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A cross-section study of the comparison of plasma inflammatory cytokines and short-chain fatty acid in patients with depression and schizophrenia

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Abstract

Background Major depressive disorder (MDD) and schizophrenia (SCH) are common and severe mental disorders that are mainly diagnosed depending on the subjective identification by psychiatrists. Finding potential objective biomarkers that can distinguish these two diseases is still meaningful.

Methods In the present study, we investigate the differences in plasma inflammatory cytokines and short-chain fatty acids (SCFAs) among patients with MDD ($n=24$) and SCH ($n=24$), and gender- and age-matched healthy controls (HC, $n=27$) and identify potential plasma biomarkers.

Results We found that the concentrations of pro-inflammatory cytokines were increased, whereas the anti-inflammatory cytokines were decreased in both MDD and SCH. Meanwhile, except for an increase in 4-Methylvaleric acid, other SCFAs with statistical differences were reduced in both MDD and SCH. Moreover, potential biomarker panels were developed that can effectively discriminate MDD from HC (AUC = 0.997), SCH from HC (AUC = 0.999), and from each other (MDD from SCH, AUC = 0.983).

Conclusions These data suggest that alterations in plasma cytokines and SCFAs might be one of the potential features for distinguishing MDD and SCH.

Trial registration Chinese Clinical Trial Registry: ChiCTR2100051243, registration date: 2021/09/16.

Keywords Inflammatory cytokines, Short-chain fatty acids, Schizophrenia, Depression

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Introduction

Major depressive disorder (MDD) and schizophrenia (SCH) are two types of severe mental disorders with a high incidence and recurrence rate and bring serious social burden worldwide [1, 2]. The causes of SCH and MDD are complex and their pathogenesis is not yet fully elucidated [3, 4]. Currently, the diagnosis of MDD and SCH mainly depends on the subjective identification of relevant symptom groups by psychiatrists, such as the patient's current symptoms and history [5, 6]. However, these two disorders have noticeable overlaps in heritage patterns and symptoms [7–9]. For example, there is an overlap between negative symptoms of SCH and depressive symptoms and some argue depressive symptoms should be part of the SCH syndrome [10, 11]. Moreover, comorbid MDD in SCH has been identified, and a previous study has hypothesized that more than 50% of SCH patients may develop MDD [12]. Therefore, the development of objective molecular markers for MDD and SCH will not only help further understand the pathogenesis of these two diseases but will also assist in their diagnosis.

Growing evidence elucidated that the activation of inflammation has a great influence on the progression of MDD and SCH [13, 14], such as abnormality in antibody titers, inflammatory markers, and immune cell numbers [15, 16]. Of note, changes in inflammatory biomarkers such as cytokines and leukocytes derived from peripheral blood have been widely investigated. Multiple meta-analyses with a fairly unanimous consensus indicate that in comparison to healthy controls (HC), the concentrations of C-reactive protein (CRP), tumor necrosis factor (TNF), and interleukin (IL)-6 in the blood of MDD patients were increased [17, 18]. Similarly, a quantitative review found that plasma/serum levels of soluble IL-2 receptor (IL-2R) and IL-6 were increased in individuals with SCH [19]. Another meta-analysis also found that transforming growth factor-β (TGF-β), IL-6, and IL-1β were increased in first-episode psychosis SCH during acute exacerbations [20]. Importantly, a meta-analysis further concluded that antipsychotic treatment decreases levels of interferon-γ (IFN-γ) and IL-1β but increases IL-12 and IL-2R in the blood [21]. Altogether, altered cytokine levels in the plasma are one of the pathological manifestations of patients with MDD and SCH. However, the comparison in plasma cytokines between MDD and SCH and whether characteristic cytokines can serve as diagnostic markers that can distinguish MDD and SCH still needs further exploration. Besides, previous studies have mainly focused on TNF, IL-1β, and IL-6, the differences between other cytokines in these two diseases still need to be clarified.

Short-chain fatty acids (SCFAs) are key mediators in the interactions of the microbiota-gut-brain axis [22] and play key roles in regulating energy metabolism and maintaining intestinal homeostasis. SCFAs influence host inflammatory responses and play a role in affecting emotional states and recognition [23]. For example, SCFAs can modulate TNF-α and IL-6 release from macrophages and IL-17 production from intestinal T cells [24, 25], and inhibit the activation of cytokine-induced nuclear factor kappa-B (NF-κB) [26]. Moreover, a recent review indicated that patients with MDD may be characterized by low SCFAs-producing bacteria and a high abundance of pro-inflammatory bacteria [27] and alterations in serum SCFAs were also associated with the cognitive impairment of SCH [28]. Besides, SCFAs can also act on the G-protein coupled receptors, which were involved in the pathogenesis of SCH and MDD [29, 30]. However, there are few studies investigating the composition difference of SCFAs between MDD and SCH.

Human brain tissues are ideal biological samples for the understanding of dysfunction in psychiatric diseases [31]. However, the brain tissue of living psychiatric patients is not allowed for clinical biochemical testing. Besides, cerebrospinal fluid (CSF) is an ideal sample for reflecting central inflammation and metabolism, and abnormal inflammation in CSF has been identified as one of the pathological features of MDD and SCH [32, 33]. However, lumbar puncture is not a routine operation in psychiatry and CSF samples were not practically used because of safety and ethical concerns. In comparison, plasma samples are commonly used in clinical laboratories which can be easily acquired at minimal cost and risk [34]. Therefore, a plasma-based inflammatory and metabolic diagnostic test for MDD and SCH could be clinically practical [35–37]. Considering the above, we performed a case-control study to investigate concentrations of the plasma cytokines and SCFAs, including chemokine C-X-C motif ligand 12 (CXCL12), interleukin-1 receptor antagonist (IL-1Ra), IL-2, IL-9, IL-4, IL-10, IL-17 A, IL-24, IL-33, IL-37, CXCL10, interferon-β (IFN-β), IFN regulatory factor 5 (IRF5), TGF-β1 and chitinase-3-like protein 1 (YKL-40) by using enzyme-linked immunosorbent assay (ELISA) and liquid chromatography-mass spectrometry (LC-MS) based analysis from gender- and age-matched adult patients with MDD ($n=24$) or SCH ($n=24$) and HC ($n=27$). We also analyzed the correlation between the identified differential profiles and clinical symptoms and identified molecular panels that can distinguish MDD, SCH and HC.

Methods

Participants

This research adhered to the principles of the Declaration of Helsinki. All subjects voluntarily participated in this research and provided written informed consent. The diagnosis based on the Diagnostic and Statistical Manual (DSM-5) of Mental Disorders criteria of SCH and MDD

was administered independently by two senior psychiatrists who were unaware of the design of this study. The Positive and Negative Syndrome Scale (PANSS), Hamilton Depression Rating Scale (HAMD), and Hamilton Anxiety Scale (HAMA) were used to assess the severity of symptoms [38, 39]. The exclusion criteria including hypertension; female patients with lactation or menstruation pregnancy; alcohol abuse or dependence; a severely imbalanced diet, such as vegetarians; illicit drug use; body mass index (BMI) ≥ 28.0 and the presence of other mental disorders. Finally, 24 patients who met the DSM-5 criteria for SCH and 24 patients with MDD were recruited, along with 27 HCs. Blood samples from all participants were collected between 8 AM and 10 AM under fasting conditions. The obtained plasma (centrifuged at 2000 rpm for 15 min at 4 ℃) were stored in liquid nitrogen until analysis.

Plasma levels of cytokines

In line with the manufacturer's instructions, concentrations of plasma CXCL12, IL-1Ra, IL-2, IL-4, IL-9, IL-10, IL-17 A, IL-24, IL-33, IL-37, IFN-β, CXCL10, IRF5, TGF-β1 and YKL-40 were measured by using commercially available ELISA kits (Shanghai Fanke Industrial Co., Ltd., China).

SCFAs measurement

Preparation of short-chain fatty acid standard solution

Accurately weigh 1 mg each of isohexanoic acid and hexanoic acid, 10 mg each of butyric acid, acetic acid, isobutyric acid, propionic acid, isovaleric acid and valeric acid, add 50% acetonitrile aqueous solution, vortex and mix evenly to obtain each standard stock solution. Then prepare the working solution.

Sample preparation

Take 50 μL of the plasma sample, add 100 μL acetonitrile and ultrasound for 30 min (5 ℃, 40 kHz), then take the supernatant after centrifugation at 4 ℃ and add 20 μL 120 mM of EDC.HCL and 20 μL 200 mM 3NPH. HCL solution, react for 30 min at 40 ℃, then dilute for machine testing.

