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A systematic review of metabolite biomarkers of schizophrenia

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Abstract

Current diagnosis of schizophrenia relies exclusively on the potentially subjective interpretation of clinical symptoms and social functioning as more objective biological measurement and medical diagnostic tests are not presently available. The use of metabolomics in the discovery of disease biomarkers has grown in recent years. Metabolomic methods could aid in the discovery of diagnostic biomarkers of schizophrenia. This systematic review focuses on biofluid metabolites associated with schizophrenia. A systematic search of Web of Science and Ovid Medline databases was conducted and 63 studies investigating metabolite biomarkers of schizophrenia were included. A review of these studies revealed several potential metabolite signatures of schizophrenia including reduced levels of essential polyunsaturated fatty acids (EPUFAs), vitamin E and creatinine; and elevated levels of lipid peroxidation metabolites and glutamate. Further research is needed to validate these biomarkers and would benefit from large cohort studies and more homogeneous and well-defined subject groups.

1.0 Introduction

Schizophrenia is a debilitating mental disorder with lifetime prevalence rates of between 0.3 % and 0.7 % (American Psychiatric Association, 2013). It is characterised by positive symptoms including delusions, hallucinations, disorganised speech and catatonic behaviour; and negative symptoms such as avolition (lack of motivation) and emotional withdrawal (American Psychiatric Association, 2013). Symptoms usually appear in adolescence or early adulthood and it is important to identify individuals affected at the earliest stages of the disorder (Focking et al., 2016; Gaebel and Zielasek, 2015; Perkins et al., 2005). Currently, the diagnosis of schizophrenia relies solely on the somewhat subjective interpretation of clinical symptoms presented by patients (Chan et al., 2015; Cheniaux et al., 2009). In addition, several disorders for e.g. bipolar disorder and autism share some of the symptomology of schizophrenia and this can also lead to difficulty in providing the correct diagnosis (Quinones and Kaddurah-Daouk, 2009). Early diagnosis is important, with evidence suggesting that early

identification and treatment of subjects with psychotic illness significantly improves their clinical outcome (Larsen et al., 2011). Clinical characteristics alone are of limited predictive value and therefore biological predictors of schizophrenia and of the psychosis prodrome will be of enormous value (Cannon et al., 2016; Chan et al., 2015; Weickert et al., 2013).

The interest in identifying biomarkers of schizophrenia and other psychotic disorders has rapidly grown in recent years (Lai et al., 2016; Money, 2013; Pickard, 2015). Biomarkers of these disorders could contribute to a more objective and reliable diagnosis and help to overcome some of the problems which exist with current purely clinical diagnostic methods. Furthermore, there is the potential that such biomarkers could also help in the identification of individuals at risk of developing psychotic disorders among those in the at-risk mental state (ARMS) (Hurlemann et al., 2008; Stojanovic et al., 2014) or at ultra-high risk for psychosis (UHR) (McNamara et al., 2016; Santoro et al., 2015), provide a method of diagnosis at an early stage (Sethi and Brietzke, 2015), or help predict treatment response or measures of disease outcome. In recent years, "-omics" methods have been applied in the search for biomarkers of schizophrenia and other diseases. These methods include genomics, transcriptomics, proteomics and the more recent field of metabolomics (Money, 2013; Quinones and Kaddurah-Daouk, 2009; Sethi and Brietzke, 2015). Some recent findings of potential schizophrenia/psychosis biomarkers using "-omics" methods include elevated *MBP* and *NDEL1* gene expression in early psychosis patients (Gouvea et al., 2016) and elevated baseline levels of certain cytokines in ARMS patients who transitioned to psychotic disorder (Focking et al., 2016; Hayes et al., 2014; Sabherwal et al., 2016). The present review focuses on metabolomics which is the measurement of small molecules present in biological samples (e.g. tissue, blood, urine, cerebrospinal fluid). Together the metabolites in a sample comprise the metabolome. Metabolomics gives an instantaneous snapshot of the physiological status of the organism at a certain time (Peng et al., 2015) and unless samples are analysed prior to disease onset the metabolic alterations will reflect changes following disease onset. Traditional methods of measuring metabolite biomarkers were hypothesis driven and focused on assaying single metabolites however, current metabolomics techniques are

capable of quantifying hundreds of metabolites at one time allowing an explorative approach into investigating biomarkers of disease along with hypothesis driven approaches (Quinones and Kaddurah-Daouk, 2009).

Methods commonly used include mass spectrometry (MS) coupled with gas chromatography (GC), liquid chromatography (LC) or capillary electrophoresis (CE); and nuclear magnetic resonance (NMR) spectroscopy (Quinones and Kaddurah-Daouk, 2009; Zhang et al., 2012). These techniques each have their strengths and weaknesses and at present there is no single analytical platform capable of detecting all metabolites present in the metabolome. Therefore an integrated approach using more than one platform is often adopted in modern studies to provide the most sensitive and reliable measurements (Zhang et al., 2012).

Although biomarker research has greatly advanced in recent years, no robust biomarkers of schizophrenia or psychotic disorders generally have yet been identified (Pickard, 2015; Prata et al., 2014). This systematic review summarises previous research into the metabolomics of schizophrenia, looking at both modern metabolomics techniques along with classical methods used in earlier studies, to reveal any potential biomarkers. The review will focus on studies investigating metabolite differences between schizophrenia subjects and control subjects and also look at how metabolite levels relate to symptom severity in patients.

2.0 Methods

This systematic review was conducted in accordance with PRISMA guidelines (Moher et al., 2009). Articles were identified by searching for titles in the Ovid Medline and Web of Science (WoS) databases using the following search terms: “(schizophreni? OR psychosis OR "at risk mental state" OR "at-risk mental state" OR ARMS OR “ultra-high risk” OR UHR) AND (metabolom* OR metabolite? OR lipidom* OR lipid? OR biomarker? OR "biological marker?" OR "biological signature?") NOT (rat? or animal?)”. The search was restricted to English language journal articles with human subjects, published between January 1970 and June 2016.

The searches returned 538 records after duplicates were removed. 67 records reached inclusion criteria after screening of abstracts. Two of these did not have an accessible full text version leaving 65 full text articles to review. Two studies were discarded after a review of the full text due to not providing enough statistical or methodological information leaving 63 articles to be included in the review (Figure 1).

Abstracts from the search records were screened using the following criteria for inclusion/exclusion: Only experimental published papers were included; reviews and meta-analyses were excluded. Papers were included if they measured any biofluid metabolite levels in humans with schizophrenia, schizophrenia spectrum disorders or at risk of developing schizophrenia (e.g. At-risk mental state (ARMS) subjects and those with a family history of the disorder) AND: a) compared subjects to a healthy control group or other psychiatric disorder/psychosis patient group; OR b) measured the relationship between metabolite levels and symptom severity (measured using a reliable measurement scale e.g. brief psychiatric rating scale (BPRS), positive and negative symptoms scale (PANSS), scale for the assessment of positive symptoms (SAPS), scale for the assessment of negative symptoms (SANS)) AND; c) NOT solely focused on the effects of antipsychotic medications on metabolite levels; d) NOT focused on unrelated variables e.g. comparing patients with Tardive Dyskinesia and those without; or those who have attempted suicide and those who have not; e) NOT focused on metabolites measured in brain tissue.

3.0 Results

63 articles met search criteria and were included in this review (Figure 1). Significant findings relating to metabolites in schizophrenia patients have been summarised in Tables 1-5. Results are divided into sections based on metabolite classes which are as follows: (1) lipids and lipid-like molecules including fatty acids, steroids and other lipid-like molecules; (2) carbohydrate metabolism, organic acids and derivatives; and (3) other metabolites. Results include metabolites where significantly different levels

have been reported in schizophrenia or psychosis (Figure 2d; Tables 1, 2, 3, & 4) or metabolites that have been associated with symptomology (Table 5).

3.1 Lipids and lipid-like molecules (Table 1)

3.1.1 Fatty acids

The authors are aware that a number of fatty acid metabolites have been previously reported in relation to schizophrenia (Bates et al., 1991; Glen et al., 1994; Horrobin et al., 1989; Kaiya et al., 1991; Obi and Nwanze, 1979), however due to the criteria laid out in this systematic review they were excluded. Several inconsistencies in reported differences in fatty acid levels between patients and controls exist in the literature. Both increased and decreased serum and red blood cell (RBC) levels of stearic acid (Khan et al., 2002; Schwarz et al., 2008; Xuan et al., 2011; Yang et al., 2013); β-hydroxybutyrate (Cai et al., 2012; Fukushima et al., 2014; Yang et al., 2013); linoleic acid (Fukushima et al., 2014; Khan et al., 2002; Schwarz et al., 2008; Xuan et al., 2011; Yang et al., 2013); oleic acid (Khan et al., 2002; Schwarz et al., 2008; Xuan et al., 2011; Yang et al., 2013) and palmitic acid (Khan et al., 2002; Schwarz et al., 2008; Xuan et al., 2011; Yang et al., 2013) have been reported in schizophrenia patients compared to healthy controls. Of the fatty acids reported in more than one paper, only arachidonic acid had consistent findings across all studies with significantly decreased levels reported in schizophrenia patients compared to controls (Arvindakshan et al., 2003; Fukushima et al., 2014; Khan et al., 2002; Schwarz et al., 2008). Findings of no significant difference between patients and controls were also reported for serum levels of oleic acid (Fukushima et al., 2014), RBC arachidonic acid (Ramos-Loyo et al., 2013) and RBC docosahexaenoic acid (DHA) (Ramos-Loyo et al., 2013).

Yang et al. (Yang et al., 2013) reported increased levels of several fatty acids in serum of schizophrenia patients who had been drug-free for at least 2 weeks compared to healthy control subjects. The discriminatory fatty acids between patients and controls included tetradecanoic acid, palmitic acid, stearic acid, oleic acid, eicosenoic acid and β-Hydroxybutyrate. Oresic et al. (Oresic et al., 2011) performed metabolomic serum profiling of subjects with psychotic disorders (schizophrenia, affective

psychosis and other non-affective psychosis (ONAP)) and healthy controls using a combination of platforms (UPLC-MS and GC x GC-TOFMS). Cluster analysis identified a total of 13 lipid clusters with 6 significantly increased in the schizophrenia subjects. These 6 lipid clusters were dominated by saturated triglycerides. Cluster analysis of the metabolomic profiles identified one significantly decreased cluster in the schizophrenia subjects which contained mainly ketone bodies and free fatty acids. Concentrations for this cluster were also decreased in subjects with affective psychosis compared to controls and increased with antipsychotic use.

Arvindakshan et al. (Arvindakshan et al., 2003) measured levels of RBC fatty acids and plasma thiobarbituric acid reactive substances (TBARS) in drug naïve and medicated schizophrenia patients and healthy controls. They reported reduced levels of essential polyunsaturated fatty acids (EPUFAs; n3 and n6 fatty acids) in drug naïve patients compared to medicated schizophrenia patients and healthy controls. In medicated patients EPUFA levels were similar to those of controls with the exception of decreased DHA. There were also significant negative correlations between concentrations of arachidonic acid and BPRS scores, and concentrations of DHA and PANSS negative symptom scores (Table 5).

The most consistent findings from studies investigating associations between fatty acid concentrations and schizophrenia include reduced EPUFAs, particularly arachidonic acid, which could be potential biomarkers for schizophrenia or early psychosis.

3.1.2 Steroids and steroid derivatives

As stress has been linked to schizophrenia (Beards et al., 2013; Cotter and Pariante, 2002), studies have investigated abnormalities in cortisol concentrations in patients with schizophrenia compared with controls. Increased serum cortisol levels have been reported in drug naïve paranoid schizophrenia patients compared to healthy controls (Schwarz et al., 2012) and in male (but not female) first episode drug naïve schizophrenia patients (Bicikova et al., 2013). However, Mondelli et al. (Mondelli et al., 2015) found decreased salivary cortisol levels in schizophrenia patients. Labad et

al. (Labad et al., 2015) investigated baseline stress biomarkers among ARMS subjects and at one year follow-up found no differences between subjects who transitioned to psychotic disorder compared to those who did not, or with healthy control subjects in serum cortisol, estradiol (females), progesterone (females) or testosterone (males) levels. However significant differences were discovered in cortisol awakening response (CAR) between subjects who transitioned to psychotic disorder compared to those who did not, with the psychotic outcome group showing greater baseline increases in salivary cortisol secretion after awakening. Mondelli and colleagues (Mondelli et al., 2015) reported that CAR positively correlated with clinical improvement in first episode schizophrenia patients (Table 5). Walker et al. (Walker et al., 2002) reported no significant differences in plasma levels of cortisol between twins with schizophrenia and their healthy co-twins.

Two metabolomic profiling studies reported conflicting results in relation to cholesterol levels. Decreased serum cholesterol was reported in medicated schizophrenia patients by Al Awam et al. (Al Awam et al., 2015); however increased serum cholesterol in non-medicated patients compared to healthy controls was reported by Xuan et al. (Xuan et al., 2011). Solberg et al. (Solberg et al., 2015) reported decreased levels of serum HDL cholesterol in both medicated and non-medicated patients with schizophrenia or schizoaffective disorder compared to healthy controls and a negative correlation between global assessment of functioning symptom (GAF-S) scores and serum total cholesterol levels. Two studies reported no significant differences in serum cholesterol levels between patients and controls (Oresic et al., 2011; Scottish Schizophrenia Research Group, 2000).

Bicikova et al. (Bicikova et al., 2013) measured 39 steroids in serum from drug-naïve schizophrenia patients and healthy controls using a GC-MS approach. Schizophrenia subjects had higher levels of pregnenolone sulphate and sulphate 5- α and β saturated metabolites of C21 steroids in the progesterone pathway. Using an orthogonal projections to latent structures (OPLS) model, schizophrenia patients could be discriminated from controls with very high sensitivity (95% in males, 100% in females). Cai et al. (Cai et al., 2012) found significantly higher levels of urinary pregnanediol

in first-episode drug-naïve schizophrenia patients compared to healthy controls; the same trend was reported in the serum of males and females by Bicikova et al. (Bicikova et al., 2013)) although the differences were not significant. A negative correlation was also reported between levels of pregnanediol and improvement in PANSS activation symptom cluster subscores (Cai et al., 2012) (Table 5).

3.1.3 Lipid peroxidation metabolites

Lipid peroxidation metabolites/TBARS including malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) have been measured in several studies. Consistent findings of increased RBC, plasma and serum levels of lipid peroxidation metabolites have been reported (Arvindakshan et al., 2003; Khan et al., 2002; Kuloglu et al., 2002; Ramos-Loyo et al., 2013; Ryazantseva et al., 2002).

3.1.4 Phospholipids and lipoproteins

Increased plasma and RBC levels of lysophosphatidylcholine (LPC) have been found in schizophrenia patients (Cai et al., 2012; Ryazantseva et al., 2002), however reduced serum levels of LPC have also been observed (Oresic et al., 2012). Reduced plasma and RBC levels of phosphatidylcholine (PC) and phosphatidylethanolamine (PE) have been reported (Cai et al., 2012; He et al., 2012; Kaddurah-Daouk et al., 2007; Ryazantseva et al., 2002). Lautin et al. (Lautin et al., 1982) measured RBC phospholipid levels in medicated schizophrenia patients and healthy controls but found no significant differences in PC, PE, phosphatidylserine (PS) or sphingomyelin (SM) concentrations. McEvoy et al. (McEvoy et al., 2013) also reported no significant differences between schizophrenia patients and controls in plasma levels of overall LPC, PC or PE lipid classes however there were significant reductions in the PCn3 and PEn3 lipids in both first episode and recurrent episode patients compared to controls.

Two studies measured plasma lipoprotein concentrations in schizophrenia subjects (Cai et al., 2012; Tsang et al., 2006). Cai et al. (Cai et al., 2012) found reduced plasma lipoprotein concentrations in drug-naïve schizophrenia subjects compared to controls, whereas Tsang et al. (Tsang et al., 2006)

reported increased lipoprotein concentrations in female (but not male) monozygotic twins affected with schizophrenia compared to their healthy co-twins and a healthy control group.

The above lipid findings suggest potential biomarkers for schizophrenia could include EPUFAs, lipid peroxidation metabolites, several neuroactive steroids and the phospholipids PC and PE. Lipid findings are summarised in Tables 1 and 5. More detail can also be found in supplementary Tables S1 and S4, including reported P-values (<0.05) of the significant metabolites found between control and schizophrenia study groups

3.2 Carbohydrate metabolism, organic acids and derivatives (Table 2)

3.2.1 Amino acids

Several studies have reported abnormal biofluid concentrations of amino acids in patients with schizophrenia, although the results have been inconsistent. Increased levels of plasma serine have been reported by Yang et al. (Yang et al., 2013) whereas decreased levels of serum D-serine were also reported (Fukushima et al., 2014). Yang et al. (Yang et al., 2013) observed both increased urinary and decreased serum levels of cystine (the oxidised form of cysteine) in schizophrenia patients compared to healthy controls. Both increased and decreased levels of pyroglutamic acid (an amino acid derivative) ((Liu et al., 2014) (peripheral blood mononuclear cells (PBMCs)); (Yang et al., 2013) (urine)); creatine ((Cai et al., 2012) (urine); (Koike et al., 2014) (plasma)); serum, plasma and urine glycine (Cai et al., 2012; Xuan et al., 2011); serum and PBMC aspartate (Liu et al., 2014; Xuan et al., 2011; Yang et al., 2013); urine, PBMC and plasma valine (Bjerkenstedt et al., 1985; Cai et al., 2012; Liu et al., 2014; Yang et al., 2013); and serum, plasma and PBMC tryptophan (Fukushima et al., 2014; Kim et al., 2009; Krause et al., 2013; Xuan et al., 2011) have been reported in schizophrenia subjects. Findings that have been consistent across studies include reduced concentrations of urine and PBMC creatinine (Cai et al., 2012; Karoum et al., 1987; Liu et al., 2014); reduced plasma glutamine (Bjerkenstedt et al., 1985; He et al., 2012); reduced whole blood and serum glutathione (Ballesteros et al., 2013; Fukushima et

al., 2014) increased serum and plasma glutamate (Fukushima et al., 2014; Koike et al., 2014; Yang et al., 2013); increased plasma alanine (Bjerkenstedt et al., 1985; Cai et al., 2012); increased urine and plasma isoleucine (Bjerkenstedt et al., 1985; Yang et al., 2013); increased urine and serum pipecolinic acid (Al Awam et al., 2015; Yang et al., 2013); and increased serum and plasma phenylalanine (Bjerkenstedt et al., 1985; Yang et al., 2013) in schizophrenia patients. There were also reports of no significant differences between schizophrenia patients and controls in serum levels of glutamate and glutamine (Alfredsson and Wiesel, 1989). Oresic et al. (Oresic et al., 2011) reported higher serum concentrations in schizophrenia subjects for two metabolite clusters containing organic acids and branched chain and other amino acids.

