ORIGINAL ARTICLE

Plasma linoelaidyl carnitine levels positively correlated with symptom improvement in olanzapine-treated first-episode drug-naïve schizophrenia

Xuan Wang[1] · Meihong Xiu[2] · Keqiang Wang[1] · Xiuru Su[1] · Xirong Li[2] · Fengchun Wu[3,4,5]

Abstract

Introduction Olanzapine (OLA) is one of the most commonly used second-generation antipsychotics for the treatment of schizophrenia. However, the heterogeneity of therapeutic response to OLA among schizophrenia patients deserves further exploration. The role of carnitine in the clinical response to OLA monotherapy remains unclear.

Objectives The current study was designed to investigate whether carnitine and its derivatives are linked to the response to OLA treatment. Drug-naïve first-episode patients with schizophrenia were recruited and treated with OLA for 4 weeks. Psychiatric symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) in pre and post treatment.

Results After treatment, we found a significant decrease in 2-Octenoylcarnitine levels and a significant increase in linoelaidyl carnitine, 11Z-Octadecenylcarnitine and 9-Decenoylcarnitine levels. Furthermore, baseline linoelaidyl carnitine levels were correlated with the reduction of PANSS positive symptom subscore. Linear regression and logistic regression analyses found that the baseline linoelaidyl carnitine level was a predictive marker for the therapeutic response to OLA monotherapy for 4 weeks.

Conclusion Our pilot study suggests that linoelaidyl carnitine levels at baseline may have a predictive role for the improvement of positive symptoms after OLA monotherapy in the patients with schizophrenia.

Keywords Schizophrenia · Metabonomic analysis · Linoelaidyl carnitine · Therapeutic response · Olanzapine

Xuan Wang and Meihong Xiu have contributed equally.

✉ Fengchun Wu
  13580380071@163.com

1. Hebei Province Veterans Hospital, Baoding, China

2. Peking University HuiLongGuan Clinical Medical School, Beijing HuiLongGuan Hospital, Beijing, China

3. Department of Psychiatry, The Affiliated Brain Hospital of Guangzhou Medical University, Liwan District, Guangzhou 510370, China

4. Department of Biomedical Engineering, Guangzhou Medical University, Liwan District, Guangzhou 510370, China

5. Guangdong Engineering Technology Research Center for Translational Medicine of Mental Disorders, Liwan District, Guangzhou 510370, China

1 Introduction

Schizophrenia (SZ) is a chronic and severe mental disorder with a prevalence of 1% worldwide (Lopez & Murray, 1998). Although a number of molecular, pharmacological and clinical studies have been published, the pathogenesis and pathophysiology of SZ is poorly understood (Aleksic & Ozaki, 2017; Dawidowski et al., 2021; Owen et al., 2016). The dopaminergic hypothesis that hyperactive dopamine transmission results in the symptoms of SZ is the dominant hypothesis and current antipsychotic drug is mainly based on this hypothesis to reduce the psychiatric symptoms (Davis et al., 1991; Kapur, 2003; Meltzer & Stahl, 1976). Olanzapine (OLA) is considered to be one of the first-line atypical antipsychotic drugs for the treatment of SZ, which can be used for fist-episode SZ or long-term maintenance treatment (Correll et al., 2021). OLA binds with the following receptors: dopamine, serotonin, histamine H1, adrenergic α1, and muscarinic M (Chelkeba et al., 2017; Tollens et al., 2018). It acts an

antagonist at dopamine D_2 receptors in the mesolimbic pathway, blocking the potential action of dopamine on post-synaptic receptors. However, recent clinical evidence has shown that chronic OLA treatment causes severe metabolic disturbances, such as insulin resistance, obesity and dyslipidemia (Tek et al., 2016). In addition, there is a considerable individual variability with regard to clinical symptoms and clinical response to antipsychotics among patients with SZ (Messias et al., 2007). It is estimated that approximately 30% patients with SZ do not respond to olanzapine and develop treatment-resistant SZ during the course of the illness according to the epidemiological data from the research articles (Elkis & Buckley, 2016). From clinical perspective, identifying potential molecular pathogenic factors and finding predictive biomarkers for the response to OLA could improve the clinical management of SZ patients in the early stage of this disorder.

Pharmacometabolomics, as an application of metabolomics in drug efficacy research, have been used to map the global metabolite changes after antipsychotics treatment in SZ (Kaddurah-Daouk & Weinshilboum, 2014). A number of studies have shown significant changes in mitochondrial number, structure and function or the production of adenosine triphosphate (ATP) in patients with acute episode of psychosis, indicating a role for mitochondrial energetics in the early stage of SZ (Park et al., 2021). Recent studies reported that blood lipid metabolism involved in the altered carnitine levels and its derivatives are implicated in the pathogenesis and pathophysiology of SZ (Cao et al., 2019; Kriisa et al., 2017).

Carnitine (3-hydroxy-4-*N*-trimethylaminobutyrate, $C_7H_{15}NO_3$) is an essential dietary amino acid obtained from animal products such as meat, fish and milk, or is biosynthesized from L-lysine and L-methionine (Flanagan et al., 2010). It has various physiological and biochemical functions in the central nervous system, such as anti-inflammatory, antioxidant, anti-apoptosis and enhancement of autophagy (Moghaddas & Dashti-Khavidaki, 2016; Traina, 2016). Studies reported that L-carnitine supplementation can promote the early recovery of cerebral infarction through its antioxidant and anti-inflammatory functions (Wang et al., 2017). In addition, carnitine plays a crucial role in the protection of DNA and protein from oxidative stress throughout its antioxidant properties (Ribas et al., 2014). Particularly, carnitines are also found to regulate and promote the synaptic neurotransmission, most notably cholinergic neurotransmission (Agarwal & Said, 2004; Calvani et al., 1992; Nałecz et al., 2004). Indeed, SZ patients do show hallmarks of abnormalities in immune response regulation, neuroendocrine and molecular pathways of neurotransmitter systems (Mould et al., 2021; Rahimian et al., 2021; Upthegrove & Khandaker, 2019; van Kesteren et al., 2017; van Mierlo et al., 2019).