Liquid chromatography-mass spectrometry (LC/MS)

The LC-ESI-MS/MS (UHPLC-Qtrap) was used as described previously [40]. The default parameters are used and manual inspection is assisted for identifying and integrating ion fragments. Then draw the linear regression standard curve and calculate the concentration results.

Statistical analyses

Statistical analyses were performed using Graphpad Prism 8.0.2 software, SPSS 21.0, and R-3.5.3. Continuous variables were analyzed by using a one-way analysis of variance (normal distribution, represented by mean ± SD) or the Kruskal–Wallis test (abnormal distribution) after the Shapiro-Wilk test. The counting data was analyzed by the χ^2 Test. The random forest and ROC analysis was performed using the online software MetaboAnalyst 5.0 (https://www.metaboanalyst.ca/MetaboAnalyst/) and the metabolites of Top10 were selected as the candidate biomarker panel. The top 10 metabolites with the greatest differences were selected as the candidate biomarker panel and their correlations with clinical parameters were assessed by Spearman correlation analysis.

Results

Clinical data analysis

There were no significant differences in terms of age ($P=0.506$), gender ($P=0.942$) and BMI ($P=0.125$) among the three groups (Table 1). In comparison with the HC group, the HAMA, HAMD and PANSS (T, N and G) scores in the MDD group were increased, and HAMD and PANSS (T, P, N and G) scores in the SCH group were also increased. Meanwhile, there were also significant differences in terms of HAMA, HAMD and PANSS (T, P and N) scores between MDD and SCH groups. In

Table 1 Comparison of clinical characteristics data and symptom scale assessment among the three groups

Parameter	HC ($n=27$)	MDD ($n=24$)	SCZ ($n=24$)	F/ χ^2 value	*P*-value
Age [years, M (P_{25}, P_{75})] [a]	30 (26, 30)	30 (26, 32.5)	31 (27, 34.75)	$\chi^2=1.364$	0.506
Gender(male/female)[b]	9/18	7/17	8/16	$\chi^2=0.119$	0.942
BMI [kg/m^2, mean ± SD] [c]	21.006 ± 3.027	21.014 ± 2.507	22.586 ± 3.607	$F=2.140$	0.125
HAMA (mean ± SD) [c]	4.518 ± 2.101	23.083 ± 8.187 **	6.001 ± 2.963 ##	$F=101.460$	< 0.001
HAMD (mean ± SD) [c]	3.482 ± 1.673	21.917 ± 7.615 **	6.750 ± 2.952 **##	$F=107.419$	< 0.001
PANSS (T) (mean ± SD) [c]	36.074 ± 3.731	58.875 ± 12.319 **	73.833 ± 16.459 **##	$F=66.149$	< 0.001
PANSS (P) (mean ± SD) [c]	7.852 ± 1.199	7.375 ± 1.345	19.708 ± 5.229 **##	$F=121.260$	< 0.001
PANSS (N) (mean ± SD) [c]	8.111 ± 1.188	11.125 ± 3.722 **	15.625 ± 4.614 **##	$F=30.754$	< 0.001
PANSS (G) (mean ± SD) [c]	20.111 ± 2.501	40.375 ± 8.355 **	38.500 ± 10.241 **	$F=55.946$	< 0.001

Abbreviations: [a] Kruskal Wallis; [b] Chi-square Tests; [c] One-way analysis of variance (ANOVA). *$P<0.05$ vs. HC group, **$P<0.01$ vs. HC group; #$P<0.05$ vs. MDD group, ##$P<0.01$ vs. MDD group; BMI: body mass index; Values are shown as mean ± SD or M (P_{25}, P_{75}); SD, standard deviation; HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Rating Scale; PANSS (T), PANSS total score; PANSS (P), PANSS positive symptom score; PANSS (N), PANSS negative symptom score; PANSS (G), PANSS general psychopathological symptom score

comparison with the MDD group, the scores of HAMA and HAMD were decreased whereas PANSS (T), PANSS (P) and PANSS (N) were increased in the SCH group. Moreover, almost all recruited participants never smoked or occasionally smoked, and there was no significant difference among the three groups in terms of exposure to secondhand smoke in the past 6 months. Detailed demographic and clinical characteristics of participants are shown in Supplementary Table 1.

Alternation of plasma cytokines in MDD and SCH

A total of 15 cytokines were detected in the samples from each group. Except for IL-2 (Fig. 1C), there were significant differences in the concentrations of CXCL12 ($F=24.94$, $P<0.001$, Fig. 1A), IL-1Ra ($F=39.96$, $P<0.001$, Fig. 1B), IL-4 ($F=41.96$, $P<0.001$, Fig. 1D), IL-9 ($F=59.35$, $P<0.001$, Fig. 1E), IL-10 ($F=59.98$, $P<0.001$, Fig. 1F), IL-17 A ($F=36.35$, $P<0.001$, Fig. 1G), IL-24 ($F=70.72$, $P<0.001$, Fig. 1H), IL-33 ($F=24.94$, $P<0.001$, Fig. 1I), IL-37 ($F=129.8$, $P<0.001$, Fig. 1J), IFN-β ($F=3.999$, $P=0.026$, Fig. 1K), CXCL10 ($F=98.21$, $P<0.001$, Fig. 1L), IRF5 ($F=4.856$, $P=0.015$, Fig. 1M), TGF-β1 ($F=17.97$, $P<0.001$, Fig. 1N) and YKL-40 ($F=40.34$, $P<0.001$, Fig. 1O) among the three groups. Moreover, intercomparison showed that concentrations of CXCL12, IL-1Ra, IL-4, IL-9, IL-17 A, IL-24, IL-33, CXCL10 and YKL-40 were increased, whereas IL-10, IL-37 and IRF5 were decreased in the MDD group than that in the HC group. Similarly, concentrations of CXCL12, IL-1Ra, IL-4, IL-9, IL-17 A, IL-24, IL-33, CXCL10 and YKL-40 were

