relationship between psychological variables and more metabolites (*e.g.*, lipids and steroids) in patients with depression.

Limitations

In summary, our study provides new evidence for the biomarkers of MDD. Nevertheless, our results need careful interpretation owing to the following limitations: First, there was a considerable percentage of female volunteers in both the MDD group and the HC group. This was primarily due to the challenges in recruiting male participants, particularly in obtaining fecal biosamples from healthy male controls. To ensure a matched comparison between patients and controls, we intentionally included a higher number of healthy female participants. While this approach allowed us to maintain sample consistency and comparability, it may introduce a potential bias related to gender differences in metabolic profiles. Future studies should aim to achieve a more balanced gender distribution to further validate our findings and explore potential sex-specific metabolic signatures in MDD. Moreover, similar to other cross-sectional studies, this study did not conduct a longitudinal analysis, so it is difficult to explain causal relationships. A key limitation of this study is the recruitment of all subjects from a single clinical site, which may introduce site-specific biases and limit the generalizability of the findings. To address these limitations, future studies should recruit heterogeneous subjects from multiple clinical sites, ensuring diversity in demographics, lifestyle, and baseline health conditions.

CONCLUSION

Our study reported metabolites (some lipids, steroids, amino acids, carnitines, and alkaloids) responsible for discriminating MDD patients and HCs. This metabolite profile may facilitate the development of a laboratory-based diagnostic test for MDD. The mechanisms underlying the association between psychological or clinical variables and differential metabolites also deserve further exploration. These findings indicate that metabolomic profiling offers valuable insights into the biological mechanisms underlying psychological symptoms in MDD. The observed associations between specific metabolites and psychological variables hold promise for advancing personalized treatment strategies, enabling more targeted interventions based on individual metabolic profiles. Furthermore, metabolomic profiling could serve as a tool to monitor treatment response and refine psychotherapy interventions, potentially enhancing therapeutic outcomes.

FOOTNOTES

Author contributions: Cao B and Liu YL contributed equally to this work as co-first authors; Cao B contributed to methodology, formal analysis, data extraction, follow-up, and manuscript writing, reviewing, and editing; Liu YL contributed to data extraction, data curation, follow-up, formal analysis, and manuscript writing, reviewing, and editing; Wang N was involved in supervision and providing the software; Hang Y contributed to data curation; Lu CX performed data curation; Zou HY contributed to conceptualization, funding acquisition, methodology, and manuscript writing, reviewing, and editing; all authors contributed to the interpretation of the study and approved the final version to be published.

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