Notably, carnitine and its derivatives are known for the crucial roles in the transport of long-chain fatty acids to mitochondrial matrix and oxidation of long-chain fatty acyl coenzyme A (CoAs) (Noland et al., 2009; Siliprandi et al., 1990; Young et al., 2018). The carnitine system can enhance neuron energy metabolism as a reservoir pool of acyl CoAs or as a transfer of fatty acid beta-oxidation (Jones et al., 2010). Abnormal carnitine metabolism or carnitine deficiency decreases fatty acid beta-oxidation and thus decreases the production of mitochondrial energy (ATP), which have been implicated in mental disorders (Kępka et al., 2021). Other function of carnitine is to maintain membrane integrity and stabilize the physiologic coenzyme A (CoASH)/ acetyl-CoA ratio in mitochondria (Siliprandi et al., 1990). It is noteworthy that disturbances of mitochondrial morphology, function and genesis are gradually considered as components of psychiatric disorders, including SZ, bipolar disorder, depression and autism (Rajasekaran et al., 2015; Takahashi & Ogushi, 1953). Interestingly, the neuroprotective effect of a novel twin compound LR134 and LR143 containing carnitine substructure was correlated with the protection of mitochondria accompanied by the improvement of energy supply (Spagnoli et al., 1991; Wang et al., 2017).

Based on the previous studies, altered plasma or serum acylcarnitine can potentially be identified as a biomarker that indicates abnormalities in beta-oxidation (Cavedon et al., 2005; Kler et al., 1991; Rinaldo et al., 2008; Vreken et al., 1999). Particularly, preclinical studies have shown that elevated blood medium- and long-chain acylcarnitine levels have been correlated with incomplete fatty acid beta-oxidation in a model of depression (Chen et al., 2014). Therefore, the determination of carnitine concentration is crucial to characterize the metabolic status of SZ patients and may be critical for the development of potentially predictive factors for the therapeutic response to antipsychotics. Thus, in this study, we hypothesize that the analysis of carnitine and its derivatives before and after treatment with OLA for 4 weeks may identify critical biomarkers related to SZ. To test the hypothesis, we performed an untargeted metabolomics analysis to find the differential carnitines or its derivatives after treatment with OLA monotherapy for 1 month and to address the association between carnitine levels and treatment response to OLA in drug-naïve first-episode (DNFE) SZ.

2 Methods

2.1 Patients

Twenty-five female DNFE patients with SZ were enrolled, diagnosed via the Diagnostic and Statistical Manual of

Mental Disorders (DSM)-IV criteria and confirmed by the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID). According to the DSM-IV, a diagnosis of SZ is made if a person has two or more core symptoms, one of which must be hallucinations, delusions, or disorganized speech for at least 1 month. The other core symptoms are gross disorganization and diminished emotional expression. The inclusion criteria include: (1) female; (2) Han Chinese; (3) age from 18 to 45 years; (4) cumulative antipsychotics treatment < 2 weeks; (5) illness duration < 5 years; (6) no substance abuse including alcohol and smoking. A detailed questionnaire including sex, age, education level, smoke status and nationality was created to collect the demographic information. All patients underwent physical examination and laboratorial tests and were inquired for medical history to exclude serious physical conditions, such as diabetes, cardiovascular disease, cerebrovascular disease, cancer and pregnancy.

The procedures of this study were approved by the Institutional Review Board. Written informed consents were obtained by all patients.

2.2 Study procedures

This was a longitudinal observational study with 1-month follow-up. DNFE patients had been treated with a flexible-dose of OLA. The dose range of OLA is from 10 to 30 mg per day according to the patient's individual response to OLA as determined by the psychiatrist in charge. All patients were hospitalized during the study. Each patient was monitored by the nurses for the adherence to OLA treatment.

2.3 Clinical assessment

The severity of clinical symptoms was evaluated using the Positive and Negative Syndrome Scales (PANSS) by experienced psychiatrists (Kay et al., 1987). PANSS refers to two symptoms of SZ: positive symptoms, which refer to an excess or distortion of normal functioning (e.g., hallucinations and delusions), and negative symptoms, which represent a reduction or loss of normal functioning. Of the 30 items included in the PANSS, 7 constitute a positive scale, 7 is a negative scale, and the remaining 16 is a general psychopathology scale. To ensure consistency and reliability of the evaluation, three psychiatrists attended a training session for the use of PANSS scale following start of the study. The intraclass correlation coefficient (ICC) was computed to examine the test-retest reliability using SPSS 20.0. After training, a correlation coefficient > 0.8 was maintained for the PANSS total score by repeated assessments during the study. At baseline and at 4-week follow-up, the symptom was assessed by PANSS scale. The percentage PANSS total score reduction was calculated by using the formula $(T_b - T_a)/T_a \times 100\%$. Ta is the total score at baseline and T_b is the total score at 1-month follow-up. If the percentage total score reduction was more than 30%, we defined the patients as responders.

2.4 Extraction of metabolites and metabolomics data processing

At 7.00 A.M., fasting venous blood samples were collected for each patient at baseline and at 1-month follow-up. Plasma was separated and 200 µl of sample was divided into two parts for the extraction of water-soluble (75% methanol) and lipid-soluble (100% methanol) metabolites. The lipid-soluble and water-soluble supernatants were mixed (1:1), and 0.6 ml of the mixture was dried and re dissolved in 80 µl of 50% methanol and filtered through a 0.1-mm membrane. As described in our previous study, an untargeted metabolomics was used to profile the differential metabolites in patients. Principal component analyses (PCA) were performed using SIMCA-P 13 software (Umetrics). A PLS-DA (partial least squares discriminate analysis) model was used for the calculation of variable importance in projection (VIP) values. Statistical analyses of the quantitative data were performed using SPSS and SAS. Compounds with VIP > 1 and p < 0.05 were picked for further identification. Annotated compounds were identified by searching the accurate mass of the molecular ions and the fragment ions against compound databases. Carnitine was classified in HMDB or Lipidmap databases.

2.5 Statistical analysis

Since majority of carnitines were not normally distributed in patients, a log transformation was used in the analysis. All the following analyses were carried out using SPSS 20.0. Comparisons of the demographic and clinical data between pre and post treatment were conducted by analysis of variance (ANOVA). Pearson correlation was used to analyze the association between the changes in the levels of carnitine and the percentage of PANSS reduction and body weight. The changes in the metabolites, body weight and PANSS score were calculated by the values at follow-up subtract the values at baseline. Further linear regression analysis was conducted to identify the related factors to the changes in the psychotic symptoms and body weight, with the rate of reduction of PANSS total or weight gain as the dependent variables and with demographic data and the changes in carnitine levels as the independent variables. We considered p value < 0.05 as significant.

3 Results

3.1 Clinical symptoms before and after 4-week treatment

Demographic and clinical characteristics of all patients are summarized in Table 1. The average age was 27.4 ± 7.6 years, their mean education years was 9.1 ± 3.5, the mean age of onset was 26.4 ± 8.8 years and the average body mass index (BMI) at baseline was 21.0 ± 3.6 (Table 1).