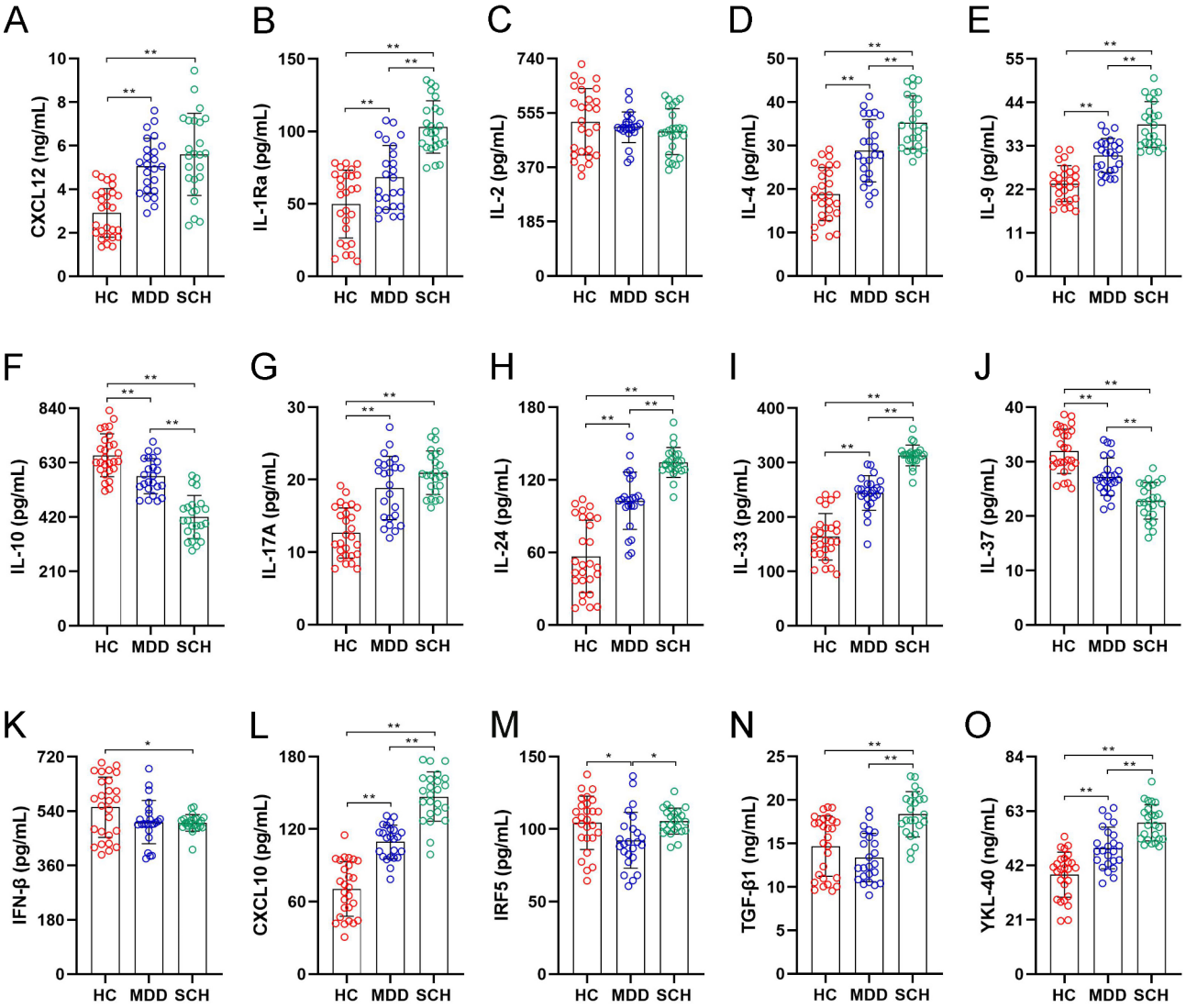

Fig. 1 The differential concentration of cytokines among MDD, SCH and HC participants. (**A**) CXCL12, (**B**) IL-1Ra, (**C**) IL-2, (**D**) IL-4, (**E**) IL-9, (**F**) IL-10, (**G**) IL-17 A, (**H**) IL-24, (**I**) IL-33, (**J**) IL-37, (**K**) IFN-β, (**L**) CXCL10, (**M**) IRF5, (**N**) TGF-β1, and (**O**) YKL-40. Abbreviation: MDD, major depressive disorder; SCH, schizophrenia; HC, healthy control; CXCL12, chemokine C-X-C motif ligand 12; IL-1Ra, interleukin-1 receptor antagonist; IFN-β, interferon-β; CXCL10, chemokine C-X-C motif ligand 10; IRF5, IFN regulatory factor 5; TGF-β1, transforming growth factor-β1; YKL-40, chitinase 3-like protein 1. *$P<0.05$; **$P<0.01$

increased, whereas IL-10 and IL-37 were decreased in the SCH group than that in the HC group. However, the concentration of IFN-β was decreased in the SCH group than in that of HC group. Importantly, concentrations of IL-1Ra, IL-4, IL-9, IL-24, IL-33, CXCL10, IRF5, TGF-β1 and YKL-40 were increased, while IL-10 and IL-37 were decreased in the SCH group when compared with the MDD group. Besides, concentrations of IL-10 and IL-37 were negatively, whereas IL-1Ra, IL-9, CXCL12, IL-17 A, IL-4, YKL-40, IL-24, IL-33 and CXCL10 were positively correlated with the PNASS score. Meanwhile, concentrations of CXCL12, IL-17 A, IL-4, YKL-40, IL-24 and IL-33 were positively, whereas TGF-β1, INF-β and IRF5 were negatively correlated with HAMD. Moreover, concentrations of CXCL12 and IL-17 A were positively, whereas TGF-β1 and IRF5 were negatively correlated with HAMA (Fig. 2A). Taken together, the concentrations of pro-inflammatory cytokines were increased, while anti-inflammatory cytokines (such as IL-37 and IL-10) were decreased in MDD and SCH, and changes in SCH were more pronounced than in MDD.

Alternation of SCFAs in MDD and SCH

As shown in Fig. 3, except for Butyric acid (Fig. 3C), there were significant differences in the concentrations of Acetic acid ($F=14.33$, $P<0.001$, Fig. 3A), Propionic acid ($F=28.94$, $P<0.001$, Fig. 3B), Isobutyric acid ($F=90.88$, $P<0.001$, Fig. 3D), Valeric acid ($F=17.36$, $P<0.001$, Fig. 3E), 4-Methylvaleric acid ($F=8.526$, $P<0.001$, Fig. 3F), Isovaleric acid ($F=39.45$, $P<0.001$, Fig. 3G) and Caproic acid ($F=36.47$, $P<0.001$, Fig. 3H) among the three groups. Furthermore, concentrations of Acetic acid, Isobutyric acid, Propionic acid, Valeric acid, Caproic acid and Isovaleric acid were decreased, while 4-Methylvaleric acid was increased in both MDD and SCH groups than that in the HC group. However, there is no significant difference in these detected SCFAs between MDD and SCH. Besides, concentrations of Caproic acid, Isovaleric acid, Acetic acid, Propionic acid, Isobutyric acid and Valeric acid were negatively correlated with PANSS (G), PANSS (T), PANSS (N) and HAMD scores (Fig. 2B). Meanwhile, concentrations of Caproic acid, Isovaleric acid, Isobutyric acid and Propionic acid were negatively correlated with scores of PANSS (P), whereas concentrations of Caproic acid, Isobutyric acid, Isovaleric acid, Acetic acid

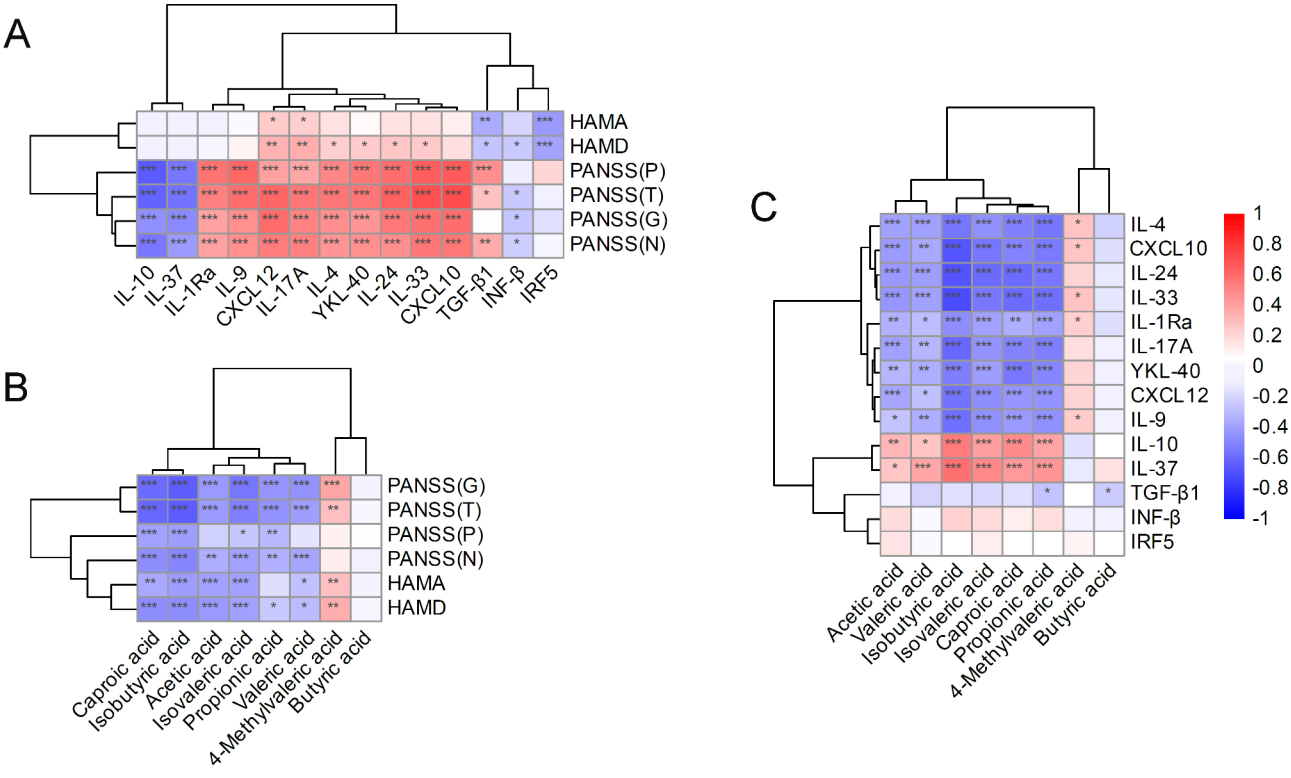

Fig. 2 Correlation between levels of cytokines, SCFAs and clinical scale score. (**A**) Correlation between levels of cytokines and scale scores of HAMA, HAMD and PANSS (**P**, **T**, **N** and **G**). (**B**) Correlation between levels of SCFAs and scale scores of HAMA, HAMD and PANSS (**P**, **T**, **N** and **G**). (**C**) Correlation between levels of SCFAs and cytokines. Red and blue squares indicate positive and negative correlations, respectively, and the intensities of the colors are proportional to the degree of correlation. $^{*}P<0.05$; $^{**}P<0.01$; $^{***}P<0.001$. Abbreviation: HAMA, Hamilton Anxiety Scale; HAMD, Hamilton Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PANSS (**T**), PANSS total score; PANSS (**P**), PANSS positive symptom score; PANSS (**N**), PANSS negative symptom score; PANSS (**G**), PANSS general psychopathological symptom score