3.2.2 Carbohydrate metabolism and other organic acids and derivatives

Reduced levels of citrate (in urine, plasma, PBMCs and serum) are reported in the majority of studies (Cai et al., 2012; Liu et al., 2015; Xuan et al., 2011; Yang et al., 2013), however Yang et al. (Yang et al., 2013) reported both increased serum citrate and reduced urine citrate concentrations in schizophrenia patients. Glucose (PBMC, serum and urine levels) was mainly reported as being increased in schizophrenia patients (Cai et al., 2012; Liu et al., 2015; Xuan et al., 2011; Yang et al., 2013) however Cai et al. (Cai et al., 2012) found increased urinary concentrations but decreased plasma concentrations in schizophrenia patients. Both increased and decreased levels of lactate (plasma (Cai et al., 2012); PBMCs (Liu et al., 2015); serum (Xuan et al., 2011); urine & serum (Yang et al., 2013)) and taurine (plasma (Bjerkenstedt et al., 1985); urine (Cai et al., 2012)) have also been reported in patients. Consistent findings have included reduced levels of urine, and serum α-Ketoglutarate (Xuan et al., 2011; Yang et al., 2013), increased levels of PBMC and serum pyruvate (Liu et al., 2015; Yang et al., 2013) and increased PBMC and serum glycerol (Liu et al., 2014; Xuan et al., 2011). In the study by Cai et al. (Cai et al., 2012) negative correlations between urinary α-ketoglutarate and PANSS negative scores were reported. They also reported a negative correlation between changes in urinary citrate concentrations and changes in PANSS depression sub-scores following treatment

(Table 5). Carbohydrate metabolism, organic acids and their derivatives are summarised in Tables 2 and 5. More detail can also be found in supplementary Tables S2 and S4, including reported P-values (<0.05) of the significant metabolites found between control and schizophrenia study groups and S4 also includes correlation coefficients for correlations found between metabolites and PANSS/GAF/BPRS/SAPS/SANS/GAS scores Supplementary Table S5 provides information on the metabolic pathway(s) and schizophrenia hypotheses associated with each reported metabolite.

3.3 Other metabolites (Table 3)

Consistent findings of increased concentrations of 3-methoxy-4-hydroxyphenylglycol (MHPG) in cerebrospinal fluid (CSF) and plasma have been reported in schizophrenia patients (Bjerkenstedt et al., 1985; Pickar et al., 1990; Zumarraga et al., 2010). Zumárraga et al. (Zumarraga et al., 2010) found elevated levels of MHPG in schizophrenia compared to bipolar patients. However, decreased levels of CSF homovanillic acid (HVA) have also been reported (Bjerkenstedt et al., 1985; Peters, 1979). Both increased and decreased levels of PBMC and urinary dopamine have been reported in the literature (Fryar-Williams and Strobel, 2015; Karoum et al., 1987; Liu et al., 2014). The metabolite levels of HVA (Alfredsson and Wiesel, 1989; Berger et al., 1980; Domino et al., 1979; Fryar-Williams and Strobel, 2015; Gattaz et al., 1982; Karoum et al., 1987; Markianos et al., 1992; Nilsson-Todd et al., 2007; Pickar et al., 1990; Post et al., 1975; Prell et al., 1995; Vankammen et al., 1978; Walker et al., 2002; Zumarraga et al., 2010) and MHPG (Berger et al., 1980; Gattaz et al., 1982; Karoum et al., 1987; Markianos et al., 1992; Nyback et al., 1983; Peters, 1979; Post et al., 1975; Prell et al., 1995) were reported in a number of separate studies as being not significant between control and schizophrenia groups. Other metabolites including 5-HIAA (Alfredsson and Wiesel, 1989; Berger et al., 1980; Bjerkenstedt et al., 1985; Cai et al., 2012; Domino et al., 1979; Karoum et al., 1987; Markianos et al., 1992; Nyback et al., 1983; Peters, 1979; Pickar et al., 1990; Prell et al., 1995; Vankammen et al., 1978), dopamine (Prell et al., 1995), adrenaline (Walker et al., 2002), noradrenaline (Karoum et al., 1987; Pickar et al., 1990; Prell et al., 1995; Walker et al., 2002) and 5-hydroxy tryptophan (Yao et al., 2010) were also measured

and compared between control and schizophrenia groups and were found not to be significantly different.

Correlations between neurotransmitter metabolite concentrations and severity of symptoms in patients have also been reported in several papers (Anand et al., 2002; Gattaz et al., 1982; Jacobsen et al., 1997; Kahn et al., 1993; Kim et al., 2009; Krause et al., 2013; Markianos et al., 1992; Miura et al., 2014; Pickar et al., 1990; Prell et al., 1995) (Table 5). Other metabolite findings have included both increased and reduced PBMC, serum and plasma levels of kynurenine (Fukushima et al., 2014; Krause et al., 2013), benzoic acid (Khan et al., 2002; Liu et al., 2014) and nitric oxide metabolites (Lee and Kim, 2008; Nakano et al., 2010; Taneli et al., 2004), although findings of no significant differences were also reported for kynurenine (Kim et al., 2009; Yao et al., 2010) and kynurenic acid (Chiappelli et al., 2014; Fukushima et al., 2014).

Whole blood, serum and PBMC levels of vitamins B6, D, E (including tocopherol-α & tocopherol- γ) and folic acid (RBCs) have been consistently reported to be reduced in patients with schizophrenia (Fryar-Williams and Strobel, 2015; Liu et al., 2014; Scottish Schizophrenia Research Group, 2000; Xuan et al., 2011). Two studies reported no significant differences in plasma and serum levels of vitamins A (Scottish Schizophrenia Research Group, 2000) and C (Young et al., 2007). Findings for other metabolites including neurotransmitter metabolites and vitamins are summarised in Tables 3 and 5. More detail can also be found in supplementary Tables S3 and S4, including reported P-values (<0.05) of the significant metabolites found between control and schizophrenia study groups and S4 also includes correlation coefficients for correlations found between metabolites and PANSS/GAF/BPRS/SAPS/SANS/GAS scores. Supplementary Table S5 provides information on the metabolic pathway(s) and schizophrenia hypotheses associated with each reported metabolite.

3.4 Biomarker panels (Table 4)

In recent years there has been growing interest in the development of biomarker panels in order to achieve the best possible discrimination between patients and control subjects. A study by Fryar-Williams & Strobel (Fryar-Williams and Strobel, 2015) identified two potential biomarker panels with reasonable discrimination between subjects with schizophrenia or schizoaffective disorder and controls. The "catecholamine domain" (elevated levels of catecholamines in schizophrenia) produced an area under the curve (AUC) of 0.859 (84% sensitivity and 75% specificity). The "Nutrition-Biochemistry domain" produced an AUC of 0.797 (sensitivity of 55% and specificity of 88%). Liu et al. (Liu et al., 2014) identified a panel consisting of pyroglutamic acid, sorbitol and tocopherol-α which could discriminate between schizophrenia subjects and healthy controls with a good predictive ability.

Yang et al. (Yang et al., 2013) identified a panel of serum schizophrenia biomarkers consisting of glycerate, eicosenoic acid, β -hydroxybutyrate, pyruvate and cystine which achieved an AUC of 0.945 in a training set and 0.895 in a test set of subjects. When urine β–hydroxybutyrate was added to this panel, schizophrenia could be accurately diagnosed in both sets of subjects and an AUC of 1.0 was achieved. He et al. (He et al., 2012) discovered a panel of 5 plasma biomarkers of schizophrenia consisting of arginine, glutamine, histidine, ornithine and PC ae C38:6 (AUC = 0.805). Xuan et al. (Xuan et al., 2011) performed GC-MS based metabolomic serum profiling of unmedicated schizophrenia patients. A panel of four schizophrenia biomarkers (citrate, palmitic acid, myo-inositol and allantoin) was identified with an AUC of 0.958. Please refer to Table 4 for a summary of biomarker panel findings.

The above results highlight many metabolites with significantly different levels found between schizophrenia patients and controls. Some of the most consistent potential biomarkers include EPUFAs, lipid peroxidation metabolites, PCs, PEs, creatinine, glutamate, MHPG and vitamin E (See Figure 3).

4.0 Discussion

Although there are many opposing findings in the articles reviewed, there are some reassuring patterns emerging for several metabolites. Potential signatures could include low levels of PUFAs

(especially arachidonic acid), vitamins (vitamin E in particular); and elevated levels of lipid peroxidation metabolites. Furthermore, reduced PC, PE, creatinine, citrate and tryptophan, and increased glutamate, glucose, valine and triglycerides (see Figure 3) could also represent a useful signature and further research is required to assess the validity of these as biomarkers of schizophrenia. Previous reviews and meta-analyses have examined more specifically the associations between schizophrenia/psychosis and PUFAS (Mossaheb et al., 2012; Terlecky et al., 2012), neuroactive steroids (Shulman and Tibbo, 2005), cortisol (Chaumette et al., 2016), vitamins (Valipour et al., 2014; Wang et al., 2016) and amino acids (Brouwer et al., 2013; Song et al., 2014). Findings, most of which are in agreement with this review, included reduced RBC PUFA levels, altered neuroactive steroid levels, vitamin D deficiency, folate deficiency and elevated blood serine and glucose levels in schizophrenia patients; however issues with sample size and subject heterogeneity were also highlighted. While certain consistencies have been reported in the literature none of the potential biomarkers have been validated and importantly many are implicated in other conditions.

4.1 Metabolite findings in relation to current schizophrenia hypotheses

4.1.1 Oxidative stress and inflammation hypothesis

One current hypothesis which is in accordance with some of the above findings is the oxidative stress and inflammation theory of schizophrenia. Oxidative stress and inflammation are exquisitely tied processes. Chronic inflammation is associated with elevated reactive oxygen species levels; anti-inflammatory cascades are related to reduced reactive oxygen species concentrations. And the converse is true-elevated oxidative stress triggers inflammation, whereas redox balance inhibits the cellular response. Therefore, oxidative stress and inflammation maybe seen as both causes and consequences of cellular pathology in a number of disorders (Terlecky et al., 2012).

The involvement of the oxidative stress cascade occurs in multiple pathological conditions such as cancers, cardiovascular disease and neurodegenerative disorders for e.g. Parkinson's disease and Alzeihmer's disease (Emiliani et al., 2014; Mahadik et al., 1998). Oxidative stress mechanisms have

also been implicated in the pathogenesis of neuropsychiatric disorders (Blesa et al., 2015; Rossignol and Frye, 2014; Salim, 2014), as the brain is considered particularly vulnerable to oxidative damage for several reasons. These reasons include its comparatively high oxygen utilisation and subsequent generation of free radical by-products, its modest antioxidant defences, its lipid-rich constitution that provides ready substrates for oxidation, the reducing potential of certain neurotransmitters and the presence of redox-catalytic metals such as iron and copper (Ng et al., 2008).

Previous studies have in general demonstrated a picture of enhanced inflammation during and preceding psychosis (Khandaker et al., 2014; Schwarz et al., 2014), however it must also be noted that environmental influences are also implicated as schizophrenia risk factors and include prenatal and birth complications such as hypoxia, neonatal infections, drug abuse and autoimmune disease (Brown, 2011). It has been postulated that these heterogeneous risk factors are all associated with increased oxidative stress and inflammation and that this perturbation of oxidative stress, particularly during sensitive stages of brain development, could negatively affect the brain circuitry relevant to development of schizophrenia (Koga et al., 2016).

The consistent metabolite findings in this review are indicative of the oxidative stress and inflammation theory as they indicate pro-oxidant/antioxidant imbalance favouring pro-oxidants in patients with schizophrenia, i. e. increased reactive species and reduced antioxidants (Boskovic et al., 2011; Mahadik, 2006). This theory could explain the low levels of the antioxidant vitamin E, high levels of lipid peroxidation metabolites and low levels of PUFAs and phospholipids, which are very susceptible to free radical peroxidation, found in patients (Mahadik, 2006). Indeed, many of the aforementioned studies included drug naïve patients suggesting that the altered metabolites are integral to the disease as opposed to a consequence of prolonged disease state or its treatment.

Notwithstanding this, many of the studies in this systematic review compared only schizophrenia patients, first episode psychosis and healthy control subjects, future research should look at whether

biomarkers can discriminate between different neuropsychiatric conditions, schizophrenia outcome and predictors of antipsychotic drug treatment response.

4.1.2 PUFA metabolism hypothesis

PUFA disturbance metabolism has been reported consistently in patients with schizophrenia (Pawelczyk et al., 2015). As PUFAs are essential for normal neurodevelopment, disturbances of PUFA metabolism may be involved in the etiology of neurodevelopmental disorders, including schizophrenia. They are the major constituents of cell membrane phospholipids and therefore have numerous important biological roles that include receptor binding, neurotransmission, signal transduction and eicosanoid synthesis (Amminger and McGorry, 2012), which control inflammation, oxidative stress and defence processes among others. Disturbances in PUFA metabolism have been shown to exist at early stages of schizophrenia prior to initiation of antipsychotic therapy and in individuals at ultra-high risk of psychosis (Pawelczyk et al., 2015). Therefore, this PUFA dysregulation is present at illness onset and is likely not mediated by antipsychotic medication.

The PUFA arachidonic acid was the most consistent finding in terms of fatty acid metabolites in the systematic review with decreased levels reported in schizophrenia patients compared to controls. Post-mortem brain studies also revealed decreased levels of PUFA, especially DHA and arachidonic acid, in the frontal lobes of schizophrenia patients. PUFA deficiencies in neuronal membranes can be the result of the increased release of PUFA from membrane phospholipids, or its decreased incorporation within them. Both processes were found to be defective in schizophrenia patients (Pawelczyk et al., 2015).

4.1.3 Membrane phospholipid hypothesis

The membrane phospholipid hypothesis postulated by Horrobin (Horrobin, 1998) suggests that cellular PUFA abnormalities can lead to schizophrenia in susceptible individuals. The basic premise of the phospholipid hypothesis is that normal neuronal phospholipid metabolism is required for normal

brain development of brain architecture during development, for its modulation around the time of puberty and for normal adult neuronal functioning (Horrobin, 1998). Because of the central role of phospholipids, particularly in neurons, a phospholipid abnormality will inevitably lead to secondary abnormalities in most neurotransmitters, ion channel and cell signalling systems as a result of slight changes in quaternary structures of proteins, and substantial changes in certain cell signalling mechanisms (Horrobin, 1998; Horrobin et al., 1994). Therefore, the large numbers of neurotransmitter-related abnormalities in schizophrenia are for the most part secondary consequences of the phospholipid changes (Horrobin and Bennett, 1999).

The consistent findings of low levels of phospholipids in schizophrenia patients in this review together with decreases reported in phospholipids in fibroblasts from neuroleptic-naïve schizophrenia patients; in platelet membranes of drug-naïve patients with schizophrenia and in post-mortem brain tissue from patients with schizophrenia support this hypothesis (Kaddurah-Daouk et al., 2007).

Messamore and Yao (Messamore and Yao, 2016) propose a model relating abnormal levels of phospholipid signalling to neurochemical abnormalities observed in schizophrenia. The model links the low levels of phospholipids, high levels of LPC and low levels of arachidonic acid found in schizophrenia patients with levels of neuroactive molecules, including dopamine and glutamate, and several neuronal signalling pathways. The authors suggest a physiological subtype of schizophrenia associated with disrupted arachidonic acid signalling. The low levels of PUFAs observed in the reviewed studies are also in keeping with findings of potential therapeutic effects of n-3 fatty acids in those in the at-risk mental state (Amminger et al., 2010).

4.1.4 Energy metabolism disorder

Elevated levels of glucose and pyruvate in schizophrenia patients were consistently reported in this review. Glucose is the major substrate for oxidative energy in the brain (Xuan et al., 2011) with converging evidence suggesting that malfunction of glucose metabolism may be a causative factor for schizophrenia (Yang et al., 2013). Increased levels of pyruvate indicate increased energy production in

schizophrenia patients, which has been found to result from inefficiency in brain circuitry (Buchsbaum et al., 2007).

4.2 Biomarker panels for schizophrenia

The biomarker panels discovered have very promising AUC values, however none of the same metabolites have come up in different biomarker panels between studies. Of the biomarkers identified in panels from the reviewed studies (see Table 4), only vitamin E (tocopherol -α or -γ) was also identified as one of the most consistent metabolites in this review (see Figure 3). Further research should be conducted to validate and assess the discriminatory capabilities of these biomarker panels in different patient groups and between different neuropsychiatric disorders. Due to the heterogeneous nature of schizophrenia, the identification of a single stand-alone biomarker with high sensitivity and specificity is highly unlikely. The concept of a panel or panels or biomarkers may provide a more reliable and robust measure as each subtype may have its own set of unique biomarkers. Disease heterogeneity introduces a number of challenges for the discovery of biomarkers such as the need for greater sample sizes to ensure that relevant subtypes have adequate representation (Wallstrom et al., 2013).

4.3 Biomarker studies challenges & limitations

Some difficulties exist in interpreting results from the biomarker studies published to date in this field. Several studies which measured multiple different metabolites did not account for false discovery rates and this could have resulted in false positive findings. Another issue is the heterogeneity of participants in these studies. Participants have varied both within and between groups in a number of variables including medication status (Figure 2a), disease sub-type/symptomology, age (Figure 2c), stage of disease and other factors. Some of the inconsistent findings in the studies reviewed could

relate to these differences. For example, tryptophan levels were decreased in 3 studies (Kim et al., 2009; Krause et al., 2013; Xuan et al., 2011) in drug-naïve or non-medicated patients but were increased in one study (Fukushima et al., 2014) where all patients were taking antipsychotic medication, suggesting that the increased levels could be due to medication effects. Another important variable to consider is the gender of the participants. Clear differences between male and female participants have been observed in some of the studies reviewed (Bicikova et al., 2013; Ramos-Loyo et al., 2013; Tsang et al., 2006) however several studies did not account for differences between sexes. Additionally, potentially important confounding variables such as diet, lifestyle, smoking status and stage of disease have not been measured or considered in the analyses. Furthermore, there is considerable clinical heterogeneity in schizophrenia and different causal mechanisms may underlie distinct potential sub-types or endophenotypic profiles (Braff et al., 2007; Guest et al., 2016). There is also evidence of similar abnormalities in metabolite levels in different neuropsychiatric disorders which could share common pathways (McNamara and Welge, 2016; Parletta et al., 2016).

In order to overcome some of the issues raised, large cohort studies are required to examine different sub-types of schizophrenia as well as other neuropsychiatric disorders (e.g. depression, bipolar disorder, ASD, Parkinson's disease). A longitudinal design looking at various stages of disease including those who are "at-risk" would be of great benefit. In addition, biomarkers identified from existing findings should be targeted in a large-scale study comparing different diseases, disease sub-types and stages of disease to validate and test the specificity of these markers and explore whether different sub-types may be associated with different physiological mechanisms. Wood (Wood, 2014) suggests that due to the heterogeneity in patient populations, it is necessary to establish a normal range for metabolites in metabolomics studies. Meta-analyses would also be beneficial; however due to the heterogeneity between subject groups and even within groups it may be difficult to obtain a large amount of data for more specifically defined groups from previous studies.

4.4 Biofluids of choice

Plasma appears to be the most frequently measured biofluid in the biomarker studies reviewed, followed by serum and CSF (Figure 2b). There have been some cases in the reviewed studies where opposing findings have occurred in different biofluids in the same set of participants (Cai et al., 2012; Yang et al., 2013). It has been suggested that this could be due to different metabolic/excretion rates in different biological compartments (Yang et al., 2013). It would be useful to explore correlations in metabolite levels between different biofluids. There has been some evidence of positive correlations between different biofluids and also between biofluids and brain tissue (Mahadik, 2006; Yao et al., 2002). Additional research is required to define metabolites whose central and peripheral levels are linked and how these correlations are influenced by schizophrenia. As suggested by Quinones and Kaddurah-Daouk comparative studies in CSF and blood would help to map central and peripheral changes in neuropsychiatric disorders to allow a more accessible way for biomarker development in blood but ensuring that these peripheral biomarkers are reflective of central changes (Quinones and Kaddurah-Daouk, 2009).