After 4 weeks of OLA treatment, DNFE patients showed significant improvement in the symptoms, including positive subscore (25.0 ± 6.0 vs 16.4 ± 5.2), general psychopathology subscore (39.7 ± 7.5 vs 32.0 ± 6.0) and total score (81.8 ± 13.9 vs 63.9 ± 13.8) (all $p_{Bonferroni} < 0.05$). However, negative symptoms were not significantly improved after OLA treatment ($p > 0.05$).

3.2 Metabolomics analysis at baseline and after treatment

As described in our previous study, after screening both with $p < 0.05$ and $VIP > 1$, 175 differential compounds were identified (Liu et al., 2021b). The score plot was shown in Supplementary Fig. 1. Among these compounds, we found five types of carnitines, including linoelaidyl carnitine (HMDB06461, m/z = 424.340465), 2-Octenoylcarnitine (HMDB13324, m/z = 286.20031), Butyrylcarnitine (HMDB02013, m/z = 232.15365), 11Z-Octadecenylcarnitine (HMDB13338, m/z = 426.35648) and 9-Decenoylcarnitine

(HMDB13205, m/z = 314.23135). The chemical structure of carnitine and the presented derivatives is shown in Supplementary Fig. 2. Of the five types of carnitines, linoelaidyl carnitine is a long-chain carnitines with a fatty ester lipid molecule. Thus, it is very hydrophobic, practically insoluble (in water), and relatively neutral.

After treatment, levels of 2-Octenoylcarnitine decreased and levels of linoelaidyl carnitine, 9-Decenoylcarnitine and 11Z-Octadecenylcarnitine increased significantly ($p < 0.05$). Butyrylcarnitine levels were not different between baseline and follow-up ($p > 0.05$).

3.3 Association between baseline carnitine levels and the changes in PANSS total score and body weight

Correlation analysis revealed that baseline linoelaidyl carnitine levels were correlated with the percentage of positive symptoms reduction ($r = 0.39$, $p = 0.05$) (Fig. 1). Regression analysis with age, age of onset, education years, and baseline linoelaidyl carnitine level as independent variables showed that baseline linoelaidyl carnitine level was significantly related to the reduction of positive symptoms after treatment (standardized coefficient $\beta = 0.44$, $t = 2.1$, $p = 0.046$), which accounted for the variance of 20.3%. Baseline linoelaidyl carnitine levels were not correlated with PANSS total score or subscores at baseline and at 1-month follow-up (all $p > 0.05$). However, no association was found between changes in carnitine level and weight gain or BMI gain (all $p > 0.05$).

3.4 Baseline metabolites and response to treatment

We identified 10 responders and 15 non-responders (Table 2). There is a significant difference in baseline linoelaidyl carnitine levels between non-responders ($n = 15$) and responders ($n = 10$) (4.9 ± 0.6 vs 5.8 ± 1.3, $F = 6.09$, $p = 0.021$). Further logistic regression analysis was conducted with percentage of total score reduction as dependent variable and with age, education years and age of onset as the independent variables. We found that the baseline linoelaidyl carnitine level was a predictor for 4-week treatment with olanzapine ($\beta = 1.19$, Wald $X^2 = 4.58$, $p = 0.033$, odds ratio = 3.28).

4 Discussion

This study has three main findings. (1) We found that the levels of 2-Octenoylcarnitine, 9-Decenoylcarnitine and 11Z-Octadecenylcarnitine were significantly changed after treatment with OLA for 1 month. (2) Linoelaidyl carnitine

Table 1 Demographic and clinical data of the patients

	First-episode n=25	After 1 month n=25	p value[#]
Linoelaidyl carnitine	5.2 ± 1.0	5.7 ± 0.2	0.014
2-Octenoylcarnitine	6.2 ± 0.3	4.8 ± 0.7	< 0.001
Butyrylcarnitine	6.1 ± 0.4	6.1 ± 0.3	0.534
11Z-Octadecenylcarnitine	5.1 ± 1.3	6.3 ± 0.3	0.003
9-Decenoylcarnitine	4.5 ± 0.3	5.3 ± 1.4	0.019
Age (years)	27.4 ± 7.6		
Education (years)	9.1 ± 3.5		
Onset age (years)	26.4 ± 8.8		
Clinical symptoms (PANSS)			
P	25.0 ± 6.0	16.4 ± 5.2	< 0.001
N	17.1 ± 4.7	15.6 ± 4.3	0.23
G	39.7 ± 7.5	32.0 ± 6.0	< 0.001
Total score	81.8 ± 13.9	63.9 ± 13.8	< 0.001

PANSS the positive and negative syndrome scale; *P* positive symptoms; *N* negative symptoms; *G* the general psychopathology

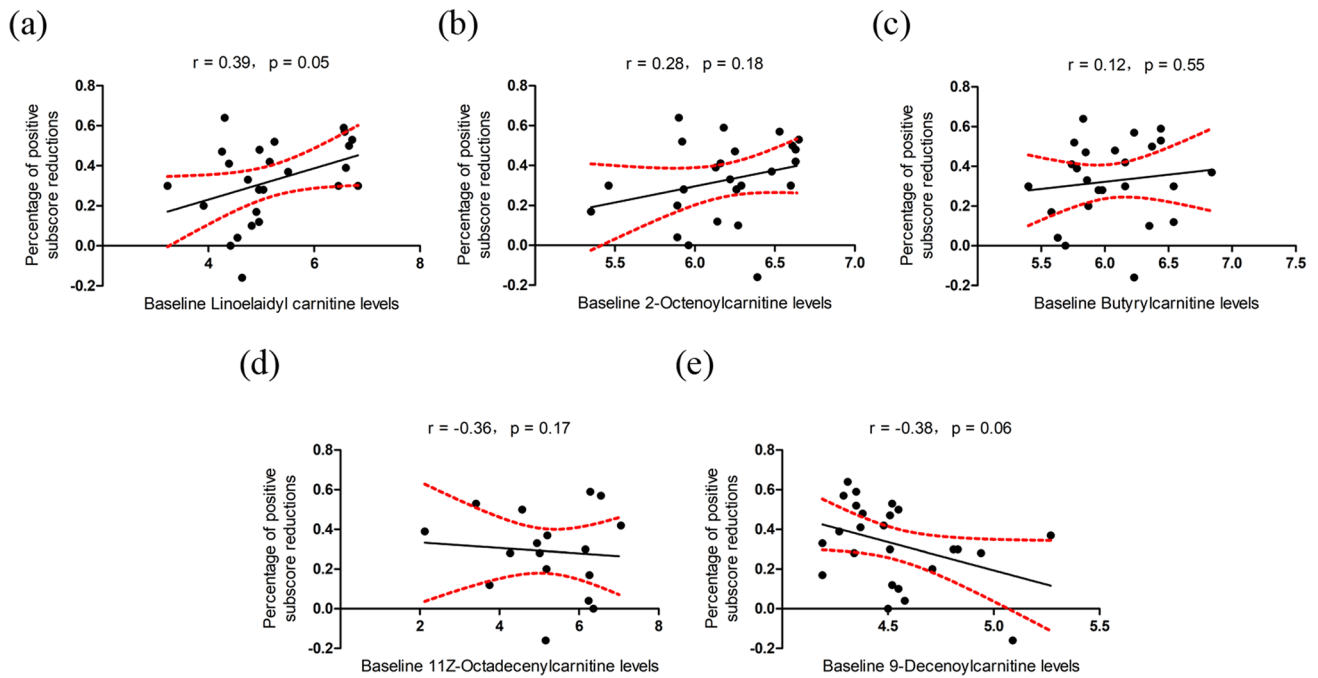[#]Comparison of psychotic symptoms between baseline and follow-up