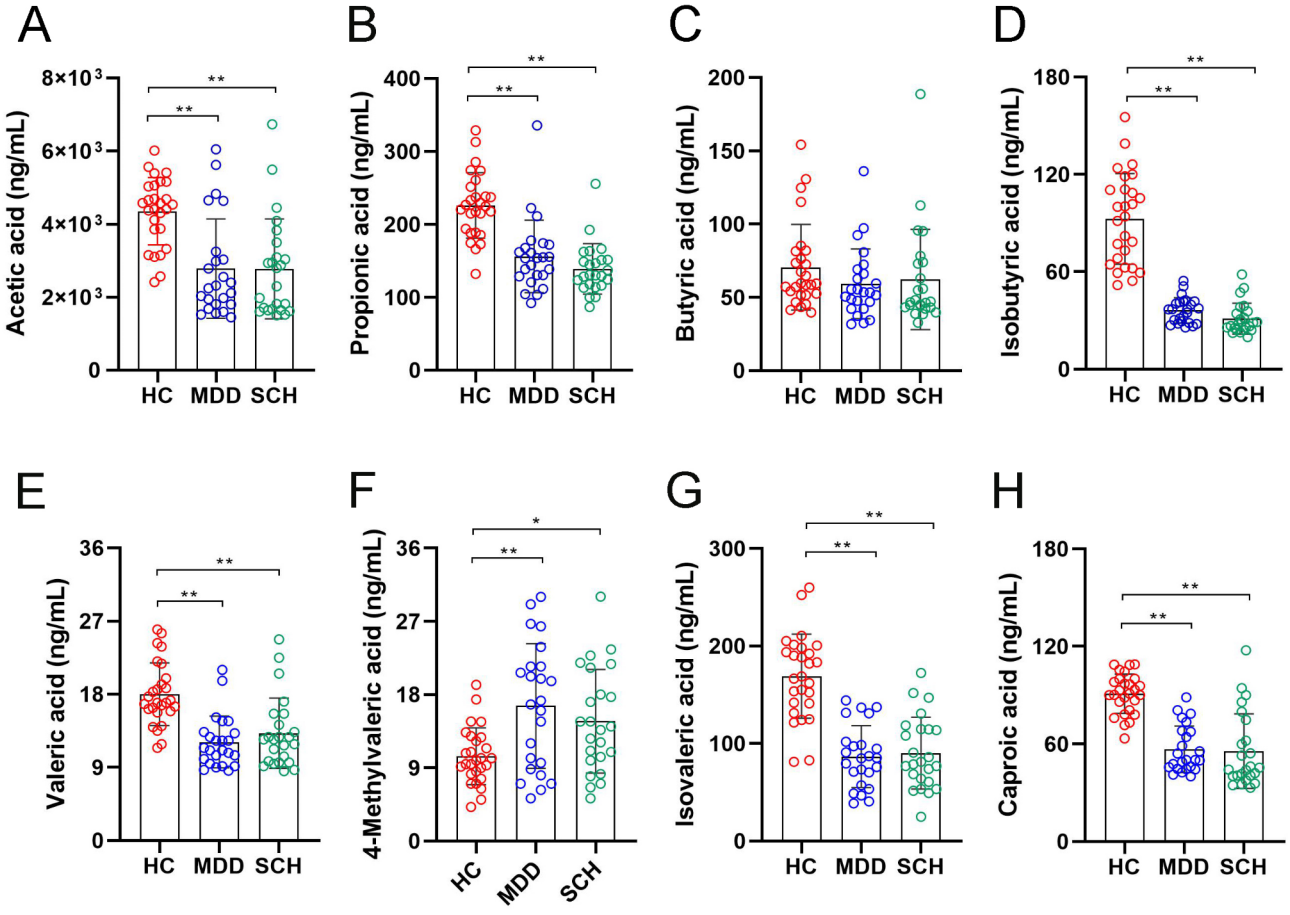

Fig. 3 The differential concentration of SCFAs among MDD, SCH and HC participants. (**A**) Acetic acid, (**B**) Propionic acid, (**C**) Butyric acid, (**D**) Isobutyric acid, (**E**) Valeric acid, (**F**) 4-Methylvaleric acid, (**G**) Isovaleric acid, (**H**) Caproic acid. *$P < 0.05$; **$P < 0.01$

and Valeric acid were negatively correlated with scores of HAMA. On the other hand, levels of 4-Methylvaleric acid were positively correlated with scores of PANSS (T), PANSS (G), HAMD and HAMA. Whereas levels of IL-4, CXCL10, IL-24, IL-33, IL-1Ra, IL-17 A, YKL-40, CXCL12 and IL-9 were negatively, whereas IL-10 and IL-37 were positively correlated with levels of Acetic acid, Valeric acid, Isobutyric acid, Isovaleric acid, Caproic acid and Propionic acid (Fig. 2C). In addition, concentrations of IL-4, CXCL10, IL-33, IL-1Ra and IL-9 were positively correlated with levels of 4-Methylvaleric acid, and concentration of TGF-β1 was negatively correlated with levels of Butyric acid and Propionic acid. Together, except for an increase in 4-Methylvaleric acid, all other SCFAs with statistical differences decreased in both MDD and SCH. Levels of proinflammatory cytokines were negatively while anti-inflammatory cytokines were positively correlated with the concentrations of changed SCFAs.

Characteristic plasma cytokines and SCFAs between *MDD and HC,SCZ and HC, and SCZ and MDD*

As shown in Fig. 4, the top 10 differential cytokines and SCFAs, including Caproic acid, Isobutyric acid, CXCL10, Isovaleric acid, IL-33, Valeric acid, Propionic acid, IL-24, CXCL12 and IL-9 were consisted as a panel that could distinguish MDD and HC effectively (AUC=0.997, Fig. 4A, B). Similarly, a panel containing IL-33, IL-24, CXCL10, Isobutyric acid, IL-9, YKL-40, IL-4, IL-1Ra, IL-10 and IL-17 A could distinguish SCH and HC effectively (AUC=0.999, Fig. 4C, D). Finally, a panel consist of IL-33, CXCL10, IL-10, IL-24, TGF-β1, IL-1Ra, IL-9, YKL-40, IL-37 and IRF5 could distinguish SCH and MDD effectively (AUC=0.983, Fig. 4E, F). These results indicate that plasma cytokines and SCFAs might be useful for screening peripheral biomarkers in patients with MDD and SCH.

Discussion

Cytokines are small proteins that are predominantly produced by immune cells and are influenced by numerous factors such as genetics, exposure to pathogens and