4.5 Concluding remarks

In summary, a number of promising metabolite markers for schizophrenia have been identified and replicated in a number of studies(see Figure 3), some of which converge on signalling and inflammatory/anti-inflammatory processes. There is however no fully validated single metabolite or panel of biomarkers which can reliably discriminate schizophrenia subjects from healthy subjects, or indeed from any other neuropsychiatric presentation. Further research is necessary to investigate discriminatory biomarkers for these disorders. Challenges exist in the metabolomic biomarker field that need consideration. One such challenge is that there is no single, universally accepted method for metabolomic analysis, different laboratories often use their own optimised protocols and therefore it can be challenging to obtain identical metabolic profiles for the same samples by independent laboratories (Nagana Gowda and Raferty, 2013)(Nagana-Gowda, 2013). Furthermore,

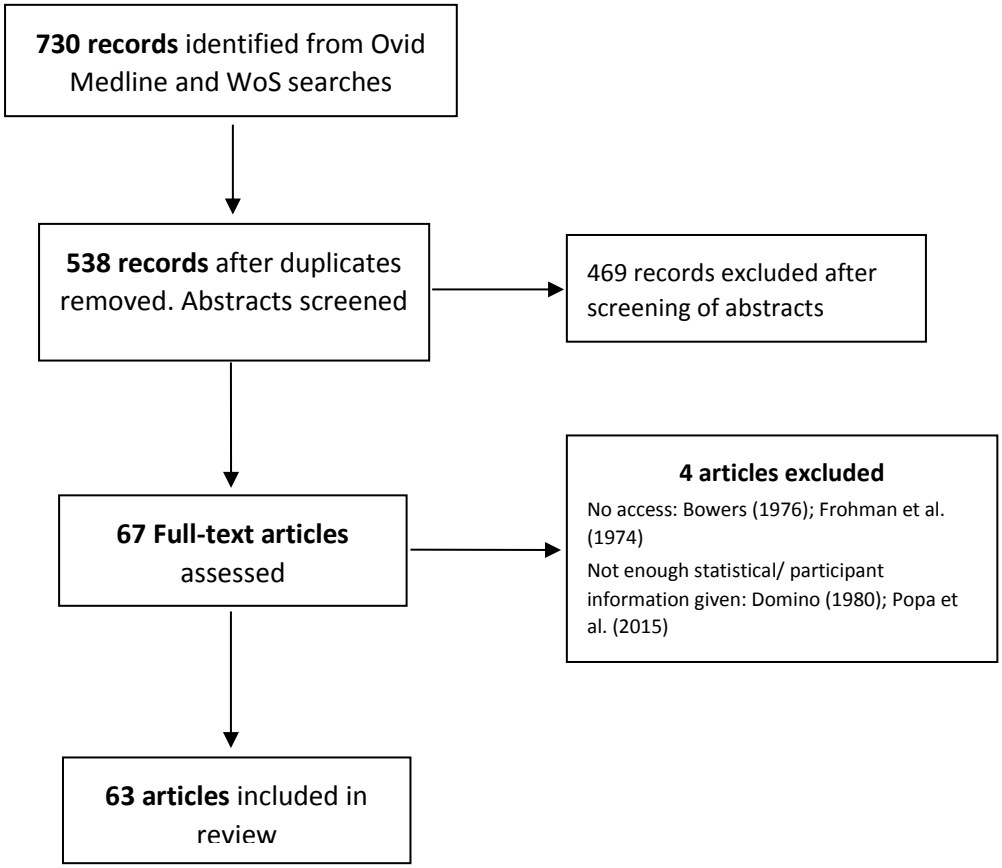
future biomarker studies would benefit from more standardised methods, detailed consideration of confounding variables and the use of large cohorts of subjects.

Another major challenge is in the area of metabolite identification; technology advancement is needed to enhance metabolite coverage and advancement in the identification of unknown metabolites to allow novel biomarker discovery (O'Gorman et al., 2013).

Although there are some promising findings in schizophrenia biomarker research, it is unlikely that these biomarkers alone will be capable of predicting disorder. However, they could be an extremely useful tool in aiding diagnosis and should be used as part of a larger assessment which considers a number of important risk factors including those discussed by Cannon et al. (Cannon et al., 2016). A combination of markers from different 'omics fields, neuroimaging and neuropsychology may in the future provide the most reliable predictions and diagnoses for schizophrenia.

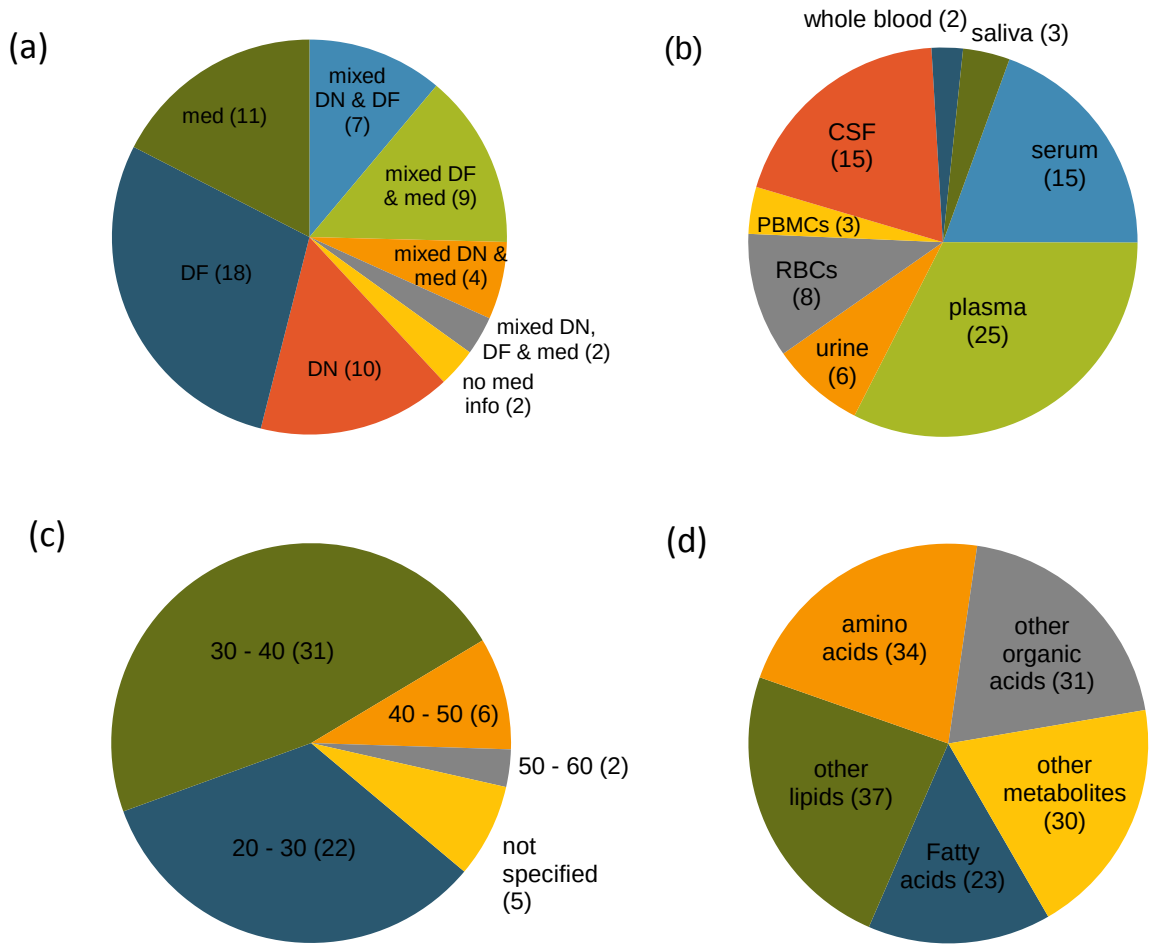
Caption for Figure 1

Figure 1. Flow chart of selection process. WoS: Web of Science



Caption for Figure 2

Figure 2. (a) Medication status of patient groups (medication status, number of studies); (b) Biofluids analysed in reviewed studies (biofluid, number of studies); (c) Mean/median age of patient groups (mean/median age, number of studies); (d) Number of metabolites from different classes which differed between patients and controls (metabolite class, number of metabolites); DF = drug-free, DN = drug-naïve, med = taking medication, CSF = cerebrospinal fluid, PBMCs = peripheral blood mononuclear cells, RBCs = red blood cells



Caption for Figure 3

Figure 3. Metabolomic biomarkers with the most consistent findings. Graph shows number of studies finding increased (↑) and decreased (↓) levels. MHPG = 3-methoxy-4-hydroxyphenylglycol; PUFA = polyunsaturated fatty acid; n3 = omega 3; n6 = omega 6; DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; EPA = eicosapentaenoic acid; AA = arachidonic acid; LA = linoleic acid; *Yang et al. (Yang et al., 2013) observed elevated serum and reduced urine levels of citrate; **Cai et al. (Cai et al., 2012) observed elevated urine and reduced serum levels of glucose; ¶ vitamin E (vitamin E, tocopherol-α or tocopherol-γ) was reduced in 3 studies, vitamins B6, D and folate were reduced in 1 study)

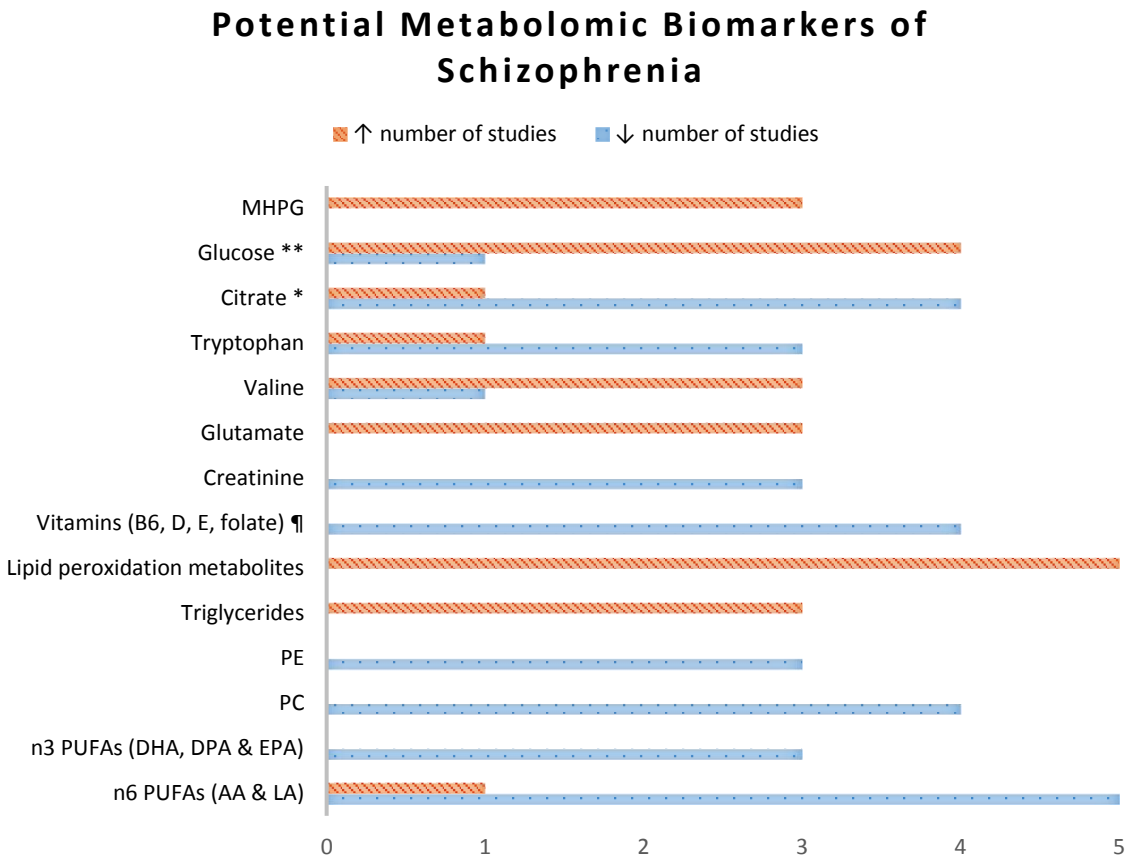


Table 1: Lipids and lipid-like molecules found at abnormal levels in subjects with schizophrenia

Metabolite	Reference	Platform	Biofluid	Subjects	Difference (SCZ v control)
Fatty acids					
octadecanoic (stearic) acid; eicosenoic acid; linoleate; tetradecanoic acid; oleic acid; hexadecanoic (palmitic) acid; α-hydroxybutyrate; β-hydroxybutyrate	(Yang et al., 2013)	GC-TOFMS	serum	SCZ (N=62; DF ≥ 2 weeks) v HC (N=62)	↑
stearic acid; linoleic acid; oleic acid; palmitic acid	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
stearic acid; arachidonic acid; linoleic acid; oleic acid; palmitic acid	(Schwarz et al., 2008)	LC-MS	RBCs	FE DN SCZ (N=7) v HC (N=20)	↓
stearic acid; oleic acid; palmitic acid	(Khan et al., 2002)	GC-FID	RBCs	FE DN SCZ (SCZ & SFD, N=22) v HC (N=16); chronic med SCZ (N=30) v HC	↑
suberic acid; 4-Pentenoic acid; α-hydroxybutyrate; β-hydroxybutyrate	(Yang et al., 2013)	GC-TOFMS	urine	SCZ (N=51, DF ≥ 2 weeks) v HC (N=51)	↑
β -hydroxybutyrate	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
β-hydroxybutyrate; arachidonic acid; linoleic acid	(Fukushima et al., 2014)	HPLC-FLD	serum	med SCZ (N=25) v HC (N=27)	↓
eicosenoic acid; heptadecanoic acid; oleic acid; pentadecanoic acid	(Al Awam et al., 2015)	GC-MS	serum	med SCZ (N=26) v HC (N=26)	↓
arachidonic acid; DHA	(Arvindakshan et al., 2003)	GC	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45); DN SCZ v med SCZ (N=32)	↓
arachidonic acid; DHA; DPA	(Khan et al., 2002)	GC- FID	RBCs	FE DN SCZ (SCZ & SFD, N=22) v HC (N=16); chronic med SCZ (N=30) v HC; FE DN SCZ v chronic med SCZ (ns for DPA)	↓
octanoic acid; 2-hydroxyethyl palmitate	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↑
eicosapentaenoic acid	(Ramos-Loyo et al., 2013)	GC	RBCs	paranoid SCZ (N=46, DF ≥ 2 weeks) v HC (N=40)	↓
linoleic acid	(Khan et al., 2002)	GC- FID	RBCs	FE DN SCZ (SCZ & SFD, N=22) v HC (N=16); chronic med SCZ (N=30) v HC; FE DN SCZ v chronic med SCZ	↓
nervonic acid	(Khan et al., 2002)	GC- FID	RBCs	chronic med SCZ (N=30) v HC (N=22); chronic med SCZ v FE DN SCZ (SCZ & SFD; N=22)	↓
nonanoic acid	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN)	↓
Steroids and steroid derivatives					
20α-Dihydroprogesterone; pregnanolone; Isopregnanolone; epietiocholanolone; etiocholanolone; pregnenolone	(Bicikova et al., 2013)	GC-MS	serum	female FE DN SCZ (N=8) v HC (N=25)	↓

conjugated 5β-Androstane-3β, 17β-diol; etiocholanolone; conjugated 5α-Pregnane-3β, 20α-diol; pregnenolone; conjugated epietiocholanolone	(Bicikova et al., 2013)	GC-MS	serum	male FE DN SCZ (N=13) v male HC (N=22)	↓
androstenediol; androsterone; epiandrosterone	(Bicikova et al., 2013)	GC-MS	serum	male FE DN SCZ (N=13) v male HC (N=22)	↓
conjugated pregnanolone; conjugated Isopregnanolone; androstenedione; conjugated epipregnanolone; conjuagted Pregnenolone sulfate; progesterone; cortisol	(Bicikova et al., 2013)	GC-MS	serum	male FE DN SCZ (N=13) v male HC (N=22)	↑
conjugated androstenediol; 5α-dihydroprogesterone; conjugated Isopregnanolone; DHEAS; conjugated 5α-Androstane-3α, 17β-diol; conjugated 5α-androstane-3β, 17β-diol; conjuagted pregnenolone sulfate; progesterone; testosterone; 20α-dihydropregnenolone; 5α, 20α-tetrahydroprogesterone	(Bicikova et al., 2013)	GC-MS	serum	female FE DN SCZ (N=8) v HC (N=25)	↑
cholesterol	(Al Awam et al., 2015)	GC-MS	serum	med SCZ (N=26) v HC (N=26)	↓
cholesterol	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↑
HDL cholesterol	(Solberg et al., 2015)	GC	serum	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF) v HC (N=51)	↓
cortisol awakening response (CAR)	(Labad et al., 2015)	assay	saliva	ARMS-P (N=10) v HC (N=44); ARMS-P v ARMS-NP (N=29)	↓ at awakening with greater ↑ after 30 mins
cortisol	(Mondelli et al., 2015)	ELISA	saliva	FE psychosis (N=68; 37 SCZ/SZA, 22 SZA/affective psychosis, 7 PD NOS, 2 delusional disorder; 7 DN, 61 med) v HC (N=57)	↓
cortisol	(Schwarz et al., 2012)	immunoassay	serum	DN paranoid SCZ (N=71) v HC (N=59)	↑
pregnanediol	(Cai et al., 2012)	UPLC-MS/MS	urine	FE DN SCZ (N=11) v HC (N=11)	↑
Other lipids and lipid-like molecules					
PC (16:0/18:2)	(Cai et al., 2012)	UPLC-MS/MS	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
PC ae C38:6	(He et al., 2012)	FIA-MS	plasma	SCZ (N=52 DF, N=213 med) v HC (N=216)	↓
PE	(Kaddurah-Daouk et al., 2007)	HPLC and GC	plasma	SCZ (SCZ, SZA & SFD; N=27; DF ≥ 3 weeks) v HC (N=16)	↓
PE	(Ryazantseva et al., 2002)	TLC	RBCs	paranoid SCZ (N=38) v HC (N=45); Scz in remission (N=20) v SCZ in exacerbation phase (N=18)	↓
PC	(Ryazantseva et al., 2002)	TLC	RBCs	paranoid SCZ during exacerbation phase (N=18) v HC (N=45); SCZ in exacerbation v SCZ in remission phase (N=20)	↓