Fig. 1 Associations between baseline carnitine levels and symptom improvements in patients with schizophrenia (SZ). **a** There was a positive association between baseline linoelaidyl carnitine levels and the percentage of positive symptoms reduction in patients with SZ (r = 0.39, p = 0.05). **b–e** There were no significant associations between baseline levels of 2-Octenoylcarnitine, Butyrylcarnitine, 11Z-Octadecenylcarnitine and 9-Decenoylcarnitine and symptom improvements in patients with SZ

Table 2 Comparisons of clinical symptoms between responders and nonresponders

	Nonresponders n = 15	Responders n = 10	p value[#]
P	5.9 ± 4.9	12.8 ± 4.0	0.001
N	− 1.1 ± 4.1	5.4 ± 6.2	0.004
G	2.5 ± 7.3	15.7 ± 5.3	< 0.001
Total score	7.2 ± 10.2	33.9 ± 9.6	< 0.001
P reduction rate	0.2 ± 0.2	0.5 ± 0.1	< 0.001
N reduction rate	− 0.1 ± 0.3	0.2 ± 0.3	0.012
G reduction rate	0.05 ± 0.2	0.4 ± 0.1	< 0.001
Total score reduction rate	0.1 ± 0.1	0.4 ± 0.1	< 0.001

P positive symptoms; *N* negative symptoms; *G* the general psychopathology

level correlated with the percentage of positive symptoms reduction after OLA monotherapy. (3) Baseline linoelaidyl carnitine was a predictive factor for the therapeutic response to OLA monotherapy.

It is the first study to simultaneously investigate the relationship of several baseline carnitine derivatives with the reduction of clinical symptoms after OLA monotherapy for 1 month in DNFE patients with SZ. Previous studies have shown that antipsychotic drugs can significantly increase the levels of acyl-carnitines (Kriisa et al., 2017; Leppik et al.,

2020; Molina et al., 2021; Yi et al., 2021). In particular, in animal studies, OLA has been reported to increase the carnitines levels (Albaugh et al., 2012; Jiang et al., 2019). Our findings were also consistent with previous studies in SZ, suggesting that carnitine pathway was regulated after treatment (Kriisa et al., 2017). It should be noted that the study from Kriisa et al. used the targeted metabolomics to identify the differential carnitines in SZ, while in our study, we used the untargeted metabolomics. Therefore, only five carnitines were identified in our study. Kriisa et al. identified 39 carnitines in his study and found antipsychotic drug had an impact on 17 metabolites in DNFE patients. Interestingly, they also found that none of these carnitines were different between DNFE patients at follow-up and healthy controls, indicating that the alteration of carnitine levels returned to control levels after treatment. Taken together, our study provides further evidence that antipsychotic treatments can regulate the levels of carnitine and the derivatives.

SZ has been found to be associated with several abnormal metabolic pathways, including mitochondrial dysfunction, aberrant gut-metabolome-immune network, oxidative stress-related cell damage, changes in embryonic neurogenesis caused by molecular disturbances during development, abnormalities in serotonergic, glutamatergic and dopaminergic signaling, and abnormal sugar metabolism and insulin resistance (Bramon et al., 2008; Campeau et al., 2021; Do

et al., 2009; Fan et al., 2022; Geyer & Vollenweider, 2008; Henkel et al., 2022; Lago et al., 2022; Liu et al., 2021a, 2021b; Moore et al., 1999; Yao & Keshavan, 2011; Zhang et al., 2010). Acute and chronic treatment with OLA can alter respiratory chain complexes activity in the rat brain, suggesting that metabolism energy was involved in the treatment with OLA (Agostinho et al., 2011). Carnitine and its derivatives are related to the fatty acid beta-oxidation, metabolic pathways in energy metabolism of mitochondrion, cellular homeostasis pathways, antioxidant, and anti-inflammatory response. Therefore, we speculated that the observed alterations of 2-Octenoylcarnitine, 9-Decenoylcarnitine and 11Z-Octadecenylcarnitine might imply that the changes of these related pathways exist after treatment with OLA in patients with SZ. SZ is a chronic brain disorder and it is known that the brain is composed mainly of fatty acids that need to be incorporated into structural lipids (Nałecz & Nałecz, 1996). Recent studies support that the pathological process of SZ is linked to abnormal lipid metabolism and related pathways in both the central and peripheral nervous systems (Misiak et al., 2017; Prabakaran et al., 2004; Taha et al., 2013), which is intimately associated with carnitine. Interestingly, studies have reported that carnitine deprivation can lead to a wide variety of disorders that affect brain functions (Kimura & Amemiya, 1990; Jones et al., 2010). However, it should be with more cautions in interpreting our findings, considering that any drug or any compound may lead to the modulation of the carnitine derivatives.

We also found that the baseline level of linoelaidyl carnitine was associated with better response to treatment, suggesting a close relationship between carnitine derivatives and OLA treatment in the early treatment stage of SZ. Moreover, our findings demonstrate that the higher levels in linoelaidyl carnitine at baseline, the better response to OLA monotherapy in DNFE patients. Linoelaidyl carnitine (acylcarnitine C18:2) belongs to a long-chain acylcarnitine, one of the derivatives of carnitine metabolism pathway. Many diseases caused by abnormalities in energy production and in intermediary metabolism are characterized by unusual acylcarnitines (Pierre et al., 2007). Mitochondria are the fundamental cellular compartment in lipid metabolism, particularly fatty acid oxidation contributed by acylcarnitine. Studies on SZ show that antipsychotic treatments affect the composition of brain lipids (such as polyunsaturated fatty acids and phospholipids) and lipid homeostasis (Kaddurah-Daouk et al., 2007; McEvoy et al., 2013; Polymeropoulos et al., 2009). The finding of altered acylcarnitines in this study may indirectly indicate changes of mitochondrial homeostasis, considering that the accumulation of acylcarnitine may mean mitochondrial dysfunctions. Particularly, previous studies found that measurement of the qualitative pattern of acylcarnitines can be of diagnostic and therapeutic prediction significance (Millington & Stevens, 2011).