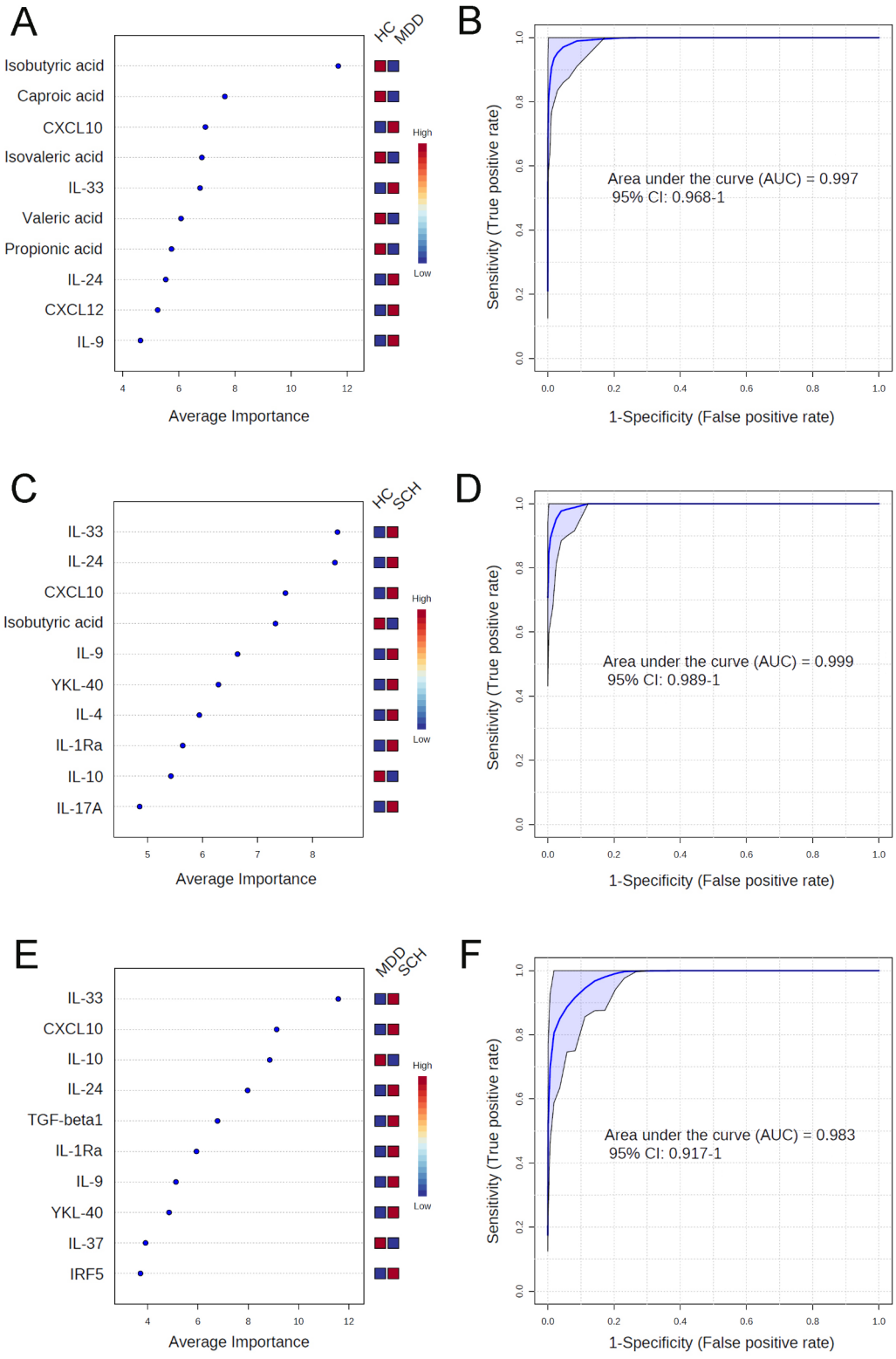

Fig. 4 Potential biomarker panels and AUC value of ROC analysis for discriminating MDD, SCH and HC. Top 10 differential markers identified from random forest classifiers based on the combination of cytokines and SCFAs and AUC value of ROC analysis for discriminating the MDD from HC (**A**, **B**), SCH from HC (**C**, **D**) and MDD from SCH (**E**, **F**)

stress [41, 42]. Cytokines can divide into several families and provide specialized functions. One of the most well-known features is either pro-inflammatory or anti-inflammatory effects. Both acute and chronic inflammation was involved in the pathogenesis of MDD, and the relationship between proinflammatory cytokines and MDD, such as TNFα, IL-1β and IL-6 has been extensively studied [43]. Recently, more cytokines and their receptors, including IL-3, IL-4, IL-17 A and TGF-β1, have been studied in association with depression [44, 45]. Consistent with previous results, we found that CXCL12, IL-1Ra, IL-4, IL-9, IL-17 A and IL-33 were increased whereas IL-10 was decreased in the MDD group than that of the HC group. Importantly, we also found that IL-24, CXCL10 and YKL-40 were increased whereas IL-37 and IRF5 were decreased in the MDD group than the HC group. IL-24 belongs to the IL-10 family and is implicated in the inflammatory processes and CXCL10 is expressed in a variety of cells including macrophages, fibroblasts, monocytes, glial cells and neurons, and plays roles in mediating the migration of inflammatory leukocytes into inflamed tissues [46]. Meanwhile, YKL-40 is an inflammatory biomarker whereas IL-37 is an inhibitor of proinflammatory IL-1 family members [47]. Although previous studies indicated that polymorphisms in IL-24 were possibly involved in the increased risk for MDD [48], the expression of CXCL10 was elevated in rats with depressive-like behaviors [49] and IL-37 might have therapeutic potential for the regulation of depression-induced inflammatory response [50], the changes in the peripheral levels of these cytokines in MDD are not yet known. Moreover, IRF5 is a central mediator of innate and adaptive immunity and its connection with depression has not been reported yet. Our recent work also found that exposure to chronic variable stress induces depressive- and anxiety-like behaviors in mice and increases IL-17 A and CXCL12 while reducing IL-33 in the plasma [51]. Therefore, consistent with previous reports, the peripheral inflammatory response was increased and anti-inflammatory levels were decreased in MDD. We further found that levels of CXCL12 and IL-17 A were positively correlated while IRF5 was negatively correlated with HAMA and HAMD scores. Meanwhile, levels of IL-4, IL-24 and IL-33 were positively correlated with HAMD scores. It suggested that levels of CXCL12 and IL-17 A were positively correlated whereas IRF5 was negatively correlated with both anxiety and depression symptoms, while IL-4, IL-24 and IL-33 were only related to depression symptoms.

Accumulation evidence indicates that immune dysfunction plays a critical role in the pathogenesis of SCH [52, 53] and the alternations of cytokines in SCH have also been widely reported. A previous meta-analysis by Goldsmith et al. showed concentrations of IL-6, IL-8, TNF-α, IL-10, IL-12, soluble IL-2 receptor (sIL-2R) and transforming growth factor-β (TGF-β) were increased whereas IL-4 was decreased in first-episode psychosis (FEP) versus HC [54]. Orhan et al. found plasma levels of monocyte chemoattractant protein-1 (MCP-1) and YKL-40 were increased in FEP patients [55]. Similar to these studies, the present results showed that IL-1Ra, IL-9, IL-33, TGF-β1, IL-4 and YKL-40 were increased in the SCH group versus HC group. Inconsistently, another study showed serum IL-1Ra was increased while there were no significant differences in IFN-γ, IL-1β, TNF-α and IL-8 in patients with SCH who were first episode and drug-naive or antipsychotic-free over the past 6 months versus HC [56]. Moreover, a meta-analysis by Frydecka et al. showed elevated levels of IL-1Ra, IL-6, IL-7, IFN-γ, IL-8, IL-9, IL-10, IL-13 in multiple-episode schizophrenia (MES) patients while there were no significant differences in those cytokines between first-episode schizophrenia (FES) patients and controls [57]. These inconsistent results suggest that the source of the sample (plasma or serum) and the number of episodes have a potential influence on the levels of peripheral cytokines. Meanwhile, we also showed that CXCL12, IL-24 and IL-17 A were increased whereas IL-37 and IFN-β1 were decreased in the SCH group than that of the HC group, which has not been reported previously. CXCL12 is an anti-inflammatory chemokine factor that regulates autoimmune inflammatory response [58]. IL-17 A is central to psoriasis pathogenesis that drives IL-24 expression in the skin [59], the latter plays a key role in the pathogenesis of pro-inflammatory autoimmune disorders [60]. On the contrary, IL-37 exerts broad protective effects on inflammatory diseases and autoimmune diseases [61]. IFN-β inhibits T cell activation and it has been used for the treatment of multiple sclerosis [62]. Importantly, these cytokines were positively or negatively correlated with PANSS scores, suggesting that SCH is accompanied by abnormal peripheral autoimmune inflammation. On the other hand, Goldsmith et al. also found that the levels of IL-6, TNF-α, soluble interleukin-2 receptor (sIL-2R) and IL-1RA were increased in patients with SCH and MDD versus controls [54]. Another work found weak evidence for causal associations of sIL-2Rα and IL-9 with SCH and it indicated that the IL-6/IL-6R pathway may represent a novel therapeutic target for both SCH and MDD [63], raising the possibility of common underlying pathways in SCH and MDD for immune dysfunction. Notably, we found that several inflammatory cytokines such as IL-4, IL-33, TGF-β1 and YKL-40 were increased whereas IL-10 and IL-37, natural suppressors of inflammatory and immune responses were decreased in SCH versus MDD. It suggests that the level of plasma inflammation in patients with SCH is higher than that in MDD in the present study.