LPC	(Ryazantseva et al., 2002)	TLC	RBCs	paranoid SCZ (N=38) v HC (N=45)	↑
LPC(16:0); LPC(18:0); LPC(18:1); LPC(18:2)	(Cai et al., 2012)	UPLC-MS/MS	plasma	FE DN SCZ (N=11) v HC (N=11)	↑
LPC(16:0); LPC(18:0); LPC(20:3)	(Oresic et al., 2012)	UPLC/TOFMS	serum	SCZ twins (N=19 (15 med), 7 MZ) v unaffected co-twins (N=19); SCZ v HC twins (N=34, 20 MZ)	↓
TG(52:2); SM(d18:1/18:0)	(Oresic et al., 2012)	UPLC/TOFMS	serum	SCZ twins (N=19 (15 med), 7 MZ) v unaffected co-twins (N=19)	↑
MDA	(Ryazantseva et al., 2002)	TLC	RBCs	paranoid SCZ (N=38) v HC (N=45)	↑
MDA	(Kuloglu et al., 2002)	colorimetric assay	plasma	SCZ (N=25) v HC (N=20)	↑
glycerol 3-phosphate	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20); FE SCZ v DF MD (N=20)	↓
perillic acid	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN)	↓
malate	(Yang et al., 2013)	GC-TOFMS	serum	SCZ (N=62; DF ≥ 2 weeks) v HC (N=62)	↑
15-keto-13,14-dihydro-PGE2	(Mathe et al., 1986)	radioimmunoassay	plasma	SCZ twins (N=8; 7 med) + co-twins (N=8) v HC twins (N=16)	↓
Clusters					
LC4 Short chain saturated TGs	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
LC5 Mainly unidentified, includes short odd-chain TG	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
LC6 Odd-chain TGs, mainly saturated or monounsaturated	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
LC7 Mainly odd-chain TGs, longer fatty acids than LC5 and LC6	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
LC8 Medium- and long-chain TGs	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
LC9 Longer-chain, SFA- and MUFA-containing TGs	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
MC2 ketone bodies, free fatty acids	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↓
Tn6 (total n6 fatty acids)	(Arvindakshan et al., 2003)	GC	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45); DN SCZ v med SCZ (N=32)	↓
Tn3 (total n3 fatty acids)	(Arvindakshan et al., 2003)	GC	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45); DN SCZ v med SCZ (N=32)	↓

TSFA (total saturated fatty acids)	(Arvindakshan et al., 2003)	GC	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45); med SCZ (N=32) v HC	↑
Tn7 (total n7 fatty acids)	(Arvindakshan et al., 2003)	GC	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45); med SCZ (N=32) v HC; DN SCZ v med SCZ	↑
total PUFA (Tn6 + Tn3+ Tn7+ Tn9)	(Arvindakshan et al., 2003)	GC	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45); DN SCZ v med SCZ	↓
TBARS	(Arvindakshan et al., 2003)	lipid peroxidation assay	RBCs	DN SCZ (SCZ, SZA & SFD; N=20) v HC (N= 45)	↑
TBARS	(Khan et al., 2002)	colorimetric assay	RBCs	FE DN SCZ (SCZ & SFD, N=22) v HC (N=16); chronic med SCZ (N=30) v HC	↑
lipid peroxidation metabolites	(Ramos-Loyo et al., 2013)	lipid peroxidation assay	serum	paranoid SCZ (N=46, DF ≥ 2 weeks) v HC (N=40)	↑
lipid (1.58ppm)	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
UFA (unsaturated fatty acids; 5.26-5.30ppm)	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
VLDL (very low density lipoproteins; 0.88-0.92 ppm; 1.28-1.32 ppm)	(Tsang et al., 2006)	^{1}H NMR	plasma	Female med SCZ affected MZ twins (N=8) v unaffected co-twins (N=8); Female med SCZ affected MZ twins v HC twins (N=10)	↑
LDL (low density lipoproteins; 0.84-0.88 ppm; 1.24-1.28 ppm)	(Tsang et al., 2006)	^{1}H NMR	plasma	Female med SCZ affected MZ twins (N=8) v unaffected co-twins (N=8); Female med SCZ affected MZ twins v HC twins (N=10); female unaffected co-twins v HC twins	↑
LDL (low density lipoproteins; 0.82-0.86ppm)	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
VLDL/LDL (low and very low density lipoproteins; 1.30-1.34ppm)	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
HDL (high density lipoproteins; 1.18-1.22ppm)	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
VLDL (very low density lipoproteins; 1.26ppm)	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
PCn3 (n3 PUFAs in the phosphatidylcholine lipid class)	(McEvoy et al., 2013)	GC-FID	plasma	FE DN SCZ (SCZ & SZA; N=20) v HC (N=29); FE DN SCZ v recurrent episode SCZ (SCZ & SZA; N=20)	↓
PEn3 (n3 PUFAs in the phosphatidylethanolamine lipid class)	(McEvoy et al., 2013)	GC-FID	plasma	FE DN SCZ (SCZ & SZA; N=20) v HC (N=29); FE DN SCZ v recurrent episode SCZ (SCZ & SZA; N=20)	↓
triglycerides	(Solberg et al., 2015)	assay	serum	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF) v HC (N=51)	↑
LC5 (abundant triglycerides)	(Oresic et al., 2012)	UPLC/TOFMS	serum	SCZ twins (N=19 (15 med), 7 MZ) v unaffected co-twins (N=19)	↑

DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; DHEAS = dehydroepiandrosterone sulfate; PC = phosphatidylcholine; PE = phosphatidylethaolamine; LPC = lysophosphatidylcholine; MDA = malondialdehyde; TG = triglycerides; n3/6/7/9 = omega 3/6/7/9; UFA = unsaturated fatty acids; PUFA = poly-unsaturated fatty acids; TBARS = thiobarbituric acid reactive substances ; LDL = low density lipoprotein; VLDL = very low density lipoprotein; HDL = high density lipoprotein; GC = gas chromatography; LC =liquid chromatography; MS = mass spectrometry; 1H NMR = proton nuclear magnetic resonance spectroscopy; TOFMS = time-of-flight MS; HPLC = high performance liquid chromatography; GC-FID = GC with flame ionisation detector; CE = capillary electrophoresis; HPLC = High-performance liquid chromatography; UPLC-MS/MS = ultra-performance liquid chromatography tandem mass spectrometry; TLC - thin layer chromatography; RBCs = red blood cells; PBMCs = peripheral blood mononuclear cells; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; HC = healthy control subjects; DN = drug naïve; DF = drug-free; med = taking medication; FE = first episode; PD NOS = psychotic disorder not otherwise specified; ARMS-P = at-risk mental state subjects who transitioned to psychosis; ARMS-NP = at-risk mental state subjects who did not transition to psychosis at 1 year follow up

Table 2: Carbohydrates, organic acids & their derivatives found at abnormal levels in subjects with schizophrenia

Metabolite	Reference	Platform	Biofluid	Subjects	difference (SCZ v control)
Amino acids					
Serine; 5-Oxoproline (pyroglutamic acid); Glutamate; 2-Aminobutyrate; aspartate; Phenylalanine	(Yang et al., 2013)	GC-TOFMS	serum	SCZ (N=62; DF ≥ 2 weeks) v HC (N=62)	↑
Serine	(Waziri et al., 1983)	GC	plasma	SCZ (N=14) v non-psychotic patients (N=12)	↑
D-Serine	(Fukushima et al., 2014)	HPLC-FLD	serum	med SCZ (N=25) v HC (N=27)	↓
Cystine	(Yang et al., 2013)	GC-TOFMS	serum	SCZ (N=62; DF ≥ 2 weeks) v HC (N=62)	↓
Cystine; Pyroglutamic acid; Glutamate; 2-Aminobutyric acid; isoleucine; Valine; Pipecolinic acid	(Yang et al., 2013)	GC-TOFMS	urine	SCZ (N=51, DF ≥ 2 weeks) v HC (N=51)	↑
Pipecolinic acid (2-piperidinecarboxylic acid)	(Al Awam et al., 2015)	GC-MS	serum	med SCZ (N=26) v HC (N=26)	↑
serine/cysteine ratio	(Waziri et al., 1983)	GC	plasma	SCZ (N=14) v non-psychotic patients (N=12)	↑
pyroglutamic acid; creatinine; valine	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↓
1-oxo-proline	(Al Awam et al., 2015)	GC-MS	serum	med SCZ (N=26) v HC (N=26)	↓
2-aminoadipic acid; glycocyamine	(Yang et al., 2013)	GC-TOFMS	urine	SCZ (N=51, DF ≥ 2 weeks) v HC (N=51)	↓
betaine	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN)	↓
creatine	(Cai et al., 2012)	^{1}H NMR	urine	FE DN SCZ (N=11) v HC (N=11)	↓
creatine	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN)	↑
creatinine	(Karoum et al., 1987)	mass fragmentography	urine	SCZ (N=20; DF ≥ 2 weeks) v HC (N=16)	↓
creatinine	(Cai et al., 2012)	UPLC-MS/MS; ^{1}H NMR	urine	FE DN SCZ (N=11) v HC (N=11)	↓
Glutamate	(Fukushima et al., 2014)	HPLC-FLD	serum	med SCZ (N=25) v HC (N=27)	↑

glutamate	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14)	↑
γ-glutamylcysteine	(Fukushima et al., 2014)	HPLC-FLD	serum	med SCZ (N=25) v HC (N=27)	↓
glutathione (GSH)	(Ballesteros et al., 2013)	assay	whole blood	med SCZ (N=29) v HC (N=25)	↓
glutathione; tyrosine; threonine	(Fukushima et al., 2014)	HPLC-FLD	serum	med SCZ (N=25) v HC (N=27)	↓
GSSG	(Ballesteros et al., 2013)	assay	whole blood	med SCZ (N=29) v HC (N=25)	↑
glycine	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
glycine	(Cai et al., 2012)	^{1}H NMR	plasma; urine	FE DN SCZ (N=11) v HC (N=11)	↑
alanine; isoleucine; lysine	(Bjerkenstedt et al., 1985)	LC	plasma	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↑
alanine	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↑
arginine; histidine	(He et al., 2012)	FIA-MS	plasma	SCZ (N=52 DF, N=213 med) v HC (N=216)	↓
aspartic acid; homoserine	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↑
aspartate	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
glutamine	(He et al., 2012)	FIA-MS	plasma	SCZ (N=52 DF, N=213 med) v HC (N=216)	↓
glutamine; histidine	(Bjerkenstedt et al., 1985)	LC	plasma	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↓
leucine; phenylalanine	(Bjerkenstedt et al., 1985)	LC	plasma	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↑
methionine; valine	(Bjerkenstedt et al., 1985)	LC	plasma	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↑
tryptophan	(Krause et al., 2013)	UPLC	PBMCs	SCZ (N=12; med & DF) v HC (N=24)	↓
tryptophan	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
tryptophan	(Kim et al., 2009)	HPLC	plasma	SCZ (N=71; 38 DN, 33 DF ≥ 4 months) v HC (N=174)	↓
L -tryptophan	(Fukushima et al., 2014)	HPLC-MS	serum	med SCZ (N=25) v HC (N=27)	↑
valine	(Cai et al., 2012)	^{1}H NMR	urine	FE DN SCZ (N=11) v HC (N=11)	↑

N-acetylaspartate	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
ornithine	(He et al., 2012)	FIA-MS	plasma	SCZ (N=52 DF, N=213 med) v HC (N=216)	↑
Other organic acids and derivatives					
2-Oxoglutarate; citrate; lactate; pyruvate; glycerate; myo-inositol	(Yang et al., 2013)	GC-TOFMS	serum	SCZ (N=62; DF ≥ 2 weeks) v HC (N=62)	↑
α-KG; citrate; 1,3-Bisphosphoglycerate	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
α-KG; citrate; acetoacetate	(Cai et al., 2012)	^{1}H NMR	urine; plasma	FE DN SCZ (N=11) v HC (N=11)	↓
cis-aconitic acid	(Yang et al., 2013)	GC-TOFMS	urine	SCZ (N=51, DF ≥ 2 weeks) v HC (N=51)	↑
citrate; lactate	(Yang et al., 2013)	^{1}H NMR	urine	SCZ (N=41 DF ≥ 2 weeks) v HC (N=41)	↓
glucose	(Yang et al., 2013)	^{1}H NMR	urine	SCZ (N=41 DF ≥ 2 weeks) v HC (N=41)	↑
citric acid	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20); FE SCZ v DF MD (N=20)	↓
D-lactate	(Fukushima et al., 2014)	HPLC-FLD	serum	med SCZ (N=25) v HC (N=27)	↑
lactate; glucose; glucuronic acid; glycerol; erythrose; myo-inositol; lactobionic acid	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↑
lactate	(Liu et al., 2015)	GC-MS	PBMCs	Test set: SCZ (N=20; 6 med) v HC (N=20)	↓
lactate	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↑
hydroxyacetic acid; 2,3-dihydroxybutanoic acid	(Yang et al., 2013)	GC-TOFMS	urine	SCZ (N=51, DF ≥ 2 weeks) v HC (N=51)	↓
pyruvate	(Liu et al., 2015)	GC-MS	PBMCs	Test set: SCZ (N=20; 6 med) v HC (N=20)	↑
glycerate 3-phosphate	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v DF MD (N=20)	↑
fructose	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20)	↑
glucose	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20)	↑
glucose	(Cai et al., 2012)	^{1}H NMR	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
glucose	(Cai et al., 2012)	^{1}H NMR	Urine	FE DN SCZ (N=11) v HC (N=11)	↑

glyceraldehyde-3-phosphate; dihydroxyacetone phosphate	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20)	↓
ribose 5-phosphate	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35)	↑
gluconic acid	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14)	↑
glucose 6-phosphate; fructose 6-phosphate	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20); FE SCZ v DF MD (N=20)	↑
glycerol	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↑
maltose; inositol; sorbitol; methyl phosphate	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↓
galactose oxime	(Al Awam et al., 2015)	GC-MS	serum	med SCZ (N=26) v HC (N=26)	↓
fumaric acid	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↓
succinic acid	(Liu et al., 2015)	GC-MS	PBMCs	Training set: FE DN SCZ (N=35) v HC (N=35); FE DN SCZ v DF MD (N=35) Test set: SCZ (N=20; 6 med) v HC (N=20)	↑
taurine	(Bjerkenstedt et al., 1985)	LC	plasma	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↑
taurine	(Cai et al., 2012)	^{1}H NMR	Urine	FE DN SCZ (N=11) v HC (N=11)	↓
Clusters					
MC3 (Branched chain amino acids and other amino acids, e.g. isoleucine, phenylalanine, tyrosine, ornithine, serine, methionine, threonine)	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑
MC5 (Amino acids, organic acids, e.g. Proline, glutamic acid, α-ketoglutaric acid, pyruvic acid, alanine, lactic acid, α-hydroxybutyrate)	(Oresic et al., 2011)	UPLC-MS and GC-TOFMS	serum	SCZ (N=45; 34 med) v HC (N=45)	↑

α-KG = α-ketoglutarate ; GC = gas chromatography; TOF-MS = time-of-flight mass spectrometry; ^{1}H NMR = proton nuclear magnetic resonance spectroscopy; UPLC-MS/MS = ultra-performance liquid chromatography tandem mass-spectrometry; HPLC = high-performance liquid chromatography; LC = liquid chromatography; FIA-MS = flow injection analysis MS; CE = capillary electrophoresis; PBMCs = peripheral blood mononuclear cells; PD NOS = psychotic disorder not otherwise specified; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; HC = healthy control subjects; DN = drug naïve; DF = drug-free; med = taking medication; FE = first episode

Table 3: Other metabolites found at abnormal levels in subjects with schizophrenia

Metabolite	Reference	Platform	Biofluid	Subjects	Difference (SCZ v control)
adrenaline; noradrenaline	(Fryar-Williams and Strobel, 2015)	MS	urine	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	↑
MHPG	(Pickar et al., 1990)	HPLC-ECD	CSF	SCZ (N=22; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks) v HC (N=33)	↑
MHPG	(Bjerkenstedt et al., 1985)	mass fragmentography	CSF	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↑
MHPG	(Zumarraga et al., 2010)	HPLC and coulombimetric detection	plasma	SCZ (N=44; DF ≥ 8 days) v HC (N=96); SCZ v BP (N=71; DF ≥ 8 days)	↑
dopamine	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↓
dopamine	(Fryar-Williams and Strobel, 2015)	MS	urine	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	↑
dopamine	(Karoum et al., 1987)	mass fragmentography	urine (24h mean)	SCZ (N=20; DF ≥ 2 weeks) v HC (N=16)	↓
HVA	(Bjerkenstedt et al., 1985)	mass fragmentography	CSF	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	↓
HVA	(Sedvall and Wode-Helgodt, 1980)	mass fragmentograpy	CSF	SCZ with family history (N=11) v SCZ without (N=25)	↑
HVA	(Peters, 1979)	probenecid technique	CSF	paranoid SCZ (N=8; patients also have LTL epilepsy) v controls (N=8; with LTL epilepsy)	↓
5-HT	(Fukushima et al., 2014)	HPLC-ECD	serum	med SCZ (N=25) v HC (N=27)	↓
IAA	(Domino et al., 1979)	GC-MS	urine	male chronic SCZ (N=7; DF ≥ 2 years) v male HC (N=7)	↑
NA5HT	(Yao et al., 2010)	LCECA	plasma	FE DN SCZ (N=25) v HC (N=30)	↑
5-HIAA	(Gattaz et al., 1982)	LC	CSF	paranoid SCZ (N=28; 15 med) v controls (N=16; symptomology requiring a lumbar puncture e.g. headaches, dizziness)	↓
5-HIAA	(Sedvall and Wode-Helgodt, 1980)	mass fragmentograpy	CSF	SCZ with family history (N=11) v SCZ without (N=25)	↑ and (↑↓)
NA5HT/tryptophan; melatonin/5-HT	(Yao et al., 2010)	LCECA	plasma	FE DN SCZ (N=25) v HC (N=30)	↑
5-HT/tryptophan; 5-HT/5-HTP; NA5HT/5-HTP	(Yao et al., 2010)	LCECA	plasma	FE DN SCZ (N=25) v HC (N=30)	↑
melatonin/N-acetylserotonin	(Yao et al., 2010)	LCECA	plasma	FE DN SCZ (N=25) v HC (N=30)	↓
kynurenine	(Krause et al., 2013)	UPLC	PBMCs	SCZ (N=12; med & DF) v HC (N=24)	↓
L-kynurenine	(Fukushima et al., 2014)	HPLC-MS	serum	med SCZ (N=25) v HC (N=27)	↑

KYNA	(Nilsson-Todd et al., 2007)	HPLC-FLD	CSF	male SCZ (N=53; 4 FE DN, 19 DF ≥ 20 days; 30 med) v male HC (N=43); male DN SCZ (N=4) v male HC	↑
uric acid	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
uric acid	(Cai et al., 2012)	UPLC-MS/MS	plasma	FE DN SCZ (N=11) v HC (N=11)	↓
uric acid	(Cai et al., 2012)	UPLC-MS/MS	urine	FE DN SCZ (N=11) v HC (N=11)	↑
allantoin	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↑
3-Indolebutyrate fragments	(Cai et al., 2012)	UPLC-MS/MS	plasma	FE DN SCZ (N=11) v HC (N=11)	↑
benzoic acid; hydroxylamine	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↑
benzoic acid; Imidazolelactic acid; cyclohexylamine	(Koike et al., 2014)	CE-TOFMS	plasma	1st set: FE SCZ (N= 18; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS) v HC (N=14) 2nd set (only benzoic acid detected): FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN)	↓
hippurate	(Cai et al., 2012)	UPLC-MS/MS; ^{1}H NMR	urine	FE DN SCZ (N=11) v HC (N=11)	↓
Catechol	(Yang et al., 2013)	GC-TOFMS	urine	SCZ (N=51, DF ≥ 2 weeks) v HC (N=51)	↓
NO_x	(Nakano et al., 2010)	Griess reagent method	plasma	SCZ (N=30 DF ≥ 1 week) v HC (N=30)	↓
NO_x	(Lee and Kim, 2008)	Griess reagent method	plasma	SCZ (N=55; 31 DN, 24 DF ≥ 4 weeks) v HC (N=55)	↓
NO_x	(Taneli et al., 2004)	Griess reagent method	serum	SCZ (N=20; DF ≥ 2 weeks) v HC (N=20)	↑
folate	(Fryar-Williams and Strobel, 2015)	assay	RBCs	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	↓
vitamin B6	(Fryar-Williams and Strobel, 2015)	HPLC	whole blood	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	↓
vitamin D	(Fryar-Williams and Strobel, 2015)	assay	whole blood	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	↓
vitamin E	(Scottish Schizophrenia Research Group, 2000)	HPLC	serum	FE DN SCZ (N=30; 21 SCZ, 9 SFD) v HC (N=30)	↓
tocopherol-α; tocopherol-γ	(Liu et al., 2014)	GC-MS	PBMCs	SCZ (N=45; 19 FE DN, 26 med) v HC (N=50)	↓
tocopherol- γ	(Xuan et al., 2011)	GC-MS	serum	DF SCZ (N=18) v HC (N=18)	↓
free copper to zinc ratio	(Fryar-Williams and Strobel, 2015)	serum Copper - FAAS RBC Zinc - ICP-MS	serum/ RBCs	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	↑
biopyrrins (bilirubin oxidative metabolites)	(Yasukawa et al., 2007)	ELISA	urine		↑
tele-methylhistamine	(Prell et al., 1995)	GC-MS	CSF	SCZ (N=36; med & DF) v controls (N=8; 3 healthy, 1 depression, 1 bipolar, 2 atypical psychosis, 1 personality disorder & anorexia nervosa)	↑
TMAO	(Cai et al., 2012)	^{1}H NMR	Urine	FE DN SCZ (N=11) v HC (N=11)	↓