Consistent to our findings, aylcarnitines have been reported to be involved in the pathogenesis of SZ and treatment response related to antipsychotics (Kriisa et al., 2017).

However, due to the general features of SZ is not well understood, we do not give an exact explanation for this relationship. Based on previous findings, we speculated several possible reasons for the relationship. One possible explanation is that the shift in oxidative stress and inflammatory status caused by antipsychotics in DNFE may be correlated with the modifications in linoelaidyl carnitine. Linoelaidyl carnitine may reflect the severity of oxidative stress or inflammatory status (Kriisa et al., 2017). Antipsychotic drugs have been reported to directly reduce a low-grade inflammation and oxidative stress status in patients (Haring et al., 2015; Kriisa et al., 2016; Miller et al., 2011; Upthegrove et al., 2014). Specifically, the levels of oxidative stress and inflammatory markers may be altered in the different stages of the illness after treatment with antipsychotics. Previous studies provide ample evidence for the link of alteration of oxidative stress and inflammatory cytokines accompanied by the improvement of clinical symptoms after treatment with antipsychotics in SZ (Li et al., 2021). Another possible explanation is related to the pre-diabetes and glucose dysregulation in DNFE patients with SZ. A previous meta-analysis in SZ concluded that glucose abnormality exists in the early stage of this disorder and is intrinsic to SZ (Pillinger et al., 2017). Mitochondria dysfunction is implicated in the glucose dysregulation and diabetes. The role of acylcarnitines in regulating intracellular insulin signaling has been highlighted in previous studies showing that acylcarnitine induces a decrease in Akt phosphorylation in vivo (Aguer et al., 2015; Blackburn et al., 2020). Recent evidence indicates that carnitine functions in bioenergetics and β-oxidation in mitochondrion. These mechanisms play a critical role in SZ pathogenesis. Moreover, carnitine is involved in many metabolic pathways and acylcarnitine plays an essential role in β-oxidation, oxidative stress status, and neurotransmission. Thus, it is reasonable to conclude that patients with higher baseline linoelaidyl carnitine may have better mitochondria function and display some signs of recovery from the disease after treatment. Together, acylcarnitine has an impact on lipid metabolism, mitochondria functions, insulin sensitivity, inflammatory response and oxidative stress, which provide the underlying mechanism for its involvement in the improvement of positive symptoms.

Our study has several limitations. Firstly, our study includes the relatively small sample size (n = 25) for metabolite analysis using untargeted metabolomic profiling approach. Moreover, this study lacks the statistical power for association and logistic analyses. Secondly, our study volunteers are only female patients in the current study. This study design can help to minimize the sex difference in recruited patients, however, our findings restrict the generalization

to male patients. Thirdly, there may be measurement error in the measurement of metabolites, since each patient only were tested once without repetition. Further study should recruit several independent cohorts, including training and test samples.

In summary, we found that several types of carnitine level were significantly altered after OLA treatment for 4 weeks. Moreover, baseline linoelaidyl carnitine level was related to the percentage of positive symptoms reduction and the response to OLA monotherapy. Our findings provide preliminary evidence for the abnormal carnitines in the treatment of SZ and maybe a potentially predictive biomarker linking antipsychotics exposure and response to antipsychotics, which is warranted to be further investigated. However, because we only recruited female patients, caution is warranted in interpreting our findings.

Data availability Due to confidentiality, we are not able to share the data. Access to the data must be obtained through a formal application from the corresponding author.

Declarations

Conflict of interest All authors declare that they have no conflict of interest.

Informed consent The subjects or their parents gave written informed consent to participate in the study and for publication of results.

References

Agarwal, A., & Said, T. M. (2004). Carnitines and male infertility. *Reproductive Biomedicine Online, 8*(4), 376–384.

Agostinho, F. R., Réus, G. Z., Stringari, R. B., Ribeiro, K. F., Ferreira, G. K., Jeremias, I. C., Scaini, G., Rezin, G. T., Streck, E. L., & Quevedo, J. (2011). Olanzapine plus fluoxetine treatment alters mitochondrial respiratory chain activity in the rat brain. *Acta Neuropsychiatrica, 23*(6), 282–291.

Aguer, C., McCoin, C. S., Knotts, T. A., Thrush, A. B., Ono-Moore, K., McPherson, R., Dent, R., Hwang, D. H., Adams, S. H., & Harper, M. E. (2015). Acylcarnitines: Potential implications for skeletal muscle insulin resistance. *The FASEB Journal, 29*(1), 336–345.

Albaugh, V. L., Vary, T. C., Ilkayeva, O., Wenner, B. R., Maresca, K. P., Joyal, J. L., Breazeale, S., Elich, T. D., Lang, C. H., & Lynch, C. J. (2012). Atypical antipsychotics rapidly and inappropriately switch peripheral fuel utilization to lipids, impairing metabolic flexibility in rodents. *Schizophrenia Bulletin, 38*(1), 153–166.

Aleksic, B., & Ozaki, N. (2017). Schizophrenia polygenic risk score and prepubertal developmental impairments. *The Lancet Psychiatry, 4*(1), 7–8.

Blackburn, M. L., Ono-Moore, K. D., Sobhi, H. F., & Adams, S. H. (2020). Carnitine palmitoyltransferase 2 knockout potentiates palmitate-induced insulin resistance in C(2)C(12) myotubes. *American Journal of Physiology-Endocrinology and Metabolism, 319*(2), E265-e275.

Bramon, E., Dempster, E., Frangou, S., Shaikh, M., Walshe, M., Filbey, F. M., McDonald, C., Sham, P., Collier, D. A., & Murray, R. (2008). Neuregulin-1 and the P300 waveform—A preliminary association study using a psychosis endophenotype. *Schizophrenia Research, 103*(1–3), 178–185.

Calvani, M., Carta, A., Caruso, G., Benedetti, N., & Iannuccelli, M. (1992). Action of acetyl-ʟ-carnitine in neurodegeneration and Alzheimer's disease. *nnals of the New York Academy of Sciences, 663*, 483–486.