Except for an energy source of colonocytes, circulating short-chain fatty acids (SCFAs) can cross the blood-brain barrier (BBB) and regulate oxidative stress, metabolism and neuro-inflammation [22, 64], which are involved in the pathology of MDD and SCH [65, 66]. In the present study, we found that there was no significant difference in Acetic acid, Isobutyric acid, Propionic acid, Isovaleric acid, Valeric acid and Caproic acid between MDD and SCH, while levels of these SCFAs were decreased in both MDD and SCH versus HC. On the other hand, we also found 4-Methylvaleric acid, a precursor of pogostone [67], was increased in both MDD and SCH groups and was positively correlated with PANSS (G and T) or HAMA/HAMD scores. These results indicated that the alternation of SCFAs might be the common feature of these two diseases. Nevertheless, a recent study found the total content of serum SCFAs was increased in first-episode depression [30]. However, our recent work found that levels of Isobutyric acid, Caproic acid, and Propionic acid were decreased in the plasma of MDD and were negatively correlated with the scores of HAMD and HAMA [68]. Similarly, Peng et al. found that the level of Valeric acid was decreased in SCH than that in the HC group, whereas there were no significant differences in Acetic acid, Butyric acid, Isovaleric acid and total SCFAs' level between SCH and HC [28]. Li et al. found there was no significant difference in serum levels of butyric acid between SCH at baseline and HC, while it was increased after 24-week risperidone treatment [69]. However, another study showed reduced Acetic acid, total SCFAs and acetic acid/ propionic acid ratio in SCH than HC [70]. Therefore, differences in peripheral SCFAs observed in MDD and SCH versus HC were inconsistent across studies, and the reasons behind need to be further elucidated.

Given that propionic acid, Acetic acid, Valeric acid, isobutyric acid and pogostone showed immune-modulatory effects [71–74], we speculate that there may be an interaction between SCFAs and cytokines. We found that altered SCFAs were negatively correlated with the level of proinflammatory cytokines but positively correlated with the level of anti-inflammatory cytokines like IL-10 and IL-37, indicating the alternations in SCFAs might influence psychiatric symptoms by affecting the immune response. Besides elucidating the compositions of cytokines and SCFAs in MDD and SCH, we also wanted to know which combinational molecular could discriminate MDD and SCH (from each other and from HC). For this purpose, we identified potential molecular panels that could distinguish patients with MDD from those with SCH or HC, with AUC values of 0.983 and 0.999, respectively. A previous study reported that changes in fecal SCFAs and plasma inflammatory cytokines such as TNF-α and IL-1Ra were associated with changes in depression or anxiety symptoms [75]. Another study found that SCFAs including acetic acid, propanoic acid, butyric acid, isobutyric acid, isovaleric acid and isohexanoic acid, and several neurotransmitters were remarkably decreased in SCH cases with aggression than those without [76]. Therefore, changes in peripheral fatty acids and inflammatory cytokines may be characteristic of underlying MDD and SCH.

It should be noted that the results of IL-4 from different studies are controversial in SCH. Consistent with our result, concentrations of IL-4 in serum in relapse patients with SCH were higher than in controls [77], while another work indicated that IL-4 was not increased in patients with first-onset SCH, and it was even decreased in chronic schizophrenia-spectrum disorder [78]. Similarly, we found that CXCL10 was increased while another work showed that serum concentrations of CXCL10 were decreased in patients with SCH [79]. Nevertheless, a previous study found that all concentrations of fecal SCFAs except for isocaproic acid were diminished in depressed patients [80], whereas another work showed that levels of total SCFAs and acetic acid in serum were increased in drug-naïve, first-episode SCH [70]. Therefore, the difference in cytokines and SCFAs levels may be related to factors such as the sample source, the stage of disease development and the severity of mental symptoms.

Nevertheless, several limitations also should be clarified. The present study was only based on cross-sectional studies and has a limited number of cases, a large sample of cohort study should be considered. Meanwhile, the influence of antidepressants or antipsychotics and other treatment methods (neuroregulation and psychotherapy) on cytokines and SCFAs cannot be ruled out. Moreover, further exploration is needed to investigate the interactions between plasma cytokines and SCFAs and other reported molecular features that can distinguish MDD and SCH patients from HC, such as the kynurenine (KYN) pathway of tryptophan. KYN is not only a key link between the brain-gut axis, but also one of the underlying molecular mechanisms that was involved in MDD and SCH [81–83].

Conclusions

We characterized different plasma cytokines and SCFAs in adult patients with MDD and SCH. Moreover, we developed potential molecular panels to discriminate patients with MDD from HC, SCH from HC and each other. Although the findings might help to understand the pathogenesis of these two diseases further, they still need to be confirmed by large sample size studies including discovery and validation cohorts.

Supplementary Information

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Supplementary Material 1

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Author contributions
H. Yu, R. Li and X.J. Liang wrote the main manuscript text and W.M. Yang, L. Guo and L. Liu prepared Figs. 1, 2, 3 and 4. All authors reviewed the manuscript. Q.R. Tan and Z.W. Peng conceptualized this work and review & editing the manuscript. All authors reviewed the manuscript.

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Data availability
The LC/MS datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The research was registered in the Chinese Clinical Trial Registry (number: ChiCTR2100051243, 16th September 2021) and its protocol was approved by the China Registered Clinical Trial Ethics Review Committee (number: ChiECRCT20210335). All subjects voluntarily participated in this research and provided written informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Gur S, Weizman S, Stubbs B, Matalon A, Meyerovitch J, Hermesh H, Krivoy A. Mortality, morbidity and medical resources utilization of patients with schizophrenia: a case-control community-based study. Psychiatry Res. 2018;260:177–81.
2. Rotenstein LS, Ramos MA, Torre M, Segal JB, Peluso MJ, Guille C, Sen S, Mata DA. Prevalence of Depression, depressive symptoms, and suicidal ideation among medical students: a systematic review and Meta-analysis. JAMA. 2016;316(21):2214–36.
3. Cui L, Li S, Wang S, Wu X, Liu Y, Yu W, Wang Y, Tang Y, Xia M, Li B. Major depressive disorder: hypothesis, mechanism, prevention and treatment. Signal Transduct Target Ther. 2024;9(1):30.
4. Dietz AG, Goldman SA, Nedergaard M. Glial cells in schizophrenia: a unified hypothesis. Lancet Psychiatry. 2020;7(3):272–81.
5. Smith KM, Renshaw PF, Bilello J. The diagnosis of depression: current and emerging methods. Compr Psychiatry. 2013;54(1):1–6.
6. Tandon R, Gaebel W, Barch DM, Bustillo J, Gur RE, Heckers S, Malaspina D, Owen MJ, Schultz S, Tsuang M, et al. Definition and description of schizophrenia in the DSM-5. Schizophr Res. 2013;150(1):3–10.
7. Rosen C, Marvin R, Reilly JL, Deleon O, Harris MS, Keedy SK, Solari H, Weiden P, Sweeney JA. Phenomenology of first-episode psychosis in schizophrenia, bipolar disorder, and unipolar depression: a comparative analysis. Clin Schizophr Relat Psychoses. 2012;6(3):145–51.
8. Martinez-Aran A, Vieta E. Cognition as a target in schizophrenia, bipolar disorder and depression. Eur Neuropsychopharmacol. 2015;25(2):151–7.
9. Li Z, Li D, Chen X. Characterizing the polygenic overlaps of bipolar disorder subtypes with schizophrenia and major depressive disorder. J Affect Disord. 2022;309:242–51.
10. Bener A, Dafeeah EE, Abou-Saleh MT, Bhugra D, Ventriglio A. Co-morbidity between Major Depression and Schizophrenia: prevalence and clinical characteristics. Psychiatr Danub. 2020;32(1):78–83.
11. Samsom JN, Wong AH. Schizophrenia and Depression Co-morbidity: what we have learned from animal models. Front Psychiatry. 2015;6:13.
12. Etchecopar-Etchart D, Korchia T, Loundou A, Llorca PM, Auquier P, Lancon C, Boyer L, Fond G. Comorbid Major Depressive Disorder in Schizophrenia: a systematic review and Meta-analysis. Schizophr Bull. 2021;47(2):298–308.
13. Beurel E, Toups M, Nemeroff CB. The bidirectional relationship of depression and inflammation: double trouble. Neuron. 2020;107(2):234–56.
14. Muller N. Inflammation in Schizophrenia: pathogenetic aspects and therapeutic considerations. Schizophr Bull. 2018;44(5):973–82.
15. Rey R, Chauvet-Gelinier JC, Suaud-Chagny MF, Ragot S, Bonin B, d'Amato T, Teyssier JR. Distinct expression pattern of Epigenetic Machinery Genes in blood leucocytes and brain cortex of depressive patients. Mol Neurobiol. 2019;56(7):4697–707.
16. Ai YW, Du Y, Chen L, Liu SH, Liu QS, Cheng Y. Brain inflammatory marker abnormalities in Major Psychiatric diseases: a systematic review of Postmortem Brain studies. Mol Neurobiol. 2023;60(4):2116–34.
17. Kohler CA, Freitas TH, Maes M, de Andrade NQ, Liu CS, Fernandes BS, Stubbs B, Solmi M, Veronese N, Herrmann N, et al. Peripheral cytokine and chemokine alterations in depression: a meta-analysis of 82 studies. Acta Psychiatr Scand. 2017;135(5):373–87.
18. Miller GE, Cole SW. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol Psychiatry. 2012;72(1):34–40.
19. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry. 2008;63(8):801–8.
20. Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. Biol Psychiatry. 2011;70(7):663–71.
21. Tourjman V, Kouassi E, Koue ME, Rocchetti M, Fortin-Fournier S, Fusar-Poli P, Potvin S. Antipsychotics' effects on blood levels of cytokines in schizophrenia: a meta-analysis. Schizophr Res. 2013;151(1–3):43–7.
22. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota-gut-brain communication. Nat Rev Gastroenterol Hepatol. 2019;16(8):461–78.
23. Aho VTE, Houser MC, Pereira PAB, Chang J, Rudi K, Paulin L, Hertzberg V, Auvinen P, Tansey MG, Scheperjans F. Relationships of gut microbiota, short-chain fatty acids, inflammation, and the gut barrier in Parkinson's disease. Mol Neurodegener. 2021;16(1):6.
24. Kim CH, Park J, Kim M. Gut microbiota-derived short-chain fatty acids, T cells, and inflammation. Immune Netw. 2014;14(6):277–88.
25. Dupraz L, Magniez A, Rolhion N, Richard ML, Da Costa G, Touch S, Mayeur C, Planchais J, Agus A, Danne C, et al. Gut microbiota-derived short-chain fatty acids regulate IL-17 production by mouse and human intestinal gammadelta T cells. Cell Rep. 2021;36(1):109332.
26. Tedelind S, Westberg F, Kjerrulf M, Vidal A. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. World J Gastroenterol. 2007;13(20):2826–32.
27. Simpson CA, Diaz-Arteche C, Eliby D, Schwartz OS, Simmons JG, Cowan CSM. The gut microbiota in anxiety and depression - A systematic review. Clin Psychol Rev. 2021;83:101943.
28. Peng H, Ouyang L, Li D, Li Z, Yuan L, Fan L, Liao A, Li J, Wei Y, Yang Z, et al. Short-chain fatty acids in patients with schizophrenia and ultra-high risk population. Front Psychiatry. 2022;13:977538.
29. Joseph J, Depp C, Shih PB, Cadenhead KS, Schmid-Schonbein G. Modified Mediterranean Diet for Enrichment of short chain fatty acids: potential adjunctive therapeutic to Target Immune and metabolic dysfunction in Schizophrenia? Front Neurosci 2017, 11:155.
30. Yu S, Wang L, Jing X, Wang Y, An C. Features of gut microbiota and short-chain fatty acids in patients with first-episode depression and their relationship with the clinical symptoms. Front Psychol. 2023;14:1088268.