6-deoxy-mannofuranose	(Al Awam et al., 2015)	GC-MS	serum	med SCZ (N=26) v HC (N=26)	↓
Clusters					
sum dopamine (dopamine, DOPAC, HVA)	(Karoum et al., 1987)	mass fragmentography	urine	SCZ (N=20; DF ≥ 2 weeks) v HC (N=16)	↓
sum dopamine/sum norepinephrine (sum dopamine = dopamine + DOPAC + HVA); sum norepinephrine = norepinephrine + normetanephrine + MHPG + vanillylmandelic acid)	(Karoum et al., 1987)	mass fragmentography	urine	SCZ (N=20; DF ≥ 2 weeks) v HC (N=16)	↓
conjugated dienes	(Ryazantseva et al., 2002)		RBCs	paranoid SCZ (N=38) v HC (N=45); SCZ in exacerbation (N=18) v SCZ in remission phase (N=20)	↑

MHPG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid; IAA = indoleacetic acid; 5-HIAA = 5-Hydroxyindoleacetic acid; KYNA = kynurenic acid; 5-HT = 5-hydroxy tryptamine (serotonin); NA5HT = N-acetylserotonin; 5-HTP = 5-hydroxy tryptophan; NO_x = nitric oxide and metabolites; TMAO = trimethylamine-N-oxide; DOPAC = 3, 4-Dihydroxyphenylacetic acid; MS = mass spectrometry; HPLC = high-performance liquid chromatography; HPLC-ECD = HPLC with electrochemical detection; GC = gas chromatography; UPLC = ultra-performance liquid chromatography; LCECA = LC with electrochemical coulometric array detection; HPLC-FLD = HPLC with fluorescence detector; UPLC-MS/MS = UPLC tandem mass-spectrometry; CE-TOFMS = capillary electrophoresis time-of-flight MS; LCECA = LC with electrochemical coulometric array detection; ^{1}H NMR = proton nuclear magnetic resonance spectroscopy; ELISA = enzyme-linked immunosorbent assay; RBCs = red blood cells; PBMCs = peripheral blood mononuclear cells; CSF = cerebrospinal fluid; LTL = left temporal lobe; PD NOS = psychotic disorder not otherwise specified; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; HC = healthy control subject; BP = bipolar disorder subjects; DN = drug naïve; DF = drug-free; med = taking medication; FE = first episode

Table 4: Reported schizophrenia biomarker panels

Panel name	Metabolites	Reference	Platform	Biofluid	Difference (SCZ v control)	Subjects	AUC
Catecholamine domain	dopamine	(Fryar-Williams and Strobel, 2015)	MS	urine	↑	SCZ (N=67 SCZ & SZA; med & DF) v HC (N=67)	0.859
	noradrenaline		MS	urine	↑		
	adrenaline		MS	urine	↑		
Nutrition-Biochemistry	vitamin B6 activated	(Fryar-Williams and Strobel, 2015)	Whole blood HPLC-FLD	whole blood	↓	SCZ (N=67 SCZ & SZA; med and DF) v HC (N=67)	0.797
	free copper/zinc ratio		serum Copper - FAAS RBC Zinc - ICP-MS	serum/ RBCs	↑		
	folate		assay	RBCs	↓		
	vitamin D		assay	whole blood	↓		
	B12		assay	serum	↑		
PBMC biomarkers	pyroglutamic acid	(Liu et al., 2014)	GC-MS	PBMCs	↓	SCZ vs HC Training set: N=45 SCZ (19 FE DN, 26 med) ; N=50 HC Test set 1: N=24 SCZ all med; N=35 HC	0.82 (training set) 0.71 (test set 1)
	Sorbitol		GC-MS	PBMCs	↓		
	Tocopherol-α		GC-MS	PBMCs	↓		
serum biomarkers	glycerate	(Yang et al., 2013)	GC-TOFMS	serum	↑	SCZ vs HC Training set: N=62 SCZ (DF ≥ 2 weeks, some FE); N=62 HC Test set: N= 50 SCZ (DF ≥ 2 weeks, some FE); N=48 HC	0.945 (training set); 0.895 (test set)
	eicosenoic acid		GC-TOFMS	serum	↑		
	β-hydroxybutyrate		GC-TOFMS	serum	↑		
	pyruvate		GC-TOFMS	serum	↑		
	cystine		GC-TOFMS	serum	↓		
serum biomarkers + urine β-hydroxybutyrate	glycerate	(Yang et al., 2013)	GC-TOFMS	serum	↑	SCZ vs HC Training set: N=62 SCZ (DF ≥ 2 weeks, some FE); N=62 HC Test set: N= 50 SCZ DF ≥ 2 weeks, some FE); N=48 HC	1 (in both training and test sets)
	eicosenoic acid		GC-TOFMS	serum	↑		
	β -hydroxybutyrate		GC-TOFMS	serum	↑		
	pyruvate		GC-TOFMS	serum	↑		
	cystine		GC-TOFMS	serum	↓		

	β -hydroxybutyrate		GC-TOFMS	urine	↑		
plasma biomarkers	arginine	(He et al., 2012)	FIA-MS	plasma	↓	SCZ (N=52 DF, N=213 med) v HC (N=216)	0.805
	glutamine		FIA-MS	plasma	↓		
	histidine		FIA-MS	plasma	↓		
	ornithine		FIA-MS	plasma	↑		
	PCaeC38:6		FIA-MS	plasma	↓		
serum biomarkers	citrate	(Xuan et al., 2011)	GC-MS	serum	↓	DF SCZ (N=18) v HC (N=18)	0.958
	palmitic acid		GC-MS	serum	↓		
	myo-inositol		GC-MS	serum	↑		
	allantoin		GC-MS	serum	↑		

PC = phosphatidylcholine; MS = mass spectrometry; HPLC-FLD = high-performance liquid chromatography with fluorescence detector; FAAS = flame Atomic Absorption spectrophotometry; ICP-MS = inductively coupled plasma mass spectroscopy; GC-MS = gas chromatography mass spectrometry; GC-TOFMS = gas chromatography time of flight mass spectrometry; FIA-MS = flow injection analysis MS; SCZ = schizophrenia subjects; SZA = schizoaffective disorder; HC = healthy control subjects; DN = drug naïve; DF = drug-free; med = on medication (antipsychotics); FE = first episode

Table 5: Correlations between metabolite levels and symptom severity in patients with schizophrenia

Metabolite	Reference	Platform	Biofluid	Correlation	R Coefficient	Subjects
Lipids and lipid-like molecules						
triglyceride	(Solberg et al., 2015)	assay	serum	GAF-F; GAF-S; PANSS positive	r= -0.32 (GAF-F); r= -0.48 (GAF-S); r=0.28 (PANSS positive)	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF)

PUFA	(Solberg et al., 2015)	GC	RBCs	PANSS negative scores	r=0.32	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF)
LCPUFA	(Solberg et al., 2015)	GC	RBCs	PANSS-negative; PANSS total; GAF-S; GAF-F	r= 0.52 (PANSS-negative) r= 0.31 (PANSS total) r= -0.32 (GAF-S) r= -0.029 (GAF-F)	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF)
LDL (1.24-1.28ppm); VLDL (1.28-1.32 ppm)	(Tsang et al., 2006)	^{1}H NMR	plasma	GAF score (negative correlation)	r^2 =0.62 (LDL) r^2 =0.54 (VLDL)	Female med SCZ affected MZ twins (N=8); unaffected co-twins (N=8); HC twins (N=10)
HDL cholesterol	(Solberg et al., 2015)	GC	serum	GAF-F	r=0.28	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF)
HDL cholesterol; LDL cholesterol; total cholesterol	(Solberg et al., 2015)	GC	serum	GAF-S	r= 0.37 (HDL cholesterol) r= -0.28 (LDL cholesterol) r= -0.30 (total cholesterol)	SCZ (N=44 SCZ; N=11 SZA; 44 med, 11 DF)
CAR	(Mondelli et al., 2015)	ELISA	saliva	clinical improvement	r= 0.50	FE psychosis (N=68; 37 SCZ/SZA, 22 SZA/affective psychosis, 7 PD NOS, 2 delusional disorder; 7 DN, 61 med)
pregnanediol (change in)	(Cai et al., 2012)	UPLC-MS/MS	urine	improvement in PANSS activation symptom cluster sub-scores	r= -0.832	FE DN SCZ (N=11)
citrate (change in)	(Cai et al., 2012)	^{1}H NMR	urine	changes in PANSS depression subscores	r = −0.842	FE DN SCZ (N=11)
α-KG (change in)	(Cai et al., 2012)	^{1}H NMR	urine	changes in PANSS anergia subcluster scores	r = −0.836	FE DN SCZ (N=11)
α-KG at baseline; week 3; and week 6	(Cai et al., 2012)	^{1}H NMR	urine	PANSS negative scores	r = −0.861 (baseline) r = −0.884 (week 3) r = −0.843 (week 6)	FE DN SCZ (N=11) put on 6 week course of risperidone
Organic acids						
serine/cysteine	(Waziri et al., 1983)	GC	plasma	Psychosis score	r = 0.61	SCZ (N=14); mania (N=24); other psychoses (N=13); paranoid disorder (N=7); depression (N=14); non-psychotic (N=12)
tryptophan	(Krause et al., 2013)	UPLC	PBMCs	PANSS negative scores	r = -0.451 to -0.726	SCZ (N=12; med & DF)

tryptophan	(Kim et al., 2009)	HPLC	plasma	PANSS positive symptoms score	r = -0.343	SCZ (N=71; 38 DN, 33 DF ≥ 4 months)
Other metabolites						
tele-methylhistamine	(Prell et al., 1995)	GC-MS	CSF	Psychiatric Symptom Assessment Scale positive scores	r = 0.45	SCZ (N=36; med & DF)
MHPG	(Gattaz et al., 1982)	LC	CSF	BPRS "activation" score (due to items "tension" and "excitement")	r = 0.37 (activation score) r = 0.42 (tension item) r = 0 27 (excitement item)	paranoid SCZ (N=28; 15 med)
MHPG	(Pickar et al., 1990)	HPLC-ECD	plasma	BPRS negative scores	r= 0.48	SCZ (N=22; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks)
HVA (change baseline to 6W clozapine)	(Jacobsen et al., 1997)	GC-MS	CSF	SAPS (change baseline to 6W clozapine)	r = 0.63	SCZ (N=8; age 12-18; DF ≥ 2 weeks at baseline)
HVA	(Pickar et al., 1990)	HPLC-ECD	CSF	BPRS total score	r = -0.52	SCZ (N=22; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks)
HVA	(Pickar et al., 1990)	HPLC-ECD	CSF	BPRS positive scores	r = -0.50	SCZ (N=22; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks)
HVA	(Gattaz et al., 1982)	LC	CSF	BPRS item "hostility"	r = 0.39	paranoid SCZ (N=28; 15 med)
HVA (change in)	(Miura et al., 2014)	HPLC-ECD	plasma	change in PANSS total scores	r = 0.536	med SCZ (N=22; switched to course of aripiprazole or blonanserin)
HVA (change in)	(Miura et al., 2014)	HPLC-ECD	plasma	change in PANSS positive scores	r = 0.572	med SCZ (N=22; switched to course of aripiprazole or blonanserin)
HVA	(Scheepers et al., 2001)	LC	CSF	PANSS negative scores	r = -0.591	male med SCZ (N=23; 15 paranoid, 4 disorganised, 1 undifferentiated, 1 SFD, 2 SZA)
5-HIAA	(Markianos et al., 1992)	HPLC-ECD	plasma	BPRS total score	r = 0.4651	male DN SCZ (N=20; 8 paranoid, 6 disorganised, 4 undifferentiated, 2 catatonic subtype)
5-HIAA	(Gattaz et al., 1982)	LC	CSF	BPRS item "grandiosity"	r = 0.35	paranoid SCZ (N=28; 15 med)
5-HIAA	(Gattaz et al., 1982)	LC	CSF	BPRS item "hallucinatory behaviour"	r = 0.36	paranoid SCZ (N=28; 15 med)

5-HIAA	(Gattaz et al., 1982)	LC	CSF	BPRS item "tension"	r = 0.47	paranoid SCZ (N=28; 15 med)
5-HIAA	(Gattaz et al., 1982)	LC	CSF	BPRS item "motor retardation"	r = 0.38	paranoid SCZ (N=28; 15 med)
5-HIAA	(Anand et al., 2002)	HPLC-ECD	CSF	disorganisation dimension on SAPS and SANS (positive correlation)	r^2 = 0.241	DN SCZ (N=37; 26 SCZ, 11 SFD)
5-HIAA	(Anand et al., 2002)	HPLC-ECD	CSF	negative dimension on SAPS and SANS (positive correlation)	r^2 = 0.147	DN SCZ (N=37; 26 SCZ, 11 SFD)
5HIAA/HVA ratio	(Anand et al., 2002)	HPLC-ECD	CSF	disorganisation dimension on SAPS and SANS (positive correlation)	r^2 = 0.109	DN SCZ (N=37; 26 SCZ, 11 SFD)
HVA/5-HIAA (change in)	(Kahn et al., 1993)	HPLC	CSF	BPRS total score	r = -0.60	male SCZ (N=19; 16 SCZ, 3 SZA; DF ≥ 2 weeks)
HVA/5-HIAA (change in)	(Kahn et al., 1993)	HPLC	CSF	change in BPRS factor 4 (tension-excitement)	r = -0.47	male SCZ (N=19; 16 SCZ, 3 SZA; DF ≥ 2 weeks)
kynurenine	(Krause et al., 2013)	UPLC	PBMCs	PANSS positive scores	r = 0.665	SCZ (N=12; med & DF)
NOx (NO and its metabolites)	(Nakano et al., 2010)	Griess reagent method	plasma	PANSS negative scores	r = -0.385	SCZ (N=30 DF ≥ 1 week)
uric acid/guanine ratio	(Yao et al., 2012)	HPLC with LCECA	plasma	GAS (global assessment scale)	r = -0.643	N=25 FE DN SCZ (N=25; SCZ, SFD & SZA)

PUFA = poly-unsaturated fatty acids; LCPUFA – long chain PUFA; LDL = low density lipoprotein; VLDL = very low density lipoprotein; HDL = high density lipoprotein; CAR = cortisol awakening response; α-KG = α-ketoglutarate; MHPG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid; 5-HIAA = 5-Hydroxyindoleacetic acid; NO_x = nitric oxide and metabolites; GC = gas chromatography; ^{1}H NMR = proton nuclear magnetic resonance spectroscopy; ELISA = enzyme-linked immunosorbent assay; UPLC-MS/MS = ultra-performance liquid chromatography tandem mass-spectrometry; HPLC-ECD = HPLC with electrochemical detection; LCECA = LC with electrochemical coulometric array detection; PBMCs = peripheral blood mononuclear cells; CSF = cerebrospinal fluid; PANSS = positive and negative symptoms scale; GAF = global assessment of functioning; GAF-S = GAF symptom scale; GAF-F = GAF functioning scale; BPRS = brief psychiatric rating scale; SAPS = scale for assessment of positive symptoms; SANS = scale for assessment of negative symptoms; GAS = global assessment; PD NOS = psychotic disorder not otherwise specified; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; HC = healthy control subjects; DN = drug naïve; DF = drug-free; med = taking medication; FE = first episode

Supplementary Tables

Table S1: Lipids and lipid-like molecules found at abnormal levels in subjects with schizophrenia