Campeau, A., Mills, R. H., Stevens, T., Rossitto, L. A., Meehan, M., Dorrestein, P., Daly, R., Nguyen, T. T., Gonzalez, D. J., Jeste, D. V., & Hook, V. (2021). Multi-omics of human plasma reveals molecular features of dysregulated inflammation and accelerated aging in schizophrenia. *Molecular Psychiatry, 27*(2), 1217–25.

Cao, B., Wang, D., Pan, Z., Brietzke, E., McIntyre, R. S., Musial, N., Mansur, R. B., Subramanieapillai, M., Zeng, J., Huang, N., & Wang, J. (2019). Characterizing acyl-carnitine biosignatures for schizophrenia: A longitudinal pre- and post-treatment study. *Translational Psychiatry, 9*(1), 19.

Cavedon, C. T., Bourdoux, P., Mertens, K., Van Thi, H. V., Herremans, N., de Laet, C., & Goyens, P. (2005). Age-related variations in acylcarnitine and free carnitine concentrations measured by tandem mass spectrometry. *Clinical Chemistry, 51*(4), 745–752.

Chelkeba, L., Gidey, K., Mamo, A., Yohannes, B., Matso, T., & Melaku, T. (2017). Olanzapine for chemotherapy-induced nausea and vomiting: Systematic review and meta-analysis. *Pharmacy Practice (Granada), 15*(1), 877.

Chen, S., Wei, C., Gao, P., Kong, H., Jia, Z., Hu, C., Dai, W., Wu, Y., & Xu, G. (2014). Effect of *Allium macrostemon* on a rat model of depression studied by using plasma lipid and acylcarnitine profiles from liquid chromatography/mass spectrometry. *Journal of Pharmaceutical and Biomedical Analysis, 89*, 122–129.

Correll, C. U., Kim, E., Sliwa, J. K., Hamm, W., Gopal, S., Mathews, M., Venkatasubramanian, R., & Saklad, S. R. (2021). Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: An overview. *CNS Drugs, 35*(1), 39–59.

Davis, K. L., Kahn, R. S., Ko, G., & Davidson, M. (1991). Dopamine in schizophrenia: A review and reconceptualization. *American Journal of Psychiatry, 148*(11), 1474–1486.

Dawidowski, B., Górniak, A., Podwalski, P., Lebiecka, Z., Misiak, B., & Samochowiec, J. (2021). The role of cytokines in the pathogenesis of schizophrenia. *Journal of Clinical Medicine, 10*(17), 3849.

Do, K. Q., Cabungcal, J. H., Frank, A., Steullet, P., & Cuenod, M. (2009). Redox dysregulation, neurodevelopment, and schizophrenia. *Current Opinion in Neurobiology, 19*(2), 220–230.

Elkis, H., & Buckley, P. F. (2016). Treatment-resistant schizophrenia. *Psychiatric Clinics of North America, 39*(2), 239–265.

Fan, Y., Gao, Y., Ma, Q., Yang, Z., Zhao, B., He, X., Yang, J., Yan, B., Gao, F., Qian, L., & Wang, W. (2022). Multi-omics analysis reveals aberrant gut-metabolome-immune network in schizophrenia. *Frontiers in Immunology, 13*, 812293.

Flanagan, J. L., Simmons, P. A., Vehige, J., Willcox, M. D., & Garrett, Q. (2010). Role of carnitine in disease. *Nutrition & Metabolism (London)*. https://doi.org/10.1186/1743-7075-7-30

Geyer, M. A., & Vollenweider, F. X. (2008). Serotonin research: Contributions to understanding psychoses. *Trends in Pharmacological Sciences, 29*(9), 445–453.

Haring, L., Koido, K., Vasar, V., Leping, V., Zilmer, K., Zilmer, M., & Vasar, E. (2015). Antipsychotic treatment reduces psychotic symptoms and markers of low-grade inflammation in first episode psychosis patients, but increases their body mass index. *Schizophrenia Research, 169*(1–3), 22–29.

Henkel, N. D., Wu, X., O'Donovan, S. M., Devine, E. A., Jiron, J. M., Rowland, L. M., Sarnyai, Z., Ramsey, A. J., Wen, Z., Hahn, M. K., & McCullumsmith, R. E. (2022). Schizophrenia: A disorder of broken brain bioenergetics. *Molecular Psychiatry, 27*(5), 2393–404.

Jiang, T., Zhang, Y., Bai, M., Li, P., Wang, W., Chen, M., Ma, Z., Zeng, S., Zhou, H., & Jiang, H. (2019). Up-regulation of hepatic fatty acid transporters and inhibition/down-regulation of hepatic OCTN2 contribute to olanzapine-induced liver steatosis. *Toxicology Letters, 316*, 183–193.

Jones, L. L., McDonald, D. A., & Borum, P. R. (2010). Acylcarnitines: Role in brain. *Progress in Lipid Research, 49*(1), 61–75.

Kaddurah-Daouk, R., McEvoy, J., Baillie, R. A., Lee, D., Yao, J. K., Doraiswamy, P. M., & Krishnan, K. R. (2007). Metabolomic mapping of atypical antipsychotic effects in schizophrenia. *Molecular Psychiatry, 12*(10), 934–945.

Kaddurah-Daouk, R., & Weinshilboum, R. M. (2014). Pharmacometabolomics: Implications for clinical pharmacology and systems pharmacology. *Clinical Pharmacology and Therapeutics, 95*(2), 154–167.

Kapur, S. (2003). Psychosis as a state of aberrant salience: A framework linking biology, phenomenology, and pharmacology in schizophrenia. *American Journal of Psychiatry, 160*(1), 13–23.

Kay, S. R., Fiszbein, A., & Opler, L. A. (1987). The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophrenia Bulletin, 13*(2), 261–276.

Kępka, A., Ochocińska, A., Chojnowska, S., Borzym-Kluczyk, M., Skorupa, E., Knaś, M., & Waszkiewicz, N. (2021). Potential role of ʟ-carnitine in autism spectrum disorder. *Journal of Clinical Medicine, 10*(6), 1202.

Kimura, S., & Amemiya, F. (1990). Brain and liver pathology in a patient with carnitine deficiency. *Brain & Development, 12*(4), 436–439.

Kler, R. S., Jackson, S., Bartlett, K., Bindoff, L. A., Eaton, S., Pourfarzam, M., Frerman, F. E., Goodman, S. I., Watmough, N. J., & Turnbull, D. M. (1991). Quantitation of acyl-CoA and acyl-carnitine esters accumulated during abnormal mitochondrial fatty acid oxidation. *Journal of Biological Chemistry, 266*(34), 22932–22938.