31. Kelley KW, Pasca SP. Human brain organogenesis: toward a cellular understanding of development and disease. Cell. 2022;185(1):42–61.
32. Enache D, Pariante CM, Mondelli V. Markers of central inflammation in major depressive disorder: a systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain Behav Immun. 2019;81:24–40.
33. Mohammadi A, Rashidi E, Amooeian VG. Brain, blood, cerebrospinal fluid, and serum biomarkers in schizophrenia. Psychiatry Res. 2018;265:25–38.
34. Voyle N, Kim M, Proitsi P, Ashton NJ, Baird AL, Bazenet C, Hye A, Westwood S, Chung R, Ward M, et al. Blood metabolite markers of neocortical amyloid-beta burden: discovery and enrichment using candidate proteins. Transl Psychiatry. 2016;6(1):e719.
35. Bora E. Peripheral inflammatory and neurotrophic biomarkers of cognitive impairment in schizophrenia: a meta-analysis. Psychol Med. 2019;49(12):1971–9.
36. Milaneschi Y, Allers KA, Beekman ATF, Giltay EJ, Keller S, Schoevers RA, Sussmuth SD, Niessen HG, Penninx B. The association between plasma tryptophan catabolites and depression: the role of symptom profiles and inflammation. Brain Behav Immun. 2021;97:167–75.
37. Campeau A, Mills RH, Stevens T, Rossitto LA, Meehan M, Dorrestein P, Daly R, Nguyen TT, Gonzalez DJ, Jeste DV, et al. Multi-omics of human plasma reveals molecular features of dysregulated inflammation and accelerated aging in schizophrenia. Mol Psychiatry. 2022;27(2):1217–25.
38. Nikolova VL, Cleare AJ, Young AH, Stone JM. Acceptability, tolerability, and estimates of Putative Treatment effects of Probiotics as Adjunctive treatment in patients with Depression: a Randomized Clinical Trial. JAMA Psychiatry. 2023;80(8):842–7.
39. Anderson A, Wilcox M, Savitz A, Chung H, Li Q, Salvadore G, Wang D, Nuamah I, Riese SP, Bilder RM. Sparse factors for the positive and negative syndrome scale: which symptoms and stage of illness? Psychiatry Res. 2015;225(3):283–90.
40. Phulpoto IA, Bobo W, Qazi MA, Yu ZS. Lipopeptide Biosurfactants Enhanced Biohydrogen Evolution from Lignocellulose Biomass and Shaped the Microbial Community and Diversity. >Int J Energ Res 2024, 2024.
41. MacGillivray DM, Kollmann TR. The role of environmental factors in modulating immune responses in early life. Front Immunol. 2014;5:434.
42. Yamanishi K, Doe N, Mukai K, Hashimoto T, Gamachi N, Hata M, Watanabe Y, Yamanishi C, Yagi H, Okamura H, et al. Acute stress induces severe neural inflammation and overactivation of glucocorticoid signaling in interleukin-18-deficient mice. Transl Psychiatry. 2022;12(1):404.
43. Dantzer R, Wollman E, Vitkovic L, Yirmiya R. Cytokines and depression: fortuitous or causative association? Mol Psychiatry. 1999;4(4):328–32.
44. Harsanyi S, Kupcova I, Danisovic L, Klein M. Selected biomarkers of Depression: what are the effects of cytokines and inflammation? Int J Mol Sci 2022, 24(1).
45. Oglodek EA, Just MJ. The association between inflammatory markers (iNOS, HO-1, IL-33, MIP-1beta) and depression with and without posttraumatic stress disorder. Pharmacol Rep. 2018;70(6):1065–72.
46. Giladi A, Wagner LK, Li H, Dorr D, Medaglia C, Paul F, Shemer A, Jung S, Yona S, Mack M, et al. Cxcl10(+) monocytes define a pathogenic subset in the central nervous system during autoimmune neuroinflammation. Nat Immunol. 2020;21(5):525–34.
47. Conti P, Gallenga CE, Caraffa A, Ronconi G, Kritas SK. Impact of mast cells in fibromyalgia and low-grade chronic inflammation: can IL-37 play a role? Dermatol Ther. 2020;33(1):e13191.
48. Traks T, Koido K, Eller T, Maron E, Kingo K, Vasar V, Vasar E, Koks S. Polymorphisms in the interleukin-10 gene cluster are possibly involved in the increased risk for major depressive disorder. BMC Med Genet. 2008;9:111.
49. Huang X, Yang C, Huang M. Protective mechanism of the EZH2/microRNA-15a-5p/CXCL10 axis in rats with depressive-like behaviors. J Chem Neuroanat. 2023;132:102283.
50. Conti P, Caraffa A, Ronconi G, Conti CM, Kritas SK, Mastrangelo F, Tettamanti L, Theoharides TC. Impact of mast cells in depression disorder: inhibitory effect of IL-37 (new frontiers). Immunol Res. 2018;66(3):323–31.
51. Chen H, Zhao X, Ma X, Ma H, Zhou C, Zhang Y, Peng Z, Xue S, Cai M. Effects of esketamine and fluoxetine on depression-like behaviors in chronic variable stress: a role of plasma inflammatory factors. Front Psychiatry. 2024;15:1388946.
52. Birnbaum R, Weinberger DR. A Genetics Perspective on the role of the (Neuro)Immune System in Schizophrenia. Schizophr Res. 2020;217:105–13.
53. Gangadin SS, Enthoven AD, van Beveren NJM, Laman JD, Sommer IEC. Immune Dysfunction in Schizophrenia Spectrum disorders. Annu Rev Clin Psychol. 2024;20(1):229–57.
54. Goldsmith DR, Rapaport MH, Miller BJ. A meta-analysis of blood cytokine network alterations in psychiatric patients: comparisons between schizophrenia, bipolar disorder and depression. Mol Psychiatry. 2016;21(12):1696–709.
55. Orhan F, Schwieler L, Fatouros-Bergman H, Malmqvist A, Cervenka S, Collste K, Flyckt L, Farde L, Sellgren CM, Piehl F, et al. Increased number of monocytes and plasma levels of MCP-1 and YKL-40 in first-episode psychosis. Acta Psychiatr Scand. 2018;138(5):432–40.
56. Lin Y, Peng Y, He S, Xu J, Shi Y, Su Y, Zhu C, Zhang X, Zhou R, Cui D. Serum IL-1ra, a novel biomarker predicting olanzapine-induced hypercholesterolemia and hyperleptinemia in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2018;84(Pt A):71–8.
57. Frydecka D, Krzystek-Korpacka M, Lubeiro A, Stramecki F, Stanczykiewicz B, Beszlej JA, Piotrowski P, Kotowicz K, Szewczuk-Boguslawska M, Pawlak-Adamska E, et al. Profiling inflammatory signatures of schizophrenia: a cross-sectional and meta-analysis study. Brain Behav Immun. 2018;71:28–36.
58. Mousavi A. CXCL12/CXCR4 signal transduction in diseases and its molecular approaches in targeted-therapy. Immunol Lett. 2020;217:91–115.
59. Xu X, Prens E, Florencia E, Leenen P, Boon L, Asmawidjaja P, Mus AM, Lubberts E. Interleukin-17A drives IL-19 and IL-24 expression in skin stromal cells regulating keratinocyte proliferation. Front Immunol. 2021;12:719562.
60. Mitamura Y, Nunomura S, Furue M, Izuhara K. IL-24: a new player in the pathogenesis of pro-inflammatory and allergic skin diseases. Allergol Int. 2020;69(3):405–11.
61. Su Z, Tao X. Current understanding of IL-37 in Human Health and Disease. Front Immunol. 2021;12:696605.
62. Hedegaard CJ, Krakauer M, Bendtzen K, Sorensen PS, Sellebjerg F, Nielsen CH. The effect of beta-interferon therapy on myelin basic protein-elicited CD4 + T cell proliferation and cytokine production in multiple sclerosis. Clin Immunol. 2008;129(1):80–9.
63. Perry BI, Upthegrove R, Kappelmann N, Jones PB, Burgess S, Khandaker GM. Associations of immunological proteins/traits with schizophrenia, major depression and bipolar disorder: a bi-directional two-sample mendelian randomization study. Brain Behav Immun. 2021;97:176–85.
64. Sampson TR, Debelius JW, Thron T, Janssen S, Shastri GG, Ilhan ZE, Challis C, Schretter CE, Rocha S, Gradinaru V, et al. Gut microbiota regulate Motor deficits and neuroinflammation in a model of Parkinson's Disease. Cell. 2016;167(6):1469–e14801412.
65. Fraguas D, Diaz-Caneja CM, Ayora M, Hernandez-Alvarez F, Rodriguez-Quiroga A, Recio S, Leza JC, Arango C. Oxidative stress and inflammation in first-episode psychosis: a systematic review and Meta-analysis. Schizophr Bull. 2019;45(4):742–51.
66. Kennis M, Gerritsen L, van Dalen M, Williams A, Cuijpers P, Bockting C. Prospective biomarkers of major depressive disorder: a systematic review and meta-analysis. Mol Psychiatry. 2020;25(2):321–38.
67. Wang C, Wang Y, Chen J, Liu L, Yang M, Li Z, Wang C, Pichersky E, Xu H. Synthesis of 4-methylvaleric acid, a precursor of pogostone, involves a 2-isobutylmalate synthase related to 2-isopropylmalate synthase of leucine biosynthesis. New Phytol. 2022;235(3):1129–45.
68. Li R, Fu R, Yang WM, Cui ZQ, Liang XJ, Yang JB, Liu L, Tan QR, Peng ZW. Acute treatment of bilateral rTMS combined with antidepressants on the plasma fatty acids for major depressive episodes. Brain Res. 2024;1843:149125.
69. Li X, Fan X, Yuan X, Pang L, Hu S, Wang Y, Huang X, Song X. The role of Butyric Acid in Treatment Response in Drug-Naive First Episode Schizophrenia. Front Psychiatry. 2021;12:724664.
70. Li X, Yuan X, Pang L, Zhang S, Li Y, Huang X, Fan X, Song X. The effect of serum lipids and short-chain fatty acids on cognitive functioning in drug-naive, first episode schizophrenia patients. Psychiatry Res. 2022;313:114582.
71. Murayama M, Hosonuma M, Kuramasu A, Kobayashi S, Sasaki A, Baba Y, Narikawa Y, Toyoda H, Isobe J, Funayama E, et al. Isobutyric acid enhances the anti-tumour effect of anti-PD-1 antibody. Sci Rep. 2024;14(1):11325.
72. Ormsby MJ, Johnson SA, Carpena N, Meikle LM, Goldstone RJ, McIntosh A, Wessel HM, Hulme HE, McConnachie CC, Connolly JPR, et al. Propionic Acid promotes the virulent phenotype of Crohn's Disease-Associated adherent-invasive Escherichia coli. Cell Rep. 2020;30(7):2297–e23052295.
73. Li D, Xing Z, Yu T, Dong W, Wang Z, Peng C, Yang C. Pogostone attenuates adipose tissue inflammation by regulating the adipocyte-macrophage crosstalk via activating SIRT1. Food Funct. 2022;13(22):11853–64.