Metabolite	Reference	Biofluid	Difference (SCZ v control)	Subjects	P-value
Fatty acids					
octadecanoic (stearic) acid; eicosenoic acid; linoleate; tetradecanoic acid; oleic acid; hexadecanoic (palmitic) acid; α-hydroxybutyrate; β-hydroxybutyrate; α-hydroxybutyrate	Yang et al. (2013)	serum	↑	SCZ (N=62; 25M; age = 36.9 ± 11.9; DF ≥ 2 weeks, some FE) v HC (N=62; 25M; age = 36.9 ± 9.3)	p <0.04, q <0.04 (stearic acid, linoleate); p <10^{-5}, q <0.01 (eicosenoic acid; tetradecanoic acid); p <0.001, q <0.02 (palmitic acid, oleic acid; α-hydroxybutyrate; β-hydroxybutyrate)
stearic acid; linoleic acid; oleic acid; palmitic acid	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p <0.02 (stearic acid, linoleic acid, oleic acid); p =0.0037 (palmitic acid)
stearic acid; arachidonic acid; linoleic acid; oleic acid; palmitic acid	Schwarz et al. (2008)	RBCs	↓	FE DN SCZ (N=7) v HC (N=20)	p <0.005 (all); q ≤0.002 (stearic; linoleic acid); q=ns (arachidonic acid, oleic acid, palmitic acid)
stearic acid; oleic acid; palmitic acid	Khan et al. (2002)	RBCs	↑	FE DN SCZ (N=22; 18M; age = 22.4 ± 4.1); chronic med SCZ (N=30; 30M; age = 45.9 ± 6.3); HC (N=16; 14M; age = 24 ± 5.6)	p <0.001 (for DN SCZ v HC & chronic SCZ v HC); p <0.001 for chronic SCZ v FE SCZ (only for oleic acid, HC<FE SCZ<chronic SCZ)
suberic acid; 4-Pentenoic acid; α-hydroxybutyrate; β-hydroxybutyrate	Yang et al. (2013)	urine	↑	SCZ (N=51; DF ≥ 2 weeks, some FE) v HC (N=51)	p <0.007; q <0.025
β -hydroxybutyrate	Cai et al. (2012)	plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p= 0.011 (ns after Bonferroni correction)
β-hydroxybutyrate; arachidonic acid; linoleic acid	Fukushima et al. (2014)	serum	↓	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p <0.005 (β-Hydroxybutyrate; arachidonic acid; ns after Bonferroni); p =1.61 x 10^{-5} (linoleic acid; survived Bonferroni)
eicosenoic acid; heptadecanoic acid; oleic acid; pentadecanoic acid	Al Awam et al. (2015)	serum	↓	med SCZ (N=26; 20M; age = 37.3 ± 12.4) v HC (N=26; 20M; age = 37.0 ± 10.7)	p <0.001 (eicosenoic acid); p <0.01 (heptadecanoic acid; pentadecanoic acid); p <0.05 (oleic acid)
arachidonic acid; DHA	Arvindakshan et al. (2003)	RBCs	↓	DN SCZ (SCZ, SZA & SFD; N=20; 12M; age = 29.4 ± 9.7) v HC (N= 45; 25M; age = 29.2 ± 8.9); DN SCZ v med SCZ (N=32; 21M; age = 31.3 ± 10.3)	p <0.001
arachidonic acid; DHA; DPA	Khan et al. (2002)	RBCs	↓	FE DN SCZ (N=22; 18M; age = 22.4 ± 4.1); chronic med SCZ (N=30; 30M; age = 45.9 ± 6.3); HC (N=16; 14M; age = 24 ± 5.6)	p <0.001 (for both DN SCZ v HC & for chronic SCZ v HC); p <0.001 for FE SCZ v chronic (only for Arachidonic acid and DHA, SCZ FE<chronic <HC)
octanoic acid; 2-hydroxyethyl palmitate	Liu et al. (2014)	PBMCs	↑	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	p =1.39×10^{-3} (octanoic acid); p <0.05 (2-hydroxyethyl palmitate)
eicosapentaenoic acid	Ramos-Loyo et al. (2013)	RBCs	↓	paranoid SCZ (N=46; 21M; DF ≥ 2 weeks; age = 28.4 ± 7.2 (M) & 35.4 ± 9.5 (F)) v HC (N=40; 17M; age = 29.8 ± 4.9 (M) & 34.0 ± 8.5 (F))	p <0.001

linoleic acid	Khan et al. (2002)	RBCs	↓	FE DN SCZ (N=22; 18M; age = 22.4 ± 4.1); chronic med SCZ (N=30; 30M; age = 45.9 ± 6.3); HC (N=16; 14M; age = 24 ± 5.6)	p <0.001 (FE SCZ v HC); p = 0.005 (chronic SCZ v HC); p = 0.017 (FE SCZ v chronic SCZ) FE<chronic<HC
nervonic acid	Khan et al. (2002)	RBCs	↓	FE DN SCZ (N=22; 18M; age = 22.4 ± 4.1); chronic med SCZ (N=30; 30M; age = 45.9 ± 6.3); HC (N=16; 14M; age = 24 ± 5.6)	Only sig for chronic SCZ v HC and FE SCZ v chronic (p <0.001)
nonanoic acid	Koike et al. (2014)	plasma	↓	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN; age = 24.6 ± 7.1) v HC (N=24 HC; 10M; age = 26.1 ± 2.6)	p = 0.025 (1st set); $p < 3 \times 10^{-4}$ (2nd set) (p values for SCZ v HC)
20α-Dihydroprogesterone; pregnanolone; Isopregnanolone; epietiocholanolone; etiocholanolone; pregnenolone	Bicikova et al. (2013)	serum	↓	female FE DN SCZ (N=8; age (median) = 35) v HC (N=25; age (median) = 35)	p <0.001 (all except isopregnanolone & pregnenolone (p <0.01))
conjugated 5β-Androstane-3β, 17β-diol; etiocholanolone; conjugated 5α-Pregnane-3β, 20α-diol; pregnenolone; conjugated epietiocholanolone	Bicikova et al. (2013)	serum	↓	male FE DN SCZ (N=13; age (median) = 31) v male HC (N=22; age (median) = 35)	p <0.001 (all except pregnenolone & conjugated epietiocholanolone (p <0.01))
androstenediol; androsterone; epiandrosterone	Bicikova et al. (2013)	serum	↓	male FE DN SCZ (N=13; age (median) = 31) v male HC (N=22; age (median) = 35)	p <0.05
conjugated pregnanolone; conjugated Isopregnanolone; androstenedione; conjugated epipregnanolone; conjuagted Pregnenolone sulfate; progesterone; cortisol	Bicikova et al. (2013)	serum	↑	male FE DN SCZ (N=13; age (median) = 31) v male HC (N=22; age (median) = 35)	p <0.01 (all except conjugated epipregnanolone & progesterone (p <0.001))
conjugated androstenediol; 5α-dihydroprogesterone; conjugated Isopregnanolone; DHEAS; conjugated 5α-Androstane-3α, 17β-diol; conjugated 5α-androstane-3β, 17β-diol; conjuagted pregnenolone sulfate; progesterone; testosterone; 20α-dihydropregnenolone; 5α, 20α-tetrahydroprogesterone	Bicikova et al. (2013)	serum	↑	female FE DN SCZ (N=8; age (median) = 35) v HC (N=25; age (median) = 35)	p <0.001 (all except conjugated androstenediol & conjugated 5α -Androstane-3β ,17β -diol (p <0.01); DHEAS & 20α-Dihydropregnenolone (p <0.05))
cholesterol	Al Awam et al. (2015)	serum	↓	med SCZ (N=26; 20M; age = 37.3 ± 12.4) v HC (N=26; 20M; age = 37.0 ± 10.7)	p <0.001
cholesterol	Xuan et al. (2011)	serum	↑	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.029
HDL cholesterol	Solberg et al. (2015)	serum	↓	SCZ (N=44 SCZ, N=11 SZA; 44 med, 11 DF; 38M; age = 31.3 ± 5.7) v HC (N=51; 28M; age = 33.0 ± 5.7)	p = 0.02 (unmedicated v HC); p<0.001 (medicated v HC)

cortisol awakening response (CAR)	Labad et al. (2015)	saliva	↓ at awakening with greater ↑ after 30 mins	ARMS-P (N=10; 5M; age = 20.4 ± 3.1) v HC (N=44; 29M; age = 23.2 ± 4.4); ARMS-P v ARMS-NP (N=29; 22M; age = 23.0 ± 4.9)	p = 0.037 (ARMS-P v ARMS-NP); p = 0.017 (ARMS-P v HC)
cortisol	Mondelli et al. (2015)	saliva	↓	FE psychosis (N=68; 46M; 37 SCZ/SZA, 22 SZA/affective psychosis, 7 PD NOS, 2 delusional disorder; 7 DN, 61 med; age = 29 ± 1) v HC (N=57; 36M; age = 27 ± 1)	p = 0.001
cortisol	Schwarz et al. (2012)	serum	↑	DN paranoid SCZ (N=71; 42M; age = 31 ± 10) v HC (N=59; 31M; age = 30 ± 8)	p = 0.003, q=0.036
pregnanediol	Cai et al. (2012)	urine	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.033 (ns after Bonferoni correction)
PC (16:0/18:2)	Cai et al. (2012)	plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.038 (ns after Bonferroni correction)
PC ae C38:6	He et al. (2012)	plasma	↓	SCZ (N=52 DF (29M; age = 39.3 ± 11.2), N=213 med (132 M; age = 36.9 ± 11.7)) v HC (N=216; 112M; age = 38.9 ± 10.6)	p = 0.03
PE	Kaddurah-Daouk et al. (2007)	plasma	↓	SCZ (SCZ, SZA & SFD; N=27; 23M; DF ≥ 3 weeks) v HC (N=16)	p = 0.02
PE	Ryazantseva et al. (2002)	RBCs	↓	paranoid SCZ (N=38; age 21-49) v HC (N=45; age 19-48); SCZ in remission (N=20) v SCZ in exacerbation phase (N=18)	P <0.05
PC	Ryazantseva et al. (2002)	RBCs	↓	paranoid SCZ during exacerbation phase (N=18; age 21-49) v HC (N=45; age 19-48); SCZ in exacerbation v SCZ in remission phase (N=20)	P <0.05
LPC	Ryazantseva et al. (2002)	RBCs	↑	paranoid SCZ (N=38; age 21-49) v HC (N=45; age 19-48)	P <0.05
LPC(16:0); LPC(18:0); LPC(18:1); LPC(18:2)	Cai et al. (2012)	plasma	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p <0.0001 (LPC(16:0)); p <0.01 (others). Only LPC(16:0) sig. after Bonferroni correction
LPC(16:0); LPC(18:0); LPC(20:3)	Oresic et al. (2012)	serum	↓	SCZ twins (N=19; 15 med; 6M; 7 MZ; age = 51 ± 10) v unaffected co-twins (N=19; matched gender); SCZ v HC twins (N=34; 10M; 20 MZ; age = 53.4)	p<0.05
TG(52:2); SM(d18:1/18:0)	Oresic et al. (2012)	serum	↑		p<0.05
MDA	Ryazantseva et al. (2002)	RBCs	↑	paranoid SCZ (N=38; age 21-49) v HC (N=45; age 19-48)	p <0.05
MDA	Kuloglu et al. (2002)	plasma	↑	SCZ (N=25) v HC (N=20)	p <0.05
glycerol 3-phosphate	Liu et al. (2015)	PBMCs	↓	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7)	P <0.001 training set; p = 0.001 test set (SCZ v HC) p <0.001 training set; p = 0.020 test set (SCZ v MD)

				Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	
perillic acid	Koike et al. (2014)	plasma	↓	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN; age = 24.6 ± 7.1) v HC (N=24 HC; 10M; age = 26.1 ± 2.6)	p = 0.018 (1st set); p=0.0040 (2nd set) [SCZ v HC]
malate	Yang et al. (2013)	serum	↑	SCZ (N=62; 25M; age = 36.9 ± 11.9; DF ≥ 2 weeks, some FE) v HC (N=62; 25M; age = 36.9 ± 9.3)	$p = 2.21 \times 10^{-8}$, $q = 1.82 \times 10^{-3}$
15-keto-13,14-dihydro-PGE2	Mathe et al. (1986)	plasma	↓	SCZ twins (N=8; 7 med) + co-twins (N=8) v HC twins (N=16)	p<0.01
Clusters					
LC4: Short chain saturated TGs	Oresic et al. (2011)	serum	↑	SCZ (N=45; 19M; 34 med; age = 53.7 ± 12.9) v HC (N=45; 19M; age = 53.7 ± 12.9)	p = 0.0003
LC5 Mainly unidentified, includes short odd-chain TG	Oresic et al. (2011)	serum	↑		p = 0.045
LC6 Odd-chain TGs, mainly saturated or monounsaturated	Oresic et al. (2011)	serum	↑		p = 0.025
LC7 Mainly odd-chain TGs, longer fatty acids than LC5 and LC6	Oresic et al. (2011)	serum	↑		p = 0.002
LC8 Medium- and long-chain TGs	Oresic et al. (2011)	serum	↑		p = 0.003
LC9 Longer-chain, SFA- and MUFA-containing TGs	Oresic et al. (2011)	serum	↑		p <0.0001
MC2 (ketone bodies, free fatty acids)	Oresic et al. (2011)	serum	↓	SCZ (N=45; 19M; 34 med; age = 53.7 ± 12.9) v HC (N=45; 19M; age = 53.7 ± 12.9); affective psychosis (N=37; 23M; 8 med; age = 54.7 ± 14.8) v HC (N=37; 23M; age = 54.7 ± 14.9)	p = 0.009 (SCZ as predictor); also ↓ in affective psychosis (p = 0.006); and ↑ with AP use (P = 0.016)
Tn6 (total n6 fatty acids)	Arvindakshan et al. (2003)	RBCs	↓	DN SCZ (SCZ, SZA & SFD; N=20; 12M; age = 29.4 ± 9.7) v HC (N= 45; 25M; age = 29.2 ± 8.9); DN SCZ v med SCZ (N=32; 21M; age = 31.3 ± 10.3)	p <0.001
Tn3 (total n3 fatty acids)	Arvindakshan et al. (2003)	RBCs	↓		p <0.001
TSFA (total saturated fatty acids)	Arvindakshan et al. (2003)	RBCs	↑		p <0.001

Tn7 (total n7 fatty acids)	Arvindakshan et al. (2003)	RBCs	↑		p <0.001 (DN SCZ/med SCZ v HC); p = 0.01 (DN SCZ v med SCZ)
total PUFA (Tn6 + Tn3+ Tn7+ Tn9)	Arvindakshan et al. (2003)	RBCs	↓		p <0.001 (DN SCZ v HC); p = 0.01 (DN SCZ v med SCZ)
TBARS (thiobarbituric acid reactive substances)	Arvindakshan et al. (2003)	RBCs	↑		p <0.001
TBARS (thiobarbituric acid reactive substances)	Khan et al. (2002)	RBCs	↑	FE DN SCZ (N=22; 18M; age = 22.4 ± 4.1); chronic med SCZ (N=30; 30M; age = 45.9 ± 6.3); HC (N=16; 14M; age = 24 ± 5.6)	p <0.001 (both FE SCZ v HC and chronic SCZ v HC)
lipid peroxidation metabolites	Ramos-Loyo et al. (2013)	serum	↑	paranoid SCZ (N=46; 21M; DF ≥ 2 weeks; age = 28.4 ± 7.2 (M) & 35.4 ± 9.5 (F)) v HC (N=40; 17M; age = 29.8 ± 4.9 (M) & 34.0 ± 8.5 (F))	p <0.01 (SCZ v HC); p <0.001 (male v female)
lipid (1.58ppm)	Cai et al. (2012)	Plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.009 (ns after Bonferoni correction)
UFA (unsaturated fatty acids; 5.26-5.30ppm)	Cai et al. (2012)	Plasma	↓		p = 0.014 (ns after Bonferroni correction)
VLDL (very low density lipoproteins; 0.88-0.92 ppm; 1.28-1.32 ppm)	Tsang et al. (2006)	plasma	↑	Female med SCZ affected MZ twins (N=8; age = 33.9 ± 6.4) v unaffected co-twins (N=8); Female med SCZ affected MZ twins v HC twins (N=10; age = 29.3 ± 6.4)	p <0.05
LDL (low density lipoproteins; 0.84-0.88 ppm; 1.24-1.28 ppm)	Tsang et al. (2006)	plasma	↑		p <0.05
LDL (low density lipoproteins; 0.82-0.86ppm)	Cai et al. (2012)	Plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.039 (ns after Bonferoni correction)
VLDL/LDL (low and very low density lipoproteins; 1.30-1.34ppm)	Cai et al. (2012)	Plasma	↓		p = 0.009 (ns after Bonferoni correction)
HDL (high density lipoproteins; 1.18-1.22ppm)	Cai et al. (2012)	Plasma	↓		p = 0.015 (ns after Bonferoni correction)
VLDL (very low density lipoproteins; 1.26ppm)	Cai et al. (2012)	Plasma	↓		p = 0.020 (ns after Bonferoni correction)
PCn3 (n3 PUFAs in the phosphatidylcholine lipid class)	McEvoy et al. (2013)	Plasma	↓	FE DN SCZ (SCZ & SZA; N=20; 13M; age = 27.0 ± 9.8) v HC (N=29; 6M; age = 41.0 ± 9.5); FE DN SCZ v recurrent episode SCZ (SCZ & SZA; N=20; 16M; age = 36.7 ± 12.7)	p = 0.0052 (FE v HC, sig after Bonferroni); p = 0.0238 (FE v RE)
PEn3 (n3 PUFAs in the phosphatidylethanolamine lipid class)	McEvoy et al. (2013)	plasma	↓		p = 0.001 (FE v HC, sig after Bonferroni) p = 0.0032 (FE v RE)
triglycerides	Solberg et al. (2015)	serum	↑	SCZ (N=44 SCZ, N=11 SZA; 44 med, 11 DF; 38M; age = 31.3 ± 5.7) v HC (N=51; 28M; age = 33.0 ± 5.7)	p <0.001 (med v HC and all patients v HC); p = 0.11 (ns, non-med v HC)
LC5 (abundant triglycerides)	Oresic et al. (2012)	Serum	↑	SCZ twins (N=19; 15 med; 6M; 7 MZ; age = 51 ± 10) v unaffected co-twins (N=19; matched gender); SCZ v HC twins (N=34; 10M; 20 MZ; age = 53.4)	p = 0.039 (SCZ twins v co-twins); p = ns (SCZ twins v HC & HC v co-twins)

DHA = docosahexaenoic acid; DPA = docosapentaenoic acid; DHEAS = dehydroepiandrosterone sulfate; PC = phosphatidylcholine; PE = phosphatidylethaolamine; LPC = lysophosphatidylcholine; MDA = malondialdehyde; TG = triglycerides; n3/6/7/9 = omega 3/6/7/9; UFA = unsaturated fatty acids; PUFA = poly-unsaturated fatty acids; LDL = low density lipoprotein; VLDL = very low density lipoprotein; HDL = high density lipoprotein; GC = gas chromatography; LC =liquid chromatography; MS = mass spectrometry; 1H NMR = proton nuclear magnetic resonance spectroscopy; TOFMS = time-of-flight MS; HPLC = high performance liquid chromatography; GC- FID = GC with flame ionisation detector; CE =

capillary electrophoresis; HPLC = High-performance liquid chromatography; UPLC-MS/MS = ultra-performance liquid chromatography tandem mass spectrometry; TLC - thin layer chromatography; RBCs = red blood cells; PBMCs = peripheral blood mononuclear cells; SCZ = schizophrenia subjects; HC = healthy control subjects; med = taking medication; FE = first episode; RE = recurrent episode; DN = drug naïve; DF = drug-fee; AD = affective disorder; MD = major depressive disorder; ASD = autism spectrum disorder; MZ = monozygotic ; DZ = dizygotic; SZA = schizoaffective disorder; SFD = schizophreniform disorder; PD NOS = psychotic disorder not otherwise specified; ARMS-P = at-risk mental state subjects who transitioned to psychosis; ARMS-NP = at-risk mental state subjects who did not transition to psychosis at 1 year follow up; ns = not significant; M = male; F = female