Kriisa, K., Haring, L., Vasar, E., Koido, K., Janno, S., Vasar, V., Zilmer, K., & Zilmer, M. (2016). Antipsychotic treatment reduces indices of oxidative stress in first-episode psychosis patients. *Oxidative Medicine and Cellular Longevity*. https://doi.org/10.1155/2016/9616593

Kriisa, K., Leppik, L., Balõtšev, R., Ottas, A., Soomets, U., Koido, K., Volke, V., Innos, J., Haring, L., Vasar, E., & Zilmer, M. (2017).

Profiling of acylcarnitines in first episode psychosis before and after antipsychotic treatment. *Journal of Proteome Research, 16*(10), 3558–3566.

Lago, S. G., Tomasik, J., van Rees, G. F., Rustogi, N., Vázquez-Bourgon, J., Papiol, S., Suarez-Pinilla, P., Crespo-Facorro, B., & Bahn, S. (2022). Peripheral lymphocyte signaling pathway deficiencies predict treatment response in first-onset drug-naïve schizophrenia. *Brain, Behavior, and Immunity, 103*, 37–49.

Leppik, L., Parksepp, M., Janno, S., Koido, K., Haring, L., Vasar, E., & Zilmer, M. (2020). Profiling of lipidomics before and after antipsychotic treatment in first-episode psychosis. *European Archives of Psychiatry and Clinical Neuroscience, 270*(1), 59–70.

Li, X. R., Xiu, M. H., Guan, X. N., Wang, Y. C., Wang, J., Leung, E., & Zhang, X. Y. (2021). Altered antioxidant defenses in drug-naive first episode patients with schizophrenia are associated with poor treatment response to risperidone: 12-Week results from a prospective longitudinal study. *Neurotherapeutics, 18*(2), 1316–24.

Liu, H., Liu, H., Jiang, S., Su, L., Lu, Y., Chen, Z., Li, X., Wang, X., Xiu, M., & Zhang, X. (2021a). Sex-specific association between antioxidant defense system and therapeutic response to risperidone in schizophrenia: A prospective longitudinal study. *Current Neuropharmacology*. https://doi.org/10.2174/1570159X1966621111123918

Liu, J. H., Chen, N., Guo, Y. H., Guan, X. N., Wang, J., Wang, D., & Xiu, M. H. (2021b). Metabolomics-based understanding of the olanzapine-induced weight gain in female first-episode drug-naïve patients with schizophrenia. *Journal of Psychiatric Research, 140*, 409–415.

Lopez, A. D., & Murray, C. C. (1998). The global burden of disease, 1990–2020. *Nature Medicine, 4*(11), 1241–1243.

McEvoy, J., Baillie, R. A., Zhu, H., Buckley, P., Keshavan, M. S., Nasrallah, H. A., Dougherty, G. G., Yao, J. K., & Kaddurah-Daouk, R. (2013). Lipidomics reveals early metabolic changes in subjects with schizophrenia: Effects of atypical antipsychotics. *PLoS ONE, 8*(7), e68717.

Meltzer, H. Y., & Stahl, S. M. (1976). The dopamine hypothesis of schizophrenia: A review. *Schizophrenia Bulletin, 2*(1), 19–76.

Messias, E. L., Chen, C. Y., & Eaton, W. W. (2007). Epidemiology of schizophrenia: Review of findings and myths. *Psychiatric Clinics of North America, 30*(3), 323–338.

Miller, B. J., Buckley, P., Seabolt, W., Mellor, A., & Kirkpatrick, B. (2011). Meta-analysis of cytokine alterations in schizophrenia: Clinical status and antipsychotic effects. *Biological Psychiatry, 70*(7), 663–671.

Millington, D. S., & Stevens, R. D. (2011). Acylcarnitines: Analysis in plasma and whole blood using tandem mass spectrometry. *Methods in Molecular Biology, 708*, 55–72.

Misiak, B., Stańczykiewicz, B., Łaczmański, Ł, & Frydecka, D. (2017). Lipid profile disturbances in antipsychotic-naive patients with first-episode non-affective psychosis: A systematic review and meta-analysis. *Schizophrenia Research, 190*, 18–27.

Moghaddas, A., & Dashti-Khavidaki, S. (2016). Potential protective effects of l-carnitine against neuromuscular ischemia–reperfusion injury: From experimental data to potential clinical applications. *Clinical Nutrition, 35*(4), 783–790.

Molina, J. D., Avila, S., Rubio, G., & López-Muñoz, F. (2021). Metabolomic connections between schizophrenia, antipsychotic drugs and metabolic syndrome: A variety of players. *Current Pharmaceutical Design, 27*(39), 4049–61.

Moore, H., West, A. R., & Grace, A. A. (1999). The regulation of forebrain dopamine transmission: Relevance to the pathophysiology and psychopathology of schizophrenia. *Biological Psychiatry, 46*(1), 40–55.

Mould, A. W., Hall, N. A., Milosevic, I., & Tunbridge, E. M. (2021). Targeting synaptic plasticity in schizophrenia: Insights from genomic studies. *Trends in Molecular Medicine, 27*(11), 1022–32.

Nałecz, K. A., Miecz, D., Berezowski, V., & Cecchelli, R. (2004). Carnitine: Transport and physiological functions in the brain. *Molecular Aspects of Medicine, 25*(5–6), 551–567.

Nałecz, K. A., & Nałecz, M. J. (1996). Carnitine—A known compound, a novel function in neural cells. *Acta Neurobiologiae Experimentalis (Wars), 56*(2), 597–609.

Noland, R. C., Koves, T. R., Seiler, S. E., Lum, H., Lust, R. M., Ilkayeva, O., Stevens, R. D., Hegardt, F. G., & Muoio, D. M. (2009). Carnitine insufficiency caused by aging and overnutrition compromises mitochondrial performance and metabolic control. *Journal of Biological Chemistry, 284*(34), 22840–22852.

Owen, M. J., Sawa, A., & Mortensen, P. B. (2016). Schizophrenia. *The Lancet, 388*(10039), 86–97.

Park, H. J., Choi, I., & Leem, K. H. (2021). Decreased brain pH and pathophysiology in schizophrenia. *International Journal of Molecular Sciences, 22*(16), 8358.

Pierre, G., Macdonald, A., Gray, G., Hendriksz, C., Preece, M. A., & Chakrapani, A. (2007). Prospective treatment in carnitine-acylcarnitine translocase deficiency. *Journal of Inherited Metabolic Disease, 30*(5), 815.

Pillinger, T., Beck, K., Gobjila, C., Donocik, J. G., Jauhar, S., & Howes, O. D. (2017). Impaired glucose homeostasis in first-episode schizophrenia: A systematic review and meta-analysis. *JAMA Psychiatry, 74*(3), 261–269.