74. Chen R, Li K, Wang Y, Song L, Wang R, Fan W, Zhao N, Zou W, Yang Z, Yan J. Valeric acid reduction by chitosan oligosaccharide induces autophagy in a Parkinson's disease mouse model. J Drug Target. 2024;32(4):423–32.
75. Burton TC, Lv N, Tsai P, Penalver Bernabe B, Tussing-Humphreys L, Xiao L, Pandey GN, Wu Y, Ajilore OA, Ma J. Associations between fecal short-chain fatty acids, plasma inflammatory cytokines, and dietary markers with depression and anxiety: Post hoc analysis of the ENGAGE-2 pilot trial. Am J Clin Nutr. 2023;117(4):717–30.
76. Deng H, He L, Wang C, Zhang T, Guo H, Zhang H, Song Y, Chen B. Altered gut microbiota and its metabolites correlate with plasma cytokines in schizophrenia inpatients with aggression. BMC Psychiatry. 2022;22(1):629.
77. Borovcanin M, Jovanovic I, Radosavljevic G, Djukic Dejanovic S, Bankovic D, Arsenijevic N, Lukic ML. Elevated serum level of type-2 cytokine and low IL-17 in first episode psychosis and schizophrenia in relapse. J Psychiatr Res. 2012;46(11):1421–6.
78. Halstead S, Siskind D, Amft M, Wagner E, Yakimov V, Shih-Jung Liu Z, Walder K, Warren N. Alteration patterns of peripheral concentrations of cytokines and associated inflammatory proteins in acute and chronic stages of schizophrenia: a systematic review and network meta-analysis. Lancet Psychiatry. 2023;10(4):260–71.
79. de Campos-Carli SM, Araujo MS, de Oliveira Silveira AC, de Rezende VB, Rocha NP, Ferretjans R, Ribeiro-Santos R, Teixeira-Carvalho A, Martins-Filho OA, Berk M, et al. Cannabinoid receptors on peripheral leukocytes from patients with schizophrenia: evidence for defective immunomodulatory mechanisms. J Psychiatr Res. 2017;87:44–52.
80. Skonieczna-Zydecka K, Grochans E, Maciejewska D, Szkup M, Schneider-Matyka D, Jurczak A, Loniewski I, Kaczmarczyk M, Marlicz W, Czerwinska-Rogowska M et al. Faecal Short Chain Fatty Acids Profile is Changed in Polish Depressive Women.Nutrients 2018, 10(12).
81. Correia AS, Vale N. Tryptophan Metabolism in Depression: a narrative review with a focus on serotonin and Kynurenine Pathways. Int J Mol Sci 2022, 23(15).
82. Sapienza J, Agostoni G, Comai S, Nasini S, Dall'Acqua S, Sut S, Spangaro M, Martini F, Bechi M, Buonocore M, et al. Neuroinflammation and kynurenines in schizophrenia: impact on cognition depending on cognitive functioning and modulatory properties in relation to cognitive remediation and aerobic exercise. Schizophr Res Cogn. 2024;38:100328.
83. Zhu F, Guo R, Wang W, Ju Y, Wang Q, Ma Q, Sun Q, Fan Y, Xie Y, Yang Z, et al. Transplantation of microbiota from drug-free patients with schizophrenia causes schizophrenia-like abnormal behaviors and dysregulated kynurenine metabolism in mice. Mol Psychiatry. 2020;25(11):2905–18.

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