Table S2: Organic acids found at abnormal levels in patients with schizophrenia

Metabolite	Reference	biofluid	difference (SCZ v control)	subjects	P value
Amino acids					
Serine; 5-Oxoproline (pyroglutamic acid); Glutamate; 2-Aminobutyrate; aspartate; Phenylalanine	Yang et al. (2013)	serum	↑	SCZ (N=62; 25M; age = 36.9 ± 11.9; DF ≥ 2 weeks, some FE) v HC (N=62; 25M; age = 36.9 ± 9.3)	p <0.025, q <0.035
Serine	Waziri et al. (1983)	plasma	↑	SCZ (N=14; 9M; age = 30.0 ± 10.0) v non-psychotic patients (N=12; 1M; age = 25.1 ± 11.1)	p <0.05
D-Serine	Fukushima et al. (2014)	serum	↓	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p = 0.0016 (ns after Bonferroni correction)
Cystine	Yang et al. (2013)	serum	↓	SCZ (N=62; 25M; age = 36.9 ± 11.9; DF ≥ 2 weeks, some FE) v HC (N=62; 25M; age = 36.9 ± 9.3)	p = 1.06×10^{-6}, q = 0.00424
Cystine; Pyroglutamic acid; Glutamate; 2-Aminobutyric acid; isoleucine; Valine; Pipecolinic acid	Yang et al. (2013)	urine	↑	SCZ (N=51; DF ≥ 2 weeks, some FE) v HC (N=51)	p <0.04; q <0.045
Pipecolinic acid (2-piperidinecarboxylic acid)	Al Awam et al. (2015)	serum	↑	med SCZ (N=26; 20M; age = 37.3 ± 12.4) v HC (N=26; 20M; age = 37.0 ± 10.7)	p <0.001
serine/cysteine ratio	Waziri et al. (1983)	plasma	↑	SCZ (N=14; 9M; age = 30.0 ± 10.0) v non-psychotic patients (N=12; 1M; age = 25.1 ± 11.1)	p <0.001
pyroglutamic acid; creatinine; valine	Liu et al. (2014)	PBMCs	↓	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	p <0.02
1-oxo-proline	Al Awam et al. (2015)	serum	↓	med SCZ (N=26; 20M; age = 37.3 ± 12.4) v HC (N=26; 20M; age = 37.0 ± 10.7)	p <0.01
2-aminoadipic acid; glycocyamine	Yang et al. (2013)	urine	↓	SCZ (N=51; DF ≥ 2 weeks, some FE) v HC (N=51)	p <0.007, q <0.035
betaine	Koike et al. (2014)	plasma	↓	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN; age = 24.6 ± 7.1) v HC (N=24 HC; 10M; age = 26.1 ± 2.6)	p = 6.8×10^{-4} (1st set); p = 0.029 (2nd set) (p values for SCZ v HC)
creatine	Cai et al. (2012)	Urine	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.039 (ns after Bonferoni correction)

creatine	Koike et al. (2014)	plasma	↑	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN; age = 24.6 ± 7.1) v HC (N=24 HC; 10M; age = 26.1 ± 2.6)	p = 0.018 (1st set); p=0.031 (2nd set) (p values for SCZ v HC)
creatinine	Karoum et al. (1987)	urine	↓	SCZ (N=20; 18M; DF ≥ 2 weeks; age = 30 ± 6) v HC (N=16; 11M; age = 32 ± 5)	$p < 0.05$
creatinine	Cai et al. (2012)	urine	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.039 (UPLC-MS/MS); p = 0.014 (^{1}H NMR) (ns after Bonferoni correction)
Glutamate	Fukushima et al. (2014)	serum	↑	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p = 0.0145 (ns after Bonferroni correction)
glutamate	Koike et al. (2014)	plasma	↑	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1) 2nd set: FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN; age = 24.6 ± 7.1) v HC (N=24 HC; 10M; age = 26.1 ± 2.6)	p = 0.049 (1st set); p = 0.064 (ns, 2nd set) (p values for SCZ v HC)
γ-glutamylcysteine	Fukushima et al. (2014)	serum	↓	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	$p = 1.75 \times 10^{-6}$ (also sig after Bonferroni correction)
glutathione (GSH)	Ballesteros et al. (2013)	blood	↓	med SCZ (N=29; 20M; age = 41.1 ± 13.8) v HC (N=25; 11M; age = 38.8 ± 13.7)	$p < 0.001$
glutathione; tyrosine; threonine	Fukushima et al. (2014)	serum	↓	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	$p < 0.05$ (ns after Bonferroni correction)
GSSG	Ballesteros et al. (2013)	blood	↑	med SCZ (N=29; 20M; age = 41.1 ± 13.8) v HC (N=25; 11M; age = 38.8 ± 13.7)	p = 0.005 (levels of GSSG); p = 0.023 (% GSSG)
glycine	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0232
glycine	Cai et al. (2012)	plasma; urine	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	$p < 0.015$ (ns after Bonferoni correction)
alanine; isoleucine; lysine	Bjerkenstedt et al. (1985)	plasma	↑	SCZ (N=37; 21M; DF ≥ 2 weeks; age = 28.1 ± 6.8 (M) & 31.1 ± 7.8 (F)) v HC (N=65; 50M; age = 32.6 ± 6.4(M) & 27.1 ± 4.2 (F))	$p < 0.001$
alanine	Cai et al. (2012)	plasma	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.047 (ns after Bonferoni correction)
arginine; histidine	He et al. (2012)	plasma	↓	SCZ (N=52 DF (29M; age = 39.3 ± 11.2), N=213 med (132 M; age = 36.9 ± 11.7)) v HC (N=216; 112M; age = 38.9 ± 10.6)	$p \leq 0.03$
aspartic acid; homoserine	Liu et al. (2014)	PBMCs	↑	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	$p < 0.04$
aspartate	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0021
glutamine	He et al. (2012)	plasma	↓	SCZ (N=52 DF (29M; age = 39.3 ± 11.2), N=213 med (132 M; age = 36.9 ± 11.7)) v HC (N=216; 112M; age = 38.9 ± 10.6)	p = 0.006
glutamine; histidine	Bjerkenstedt et al. (1985)	plasma	↓		$P < 0.05$

leucine; phenylalanine	Bjerkenstedt et al. (1985)	plasma	↑	SCZ (N=37; 21M; DF ≥ 2 weeks; age = 28.1 ± 6.8 (M) & 31.1 ± 7.8 (F)) v HC (N=65; 50M; age = 32.6 ± 6.4(M) & 27.1 ± 4.2 (F))	p <0.01
methionine; valine	Bjerkenstedt et al. (1985)	plasma	↑		p <0.05
tryptophan	Krause et al. (2013)	PBMCs	↓	SCZ (N=12; med & DF) v HC (N=24)	p = 0.029
tryptophan	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0071
tryptophan	Kim et al. (2009)	plasma	↓	SCZ (N=71; 32M; 38 DN, 33 DF ≥ 4 months; age = 33.9 ± 12.2) v HC (N=174; 78M; age = 32.5 ± 10.7)	p = 0.012
L -tryptophan	Fukushima et al. (2014)	serum	↑	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p = 0.001 (also sig after Bonferroni correction)
valine	Cai et al. (2012)	urine	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.011 (ns after Bonferoni correction)
N-acetylaspartate	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0293
ornithine	He et al. (2012)	plasma	↑	SCZ (N=52 DF (29M; age = 39.3 ± 11.2), N=213 med (132 M; age = 36.9 ± 11.7)) v HC (N=216; 112M; age = 38.9 ± 10.6)	p = 0.01
Other organic acids and derivatives					
2-Oxoglutarate; citrate; lactate; pyruvate; glycerate; myo-inositol	Yang et al. (2013)	serum	↑	SCZ (N=62; 25M; age = 36.9 ± 11.9; DF ≥ 2 weeks, some FE) v HC (N=62; 25M; age = 36.9 ± 9.3)	p <0.003; q <0.035
α-KG; citrate; 1,3-Bisphosphoglycerate	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p <0.04
α-KG; citrate; acetoacetate	Cai et al. (2012)	urine; plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p <0.05 (ns after Bonferoni correction)
cis-aconitic acid	Yang et al. (2013)	urine	↑	SCZ (N=51; DF ≥ 2 weeks, some FE) v HC (N=51)	p = 0.0123, q = 0.033
citrate; lactate	Yang et al. (2013)	urine	↓	SCZ (N=41 SCZ; DF ≥ 2 weeks, some FE) v HC (N=41)	p = 0.00558 (citrate); p = 2.09 x 10-8 (lactate)
glucose	Yang et al. (2013)	urine	↑	SCZ (N=41 SCZ; DF ≥ 2 weeks, some FE) v HC (N=41)	p = 1.73 x 10-4
citric acid	Liu et al. (2015)	PBMCs	↓	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7) Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	P <0.001 training set; p = 0.001 test set (SCZ v HC) p <0.001 (training set); p = 0.008 (test set; SCZ v MD)
D-lactate	Fukushima et al. (2014)	serum	↑	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p = 2.43 x 10-5 (also sig after Bonferroni correction)
lactate; glucose; glucuronic acid; glycerol; erythrose; myo-inositol; lactobionic acid	Xuan et al. (2011)	serum	↑	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p < 0.05

lactate	Liu et al. (2015)	PBMCs	↓	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7) Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	p =ns training set; p = 0.002 test set (SCZ v HC)
lactate	Cai et al. (2012)	plasma	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.009 (ns after Bonferoni correction)
hydroxyacetic acid; 2,3-dihydroxybutanoic acid	Yang et al. (2013)	urine	↓	SCZ (N=51; DF ≥ 2 weeks, some FE) v HC (N=51)	p <0.007, q <0.025
pyruvate	Liu et al. (2015)	PBMCs	↑	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7) Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	P = ns training set; p = 0.013 test set (SCZ v HC)
glycerate 3-phosphate	Liu et al. (2015)	PBMCs	↑		P <0.001 training set; p = 0.363 (ns) test set (SCZ v HC) p <0.001 training set; p = 0.022 test set (SCZ v MD)
fructose	Liu et al. (2015)	PBMCs	↑		P <0.001 training set; p = 0.003 test set (SCZ v HC) p <0.001 (training set; SCZ v MD)
glucose	Liu et al. (2015)	PBMCs	↑		P <0.001 training set; p <0.001 test set (SCZ v HC) p <0.001 (training set); p = ns (test set; SCZ v MD)
glucose	Cai et al. (2012)	plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.045 (ns after Bonferoni correction)
glucose	Cai et al. (2012)	Urine	↑		p = 0.0171 (ns after Bonferoni correction)
glyceraldehyde-3-phosphate; dihydroxyacetone phosphate	Liu et al. (2015)	PBMCs	↓	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7) Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	P <0.001 training set; p ≤0.006 test set; SCZ v HC) p <0.001 (training set); p = ns (test set; SCZ v MD)
ribose 5-phosphate	Liu et al. (2015)	PBMCs	↑		P <0.001 training set; p = ns test set (SCZ v HC) p <0.001 (training set); p = ns (test set; SCZ v MD)
gluconic acid	Koike et al. (2014)	plasma	↑	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1)	p = 0.022 (1st set; SCZ v HC)
glucose 6-phosphate; fructose 6-phosphate	Liu et al. (2015)	PBMCs	↑	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7) Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	P <0.001 training and test sets (SCZ v HC) p ≤0.001 (training & test sets; SCZ v MD)

glycerol	Liu et al. (2014)	PBMCs	↑	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	7.64 × 10−03
maltose; inositol; sorbitol; methyl phosphate	Liu et al. (2014)	PBMCs	↓		p <0.035 (maltose, inositol); p <10−5 (sorbitol); p <0.01 (methyl phosphate)
galactose oxime	Al Awam et al. (2015)	serum	↓	med SCZ (N=26; 20M; age = 37.3 ± 12.4) v HC (N=26; 20M; age = 37.0 ± 10.7)	p <0.001
fumaric acid	Liu et al. (2014)	PBMCs	↓	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	p = 1.98 × 10−03
succinic acid	Liu et al. (2015)	PBMCs	↑	Training set: FE DN SCZ (N=35; 14M; age = 32.5 ± 14.1) v HC (N=35; 18M; age = 36.5 ± 6.0); FE DN SCZ v DF MD (N=35; 17M; age = 36.4 ± 10.7) Test set: SCZ (N=20; 9M; 6 med; age = 28.5 ± 2.1) v HC (N=20; 10M; age = 30.2 ± 1.7); FE SCZ v DF MD (N=20; 11M; age = 27.6 ± 2.1)	P <0.001 training set & test set (SCZ v HC) p <0.001 (training set; SCZ v MD)
taurine	Bjerkenstedt et al. (1985)	plasma	↑	SCZ (N=37; 21M; DF ≥ 2 weeks; age = 28.1 ± 6.8 (M) & 31.1 ± 7.8 (F)) v HC (N=65; 50 M; age = 32.6 ± 6.4 (M) & 27.1 ± 4.2 (F))	p <0.001
taurine	Cai et al. (2012)	Urine	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.013 (ns after Bonferoni correction)
Clusters					
MC3 (Branched chain amino acids and other amino acids; e.g. Isoleucine, phenylalanine, tyrosine, ornithine, serine, methionine, threonine)	Oresic et al. (2011)	serum	↑	SCZ (N=45; 19M; 34 med; age = 53.7 ± 12.9) v HC (N=45; 19M; age = 53.7 ± 12.9)	p = 0.045
MC5 (Amino acids, organic acids e.g. proline, glutamic acid, α-ketoglutaric acid, pyruvic acid, alanine, lactic acid, α-hydroxybutyrate)	Oresic et al. (2011)	serum	↑		p = 0.020

α-KG = α-ketoglutarate ; GC = gas chromatography; TOF-MS = time-of-flight mass spectrometry; ^{1}H NMR = proton nuclear magnetic resonance spectroscopy; UPLC-MS/MS = ultra-performance liquid chromatography tandem mass-spectrometry; HPLC = high-performance liquid chromatography; LC = liquid chromatography; FIA-MS = flow injection analysis MS; CE = capillary electrophoresis; PBMCs = peripheral blood mononuclear cells; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; HC = healthy control subjects; AP = antipsychotic medication; DN = drug naïve ; ns = not significant; FE = first episode; MD = major depressive disorder; ASD = autism spectrum disorder; PD NOS = psychotic disorder not otherwise specified

Table S3: Other metabolites found at abnormal levels in subjects with schizophrenia

Metabolite	Reference	Biofluid	Difference (SCZ v control)	Subjects	P-value
adrenaline; noradenaline	Fryar-Williams & Strobel (2015)	urine	↑	SCZ (N=67; 37M; SCZ & SZA; med and DF; age = 40.5 ± 1.3) v HC (N=67; 33M; age = 45.7 ±1.4)	p <0.0001
MHPG	Pickar et al. (1990)	CSF	↑	SCZ (N=22; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks) v HC (N=33)	p <0.05
MHPG	Bjerkenstedt et al. (1985)	CSF	↑	SCZ (N=37; DF ≥ 2 weeks) v HC (N=65)	p <0.05
MHPG	Zumárraga et al. (2010)	plasma	↑	N=44 SCZ; N=71 BP; N=96 HC (BP and SCZ no medication for ≥ 8 days)	p = 0.002 (SCZ v HC), p = 0.004 (BP v HC), Power (1-β) = 0.92. SCZ; also SCZ > BP (p <0.02, power (1- β) = 0.87)
dopamine	Liu et al. (2014)	PBMCs	↓	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	4.89×10^{-02}
dopamine	Fryar-Williams & Strobel (2015)	urine	↑	SCZ (N=67; 37M; SCZ & SZA; med and DF; age = 40.5 ± 1.3) v HC (N=67; 33M; age = 45.7 ±1.4)	p <0.0001
dopamine	Karoum et al. (1987)	urine (24h mean)	↓	SCZ (N=20; 18M; DF ≥ 2 weeks; age = 30 ± 6) v HC (N=16; 11M; age = 32 ± 5)	p <0.05
HVA	Bjerkenstedt et al. (1985)	CSF	↓	SCZ (N=37; 21M; DF ≥ 2 weeks; age = 28.1 ± 6.8 (M) & 31.1 ± 7.8 (F)) v HC (N=65; 50M; age = 32.6 ± 6.4(M) & 27.1 ± 4.2 (F))	p <0.01
HVA	Sedvall & Wode-Helgodt (1980)	CSF	↑	SCZ with family history (N=11) v SCZ without (N=25)	p <0.05
HVA	Peters (1979)	CSF	↓	paranoid SCZ (N=8; patients also have LTL epilepsy) v controls (N=8; with LTL epilepsy)	p <0.001
5-HT	Fukushima et al. (2014)	serum	↓	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p = 0.013 (ns after Bonferroni correction)
IAA	Domino et al. (1979)	urine	↑	SCZ v HC (N=7 drug-free ≥ 2years, chronic SCZ; N=7 HC)	p = 0.01
NA5HT	Yao et al. (2010)	plasma	↑	FE DN SCZ (N=25; 18M; age = 21.4 ± 5.5 (M) & 26.3 ± 10.6 (F)) v HC (N=30; 18M; age = 22.5 ± 4.5 (M) & 23.2 ± 4.6 (F))	p =0.0077, sig after Bonferroni of α of 0.1

5-HIAA	Gattaz et al. (1982)	CSF	↓	paranoid SCZ (N=28; 28M; 15 med; age = 30.6 ± 8.0) v controls (N=16; 14M; symptomology requiring a lumbar puncture e.g. headaches, dizziness; age = 35.0 ± 15.7)	p =0.002 (all SCZ v controls); p <0.001 (SCZ on APs v controls); p <0.005 (SCZ not on APs v controls)
5-HIAA	Sedvall & Wode-Helgodt (1980)	CSF	↑ and (↑↓)	N=36 SCZ: N=11 with fam history; N=25 without)	high (p <0.001); aberrant (i.e. higher/lower than normal levels, p <0.001)
NA5HT/tryptophan; melatonin/5-HT	Yao et al. (2010)	plasma	↑	FE DN SCZ (N=25; 18M; age = 21.4 ± 5.5 (M) & 26.3 ± 10.6 (F)) v HC (N=30; 18M; age = 22.5 ± 4.5 (M) & 23.2 ± 4.6 (F))	p <0.003, sig after Bonferroni correction
5-HT/tryptophan; 5-HT/5-HTP; NA5HT/5-HTP	Yao et al. (2010)	plasma	↑		p <0.01 (5-HT/tryptophan; NA5HT/5-HTP); p = 0.0331 (5-HT/5-HTP) not sig after Bonferroni correction
melatonin/N-acetylserotonin	Yao et al. (2010)	plasma	↓		p = 0.0011; sig after Bonferroni correction
kynurenine	Krause et al. (2013)	PBMCs	↓	SCZ (N=12; med & DF) v HC (N=24)	p = 0.05
L-kynurenine	Fukushima et al. (2014)	serum	↑	med SCZ (N=25; 11M; age = 28.2 ± 4.4) v HC (N=27; 12M; age = 26.5 ± 5.6)	p = 0.0057 (ns after Bonferroni correction)
KYNA	Nilsson-Todd et al. (2007)	CSF	↑	male SCZ (N=53; 4 FE DN, 19 DF ≥ 20 days; 30 med) v male HC (N=43); male DN SCZ (N=4) v male HC	p <0.05 (SCZ v HC); p<0.05 (DN SCZ v HC)
uric acid	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0247
uric acid	Cai et al. (2012)	plasma	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.023 (ns after Bonferoni correction)
uric acid	Cai et al. (2012)	urine	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.033 (ns after Bonferoni correction)
allantoin	Xuan et al. (2011)	serum	↑	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0298
3-Indolebutyrate fragments	Cai et al. (2012)	plasma	↑	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.045 (ns after Bonferoni correction)
benzoic acid; hydroxylamine	Liu et al. (2014)	PBMCs	↑	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	p <0.03
benzoic acid; Imidazolelactic acid; cyclohexylamine	Koike et al. (2014)	plasma	↓	1st set: FE SCZ (N= 18; 13M; most med, 2 DN; 4 disorganised, 7 paranoid, 3 SFD, 2 delusional	Benzoic acid: p = 0.037 (1st set); p = 0.039 (2nd set)

				disorder, 2 PD NOS; age = 23.2 ± 5.4) v HC (N=14; 11M; age = 25.7 ± 6.1) 2nd set (only benzoic acid detected): FE SCZ (N=12; 4 disorganised, 3 paranoid, 3 SFD, 2 PD NOS; 2 DN; age = 24.6 ± 7.1) v HC (N=24 HC; 10M; age = 26.1 ± 2.6)	imidazolelactic acid: p = 0.037 (1st set); not detected in 2nd set cyclohexamine: p = 0.0018 (1st set); not detected in 2nd set [p values for SCZ v HC]
hippurate	Cai et al. (2012)	urine	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p <0.0001 (UPLC-MS/MS); p = 0.001 (^{1}H NMR) (still sig. after Bonferoni correction)
Catechol	Yang et al. (2013)	urine	↓	SCZ (N=51; DF ≥ 2 weeks, some FE) v HC (N=51)	p = 5.82 x 10^{-4}, q = 0.00748
NO_x	Nakano et al. (2010)	plasma	↓	SCZ (N=30 DF ≥ 1 week) v HC (N=30)	p = 0.0027
NO_x	Lee & Kim (2008)	plasma	↓	SCZ (N=55; 31 DN, 24 DF ≥ 4 weeks) v HC (N=55)	p <0.01
NO_x	Taneli et al. (2004)	serum	↑	SCZ (N=20; DF ≥ 2 weeks) v HC (N=20)	p = 0.036
folate	Fryar-Williams & Strobel (2015)	RBCs	↓	SCZ (N=67; 37M; SCZ & SZA; med and DF; age = 40.5 ± 1.3) v HC (N=67; 33M; age = 45.7 ± 1.4)	p = 0.0005
vitamin B6	Fryar-Williams & Strobel (2015)	whole blood	↓		p = 0.0009
vitamin D	Fryar-Williams & Strobel (2015)	blood	↓		p = 0.0026
vitamin E	Scottish Schizophrenia Research Group (2000)	serum	↓	FE DN SCZ (N=30; 21M; 21 SCZ, 9 SFD; age = 28 ± 7 (M) & 33 ± 11 (F)) v HC (N=30; 21M; age = 30 ± 7)	p = 0.04
tocopherol-α; tocopherol-γ	Liu et al. (2014)	PBMCs	↓	SCZ (N=45; 18M; 19 FE DN, 26 med; age = 33.2 ± 12.9) v HC (N=50; 22M; age = 37.3 ± 8.7)	p = 4.39 × 10^{-4} (tocopherol-α); p = 4.75 × 10^{-3} (tocopherol-γ)
tocopherol- γ	Xuan et al. (2011)	serum	↓	N=18 DF SCZ (10M; age = 38 ± 15); N=18 HC (10M; age = 41 ± 19)	p = 0.0248
free copper to zinc ratio	Fryar-Williams & Strobel (2015)	serum/ RBCs	↑	SCZ (N=67; 37M; SCZ & SZA; med and DF; age = 40.5 ± 1.3) v HC (N=67; 33M; age = 45.7 ±1.4)	p = 0.0104
biopyrrins (bilirubin oxidative metabolites)	Yasukawa et al. (2007)	urine	↑	FE SCZ (N=15; 8M; DF; age = 31.2 ± 5.5) v HC (N=100; 50M; age = 34.0 ± 7.1)	p = 0.0164
tele-methylhistamine	Prell et al. (1995)	CSF	↑	SCZ (N=36; 27M; med & DF; age = 30.2 ± 6.7) v controls (N=8; 7M; 3 healthy, 1 depression, 1 bipolar, 2 atypical psychosis, 1 personality disorder & anorexia nervosa; age = 33.9 ± 11.3)	p = 0.006
TMAO	Cai et al. (2012)	Urine	↓	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5) v HC (N=11; 6M; age = 27.6 ± 9.5)	p = 0.028 (ns after Bonferoni correction)