Polymeropoulos, M. H., Licamele, L., Volpi, S., Mack, K., Mitkus, S. N., Carstea, E. D., Getoor, L., Thompson, A., & Lavedan, C. (2009). Common effect of antipsychotics on the biosynthesis and regulation of fatty acids and cholesterol supports a key role of lipid homeostasis in schizophrenia. *Schizophrenia Research, 108*(1–3), 134–142.

Prabakaran, S., Swatton, J. E., Ryan, M. M., Huffaker, S. J., Huang, J. T., Griffin, J. L., Wayland, M., Freeman, T., Dudbridge, F., Lilley, K. S., & Karp, N. A. (2004). Mitochondrial dysfunction in schizophrenia: Evidence for compromised brain metabolism and oxidative stress. *Molecular Psychiatry, 9*(7), 684–697.

Rahimian, R., Wakid, M., O'Leary, L. A., & Mechawar, N. (2021). The emerging tale of microglia in psychiatric disorders. *Neuroscience & Biobehavioral Reviews, 131*, 1–29.

Rajasekaran, A., Venkatasubramanian, G., Berk, M., & Debnath, M. (2015). Mitochondrial dysfunction in schizophrenia: Pathways, mechanisms and implications. *Neuroscience & Biobehavioral Reviews, 48*, 10–21.

Ribas, G. S., Vargas, C. R., & Wajner, M. (2014). L-Carnitine supplementation as a potential antioxidant therapy for inherited neurometabolic disorders. *Gene, 533*(2), 469–476.

Rinaldo, P., Cowan, T. M., & Matern, D. (2008). Acylcarnitine profile analysis. *Genetics in Medicine, 10*(2), 151–156.

Siliprandi, N., Di Lisa, F., & Menabó, R. (1990). Clinical use of carnitine. Past, present and future. *Advances in Experimental Medicine and Biology, 272*, 175–181.

Spagnoli, A., Lucca, U., Menasce, G., Bandera, L., Cizza, G., Forloni, G., Tettamanti, M., Frattura, L., Tiraboschi, P., Comelli, M., & Senin, U. (1991). Long-term acetyl-L-carnitine treatment in Alzheimer's disease. *Neurology, 41*(11), 1726–1732.

Taha, A. Y., Cheon, Y., Ma, K., Rapoport, S. I., & Rao, J. S. (2013). Altered fatty acid concentrations in prefrontal cortex of schizophrenic patients. *Journal of Psychiatric Research, 47*(5), 636–643.

Takahashi, Y., & Ogushi, T. (1953). On biochemical studies of schizophrenia. I. An enzymological study on brain tissue and serum of schizophrenic patients; choline esterase. *Folia Psychiatrica et Neurologica Japonica, 6*(4), 244–261.

Tek, C., Kucukgoncu, S., Guloksuz, S., Woods, S. W., Srihari, V. H., & Annamalai, A. (2016). Antipsychotic-induced weight gain in first-episode psychosis patients: A meta-analysis of differential effects of antipsychotic medications. *Early Intervention in Psychiatry, 10*(3), 193–202.

Tollens, F., Gass, N., Becker, R., Schwarz, A. J., Risterucci, C., Künnecke, B., Lebhardt, P., Reinwald, J., Sack, M., Weber-Fahr, W., & Meyer-Lindenberg, A. (2018). The affinity of antipsychotic drugs to dopamine and serotonin 5-HT(2) receptors determines their effects on prefrontal-striatal functional connectivity. *European Neuropsychopharmacology, 28*(9), 1035–1046.

Traina, G. (2016). The neurobiology of acetyl-L-carnitine. *Frontiers in Bioscience (Landmark Ed), 21*, 1314–1329.

Upthegrove, R., & Khandaker, G. M. (2019). Cytokines, oxidative stress and cellular markers of inflammation in schizophrenia. *Current Topics in Behavioral Neurosciences*. https://doi.org/10.1007/7854_2018_88

Upthegrove, R., Manzanares-Teson, N., & Barnes, N. M. (2014). Cytokine function in medication-naive first episode psychosis: A systematic review and meta-analysis. *Schizophrenia Research, 155*(1–3), 101–108.

van Kesteren, C. F., Gremmels, H., de Witte, L. D., Hol, E. M., Van Gool, A. R., Falkai, P. G., Kahn, R. S., & Sommer, I. E. (2017). Immune involvement in the pathogenesis of schizophrenia: A meta-analysis on postmortem brain studies. *Translational Psychiatry, 7*(3), e1075.

van Mierlo, H. C., Schot, A., Boks, M. P. M., & de Witte, L. D. (2019). The association between schizophrenia and the immune system: Review of the evidence from unbiased 'omic-studies.' *Schizophrenia Research*. https://doi.org/10.1016/j.schres.2019.05.028

Vreken, P., van Lint, A. E., Bootsma, A. H., Overmars, H., Wanders, R. J., & van Gennip, A. H. (1999). Quantitative plasma acylcarnitine analysis using electrospray tandem mass spectrometry for the diagnosis of organic acidaemias and fatty acid oxidation defects. *Journal of Inherited Metabolic Disease, 22*(3), 302–306.

Wang, Z., Zhou, Z., Wei, X., Wang, M., Wang, B. O., Zhang, Y., He, X., Sun, Y., Wang, X., Sun, M., & Zhang, Y. (2017). Therapeutic potential of novel twin compounds containing tetramethylpyrazine and carnitine substructures in experimental ischemic stroke. *Oxidative Medicine and Cellular Longevity*. https://doi.org/10.1155/2017/7191856

Yao, J. K., & Keshavan, M. S. (2011). Antioxidants, redox signaling, and pathophysiology in schizophrenia: An integrative view. *Antioxidants & Redox Signaling, 15*(7), 2011–2035.

Yi, W., Sylvester, E., Lian, J., & Deng, C. (2021). Kidney plays an important role in ketogenesis induced by risperidone and voluntary exercise in juvenile female rats. *Psychiatry Research, 305*, 114196.

Young, P. A., Senkal, C. E., Suchanek, A. L., Grevengoed, T. J., Lin, D. D., Zhao, L., Crunk, A. E., Klett, E. L., Füllekrug, J., Obeid, L. M., & Coleman, R. A. (2018). Long-chain acyl-CoA synthetase 1 interacts with key proteins that activate and direct fatty acids into niche hepatic pathways. *Journal of Biological Chemistry, 293*(43), 16724–16740.

Zhang, M., Zhao, Z., He, L., & Wan, C. (2010). A meta-analysis of oxidative stress markers in schizophrenia. *Science China Life Sciences, 53*(1), 112–124.