6-deoxy-mannofuranose	Al Awam et al. (2015)	serum	↓	med SCZ (N=26; 20M; age = 37.3 ± 12.4) v HC (N=26; 20M; age = 37.0 ± 10.7)	p <0.001
Clusters					
sum dopamine (dopamine, DOPAC, HVA)	Karoum et al. (1987)	urine	↓		p <0.05
sum dopamine /sum norepinephrine ((dopamine + DOPAC + HVA)/ (norepinephrine + normetanephrine + MHPG + vanillylmandelic acid))	Karoum et al. (1987)	urine	↓	SCZ (N=20; 18M; DF ≥ 2 weeks; age = 30 ± 6) v HC (N=16; 11M; age = 32 ± 5)	p <0.005
conjugated dienes	Ryazantseva et al. (2002)	RBCs	↑	paranoid SCZ (N=38; age 21-49) v HC (N=45; age 19-48); SCZ in exacerbation (N=18) v SCZ in remission phase (N=20)	p <0.01

MHPG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid; IAA = indoleacetic acid; 5-HIAA = 5-Hydroxyindoleacetic acid; KYNA = kynurenic acid; 5-HT = 5-hydroxy tryptamine (serotonin); NA5HT = N-acetylserotonin; 5-HTP = 5-hydroxy tryptophan; NO_x = nitric oxide and metabolites; TMAO = trimethylamine-N-oxide; MS = mass spectrometry; HPLC = high-performance liquid chromatography; HPLC-ECD = HPLC with electrochemical detection; GC = gas chromatography; UPLC = ultra-performance liquid chromatography; LCECA = LC with electrochemical coulometric array detection; HPLC-FLD = HPLC with fluorescence detector; UPLC-MS/MS = UPLC tandem mass-spectrometry; CE-TOFMS = capillary electrophoresis time-of-flight MS; LCECA = LC with electrochemical coulometric array detection; ^{1}H NMR = proton nuclear magnetic resonance spectroscopy; ELISA = enzyme-linked immunosorbent assay; RBCs = red blood cells; PBMCs = peripheral blood mononuclear cells; CSF = cerebrospinal fluid; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; HC = healthy control subjects; AP = antipsychotic medication; DN = drug naïve; FE = first episode; BP=bipolar; PD NOS = psychotic disorder not otherwise specified; ASD = autism spectrum disorder; ns = not significant

Table S4: Correlations between metabolite concentrations and symptom severity in patients with schizophrenia

Metabolite	Reference	Biofluid	Correlation	R Coefficient	Subjects	P value
Lipids and lipid-like molecules						
triglyceride	Solberg et al. (2015)	serum	GAF-F; GAF-S; PANSS positive	r = -0.32 (GAF-F); r= -0.48 (GAF-S); r = 0.28 (PANSS positive)	SCZ (N=44 SCZ, N=11 SZA; 44 med, 11 DF; 38M; age = 31.3 ± 5.7)	p = 0.01 (GAF-F); p = 0.001 (GAF-S); p = 0.04 (PANSS positive)
PUFA	Solberg et al. (2015)	RBCs	PANSS negative scores	r = 0.32		p = 0.02
LCPUFA	Solberg et al. (2015)	RBCs	PANSS-negative; PANSS total; GAF-S; GAF-F	r = 0.52 (PANSS-negative); r = 0.31 (PANSS total); r = -0.32 (GAF-S); r = -0.029 (GAF-F)		p = 0.001 (PANSS-negative); p = 0.02 (PANSS total; GAF-S); p = 0.04 (GAF-F)
LDL (1.24-1.28ppm); VLDL (1.28-1.32 ppm)	Tsang et al. (2006)	plasma	GAF score (negative correlation)	r^2 = 0.62 (LDL); r^2 = 0.54 (VLDL)	Female med SCZ affected MZ twins (N=8; age = 33.9 ± 6.4); unaffected co-twins (N=8); HC twins (N=10; age = 29.3 ± 6.4)	not reported
HDL cholesterol	Solberg et al. (2015)	serum	GAF-F	r = 0.28	SCZ (N=44 SCZ, N=11 SZA; 44 med, 11 DF; 38M; age = 31.3 ± 5.7)	p = 0.045
HDL cholesterol; LDL cholesterol; total cholesterol	Solberg et al. (2015)	serum	GAF-S	r = 0.37 (HDL cholesterol); r = -0.28 (LDL cholesterol); r = -0.30 (total cholesterol)		p=0.008 (HDL cholesterol); p=0.05 (LDL cholesterol); p=0.02 (total cholesterol)
CAR	Mondelli et al. (2015)	saliva	clinical improvement	r = 0.50	FE psychosis (N=68; 46M; 37 SCZ/SZA, 22 SZA/affective psychosis, 7 PD NOS, 2 delusional disorder; 7 DN, 61 med; age = 29 ± 1)	p = 0.003

pregnanediol (changes)	Cai et al. (2012)	urine	improvement in PANSS activation symptom cluster sub-scores	r = -0.832	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5)	p = 0.001
citrate (changes)	Cai et al. (2012)	urine	changes in PANSS depression subscores	r = −0.842		p = 0.001
α-KG changes	Cai et al. (2012)	urine	changes in PANSS anergia subcluster scores	r = −0.836		p = 0.001
α-KG at baseline; week 3; and week 6	Cai et al. (2012)	urine	PANSS negative scores	r = −0.861 (baseline); r = −0.884 (week 3) r = −0.843 (week 6)	FE DN SCZ (N=11; 6M; age = 27.6 ± 9.5; put on 6 week course of risperidone)	p ≤ 0.001
Organic acids						
serine/cysteine	Waziri et al. (1983)	plasma	Psychosis score	r = 0.61	SCZ (N=14; 9M; age = 30.0 ± 10.0); mania (N=24; 16M; age = 33.0 ± 13.6); other psychoses (N=13; 7M; age = 38.7 ± 22.9); paranoid disorder (N=7; 4M; age = 31.9 ± 14.8); depression (N=14; 7M; age = 40.8 ± 15.6); non-psychotic (N=12; 1M; age = 25.1 ± 11.1)	p <0.001
tryptophan	Krause et al. (2013)	PBMCs	PANSS negative scores	r = -0.451 to -0.726	SCZ (N=12; med & DF)	not reported
tryptophan	Kim et al. (2009)	plasma	PANSS positive symptoms score	r = -0.343	SCZ (N=71; 32M; 38 DN, 33 DF ≥ 4 months; age = 33.9 ± 12.2)	p = 0.004
Other metabolites						
tele-methylhistamine	Prell et al. (1995)	CSF	Psychiatric Symptom Assessment Scale positive scores	r = 0.45	SCZ (N=36; 27M; med & DF; age = 30.2 ± 6.7)	p <0.02

MHPG	Gattaz et al. (1982)	CSF	BPRS "activation" score (due to items "tension" and "excitement")	r = 0.37 (activation score);
				r = 0.42 (tension item);
				r = 0 27 (excitement item)
					paranoid SCZ (N=28; 28M; 15 med; age = 30.6 ± 8.0)	p = 0.027 (activation);
						p = 0.012 (tension);
						p = 0.079 (excitement)

MHPG	Pickar et al. (1990)	plasma	BPRS negative scores	r = 0.48	SCZ (N=22; 11M; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks; age = 27.8 ± 8.3)	p <0.05
HVA (change baseline to 6W clozapine)	Jacobsen et al. (1997)	CSF	SAPS (change baseline to 6W clozapine)	r = 0.63	SCZ (N=8; age 12-18; DF ≥ 2 weeks at baseline)	p = 0.04
HVA	Pickar et al. (1990)	CSF	BPRS total score	r = -0.52	SCZ (N=22; 11M; 14 paranoid, 5 undifferentiated, 2 disorganised, 1 SZA; DF ≥ 2 weeks; age = 27.8 ± 8.3)	p = 0.01
HVA	Pickar et al. (1990)	CSF	BPRS positive scores	r = -0.50		P = 0.02
HVA	Gattaz et al. (1982)	CSF	BPRS item "hostility"	r = 0.39	paranoid SCZ (N=28; 28M; 15 med; age = 30.6 ± 8.0)	p = 0.020
HVA (change in)	Miura et al. (2014)	plasma	change in PANSS total scores	r = 0.536	med SCZ (N=22; 11M; switched to course of aripiprazole or blonanserin; age = 44.1 ± 14.9)	p = 0.015
HVA (change in)	Miura et al. (2014)	plasma	change in PANSS positive scores	r = 0.572		p = 0.008
HVA	Scheepers et al. (2001)	CSF	PANSS negative scores after 6 weeks AP treatment	r = -0.591	male med SCZ (N=23; 15 paranoid, 4 disorganised, 1 undifferentiated, 1 SFD, 2 SZA; age = 31 ± 8.8)	p< 0.01
5-HIAA	Markianos et al. (1992)	plasma	BPRS total score	r = 0.4651	male DN SCZ (N=20; 8 paranoid, 6 disorganised, 4 undifferentiated, 2 catatonic subtype; age = 20.6 ± 1.7)	p = 0.039
5-HIAA	Gattaz et al. (1982)	CSF	BPRS item "grandiosity"	r = 0.35	paranoid SCZ (N=28; 28M; 15 med; age = 30.6 ± 8.0)	p = 0.033
5-HIAA	Gattaz et al. (1982)	CSF	BPRS item "hallucinatory behaviour"	r = 0.36		p = 0.029

5-HIAA	Gattaz et al. (1982)	CSF	BPRS item "tension"	r = 0.47		p = 0.006
5-HIAA	Gattaz et al. (1982)	CSF	BPRS item "motor retardation"	r = 0.38		p = 0.022
5-HIAA	Anand et al. (2002)	CSF	disorganisation dimension on SAPS and SANS (positive)	r^2 = 0.241	DN SCZ (N=37 (25M); 26 SCZ, 11 SFD; age = 28.62 ± 6.55)	p = 0.0021
5-HIAA	Anand et al. (2002)	CSF	negative dimension on SAPS and SANS (positive)	r^2 = 0.147		p = 0.0191
5HIAA/HVA ratio	Anand et al. (2002)	CSF	disorganisation dimension on SAPS and SANS	r^2 = 0.109		p = 0.0460
HVA/5-HIAA (change in)	Kahn et al. (1993)	CSF	BPRS total score	r = -0.60	male SCZ (N=19; 16 SCZ, 3 SZA; DF ≥ 2 weeks; age = 43.1 ± 10.3)	p <0.01
HVA/5-HIAA (change in)	Kahn et al. (1993)	CSF	change in BPRS factor 4 (tension-excitement)	r = -0.47		p <0.05
kynurenine	Krause et al. (2013)	PBMCs	PANSS positive scores	r = 0.665	SCZ (N=12; med & DF)	p = 0.029
NOx (NO and its metabolites)	Nakano et al. (2010)	plasma	PANSS negative scores	r = -0.385	SCZ (N=30; 18M; DF ≥ 1 week; age = 38 ± 15)	p = 0.0416
uric acid/guanine ratio	Yao et al. (2012)	plasma	GAS (global assessment scale)	r = -0.643	N=25 FE DN SCZ (N=25 (19M); SCZ, SFD & SZA; age = 21.4 ± 5.5 (M) & 26.3 ± 10.6 (F))	p = 0.001

PUFA = poly-unsaturated fatty acids; LCPUFA – long chain PUFA; LDL = low density lipoprotein; VLDL = very low density lipoprotein; HDL = high density lipoprotein; CAR = cortisol awakening response; α-KG = α-ketoglutarate; MHPG = 3-methoxy-4-hydroxyphenylglycol; HVA = homovanillic acid; 5-HIAA = 5-Hydroxyindoleacetic acid; NO_x = nitric oxide and metabolites; GC = gas chromatography; ^{1}H NMR = proton nuclear magnetic resonance spectroscopy; ELISA = enzyme-linked immunosorbent assay; UPLC-MS/MS = ultra-performance liquid chromatography tandem mass-spectrometry; HPLC = high-performance liquid chromatography; MS = mass spectrometry; LC =liquid chromatography; HPLC-ECD = HPLC with electrochemical detection; LCECA = LC with electrochemical coulometric array detection; PBMCs = peripheral blood mononuclear cells; CSF = cerebrospinal fluid; PANSS = positive and negative symptoms scale; GAF = global assessment of functioning; GAF-S = GAF symptom scale; GAF-F = GAF functioning scale; ; BPRS = brief psychiatric rating scale; SAPS = scale for assessment of positive symptoms; SANS = scale for assessment of negative symptoms; GAS = global assessment; SCZ = schizophrenia subjects; SFD = schizophreniform disorder; SZA = schizoaffective disorder; PD NOS = psychotic disorder not otherwise specified; HC = healthy control subjects; AP = antipsychotic medication; DN = drug naïve; FE = first episode; MZ = monozygotic

Table S5: Metabolites reported in Tables 1-3 with relevant pathway/biological function information and SCZ hypothesis

General Class	Specific Metabolite	Relevant Pathway	SCZ Hypothesis
Fatty acids	Stearic acid Tetradecanoic acid Palmitic acid Heptadecanoic acid Pentadecanoic acid Octanoic acid Nonanoic acid Eicosenoic acid Oleic acid	**Fatty acid metabolism**	Inflammation/oxidative stress
	Nervonic acid	Linoleic acid metabolism	
	Linoleic acid/linoleate Arachidonic acid	Arachidonic acid metabolism	
	DHA DPA α-hydroxybutyrate β-hydroxybutyrate Suberic acid 4-pentenoic acid Eicosapentaenoic acid		
Steroids & derivatives	20α-Dihydroprogesterone	**Steroid biosynthesis**	
	Pregnanolone Isopregnanolone Epietiocholanolone Pregnenolone Etiocholanolone Conjugated 5β-Androstane-3β, 17β-diol Conjugated 5α-Pregnane-3β, 20α-diol Androstenediol		

	Androsterone		
	Epiandrosterone		
	Conjugated epietiocholanolone		
	Conjugated pregnanolone Conjugated Isopregnanolone Androstenedione conjugated epipregnanolone conjuagted Pregnenolone sulfate; Progesterone Cortisol Conjugated androstenediol 5α-dihydroprogesterone DHEAS Conjugated 5α-Androstane-3α, 17β-diol Conjugated 5α-androstane-3β, 17β-diol Testosterone 20α-dihydropregnenolone 5α, 20α-tetrahydroprogesterone Cholesterol		
	HDL cholesterol		
	LDL		
	VLDL		
	Cortisol awakening response (CAR)		
	Pregnanediol		
Other lipids & lipid-like molecules	PCs PEs LPCs TGs SMs Glycerol-3-phosphate	**Lipid metabolism** Glycerophospholipid metabolism Sphingolipid signalling pathway Terpenoid and polyketides metabolism	Lipid peroxidation
	TBARS		Lipid peroxidation
	MDA		Oxidative stress
	Perilic acid		

Amino acids	2-aminobutyrate	**Amino acid metabolism:**	**I**nflammation/oxidative stress
	Cystine		
	Phenylalanine	Phenylalanine metabolism	
	5-oxoproline	Glutathione metabolism	
	Glutamate	Alanine, aspartate & glutamate metabolism	
	Leucine		
	Isoleucine		
	Valine		
	Cysteine	Glycine, serine & threonine metabolism	
	Creatinine	Arginine & proline metabolism	
	1-oxoproline		
	2-aminoadipic acid		
	Glycocyamine		
	Betaine	Glycine, serine & threonine metabolism	
	Creatine	Glycine, serine & threonine metabolism	
	γ-glutamylcysteine	Glutathione metabolism	
	Glutathione (GSH)	Glutathione metabolism, antioxidant	Antioxidant defence
	Tyrosine	Tyrosine metabolism	
	Threonine	Glycine, serine & threonine metabolism	
	Glycine	Glycine, serine & threonine metabolism	
	Serine	Glycine, serine & threonine metabolism	
	Alanine	Alanine, aspartate & glutamate metabolism	
	Aspartate	Alanine, aspartate & glutamate metabolism	
	Lysine		
	Arginine	Arginine & proline metabolism	

	Histidine	Pentose phosphate pathway	
	Homoserine	Cysteine and methionine metabolism	
	Methionine	Cysteine and methionine metabolism	
	Tryptophan	Tryptophan metabolism	
	Ornithine	Arginine & ornithine metabolism	
	N-acetylasparate	Alanine, aspartate & glutamate metabolism	
Other Organic acids & derivatives	2-Oxoglutarate	TCA cycle	
	Citrate	TCA cycle	
	Lactate	Glycolysis	
	Pyruvate	Pyruvate metabolism, glycolysis	
	Glycerate	Glycolysis	
	Myo-inositol	Amino acid metabolism	
	α-ketoglutarate	TCA cycle	
	1,3-Bisphosphoglycerate		
	Acetoacetate		
	cis-aconitic acid		
	Glucose	Glycolysis	Glucoregulatory alterations
	Glucuronic acid		
	Glycerol	Glycerolipid metabolism	
	Erythrose		
	Lactobionic acid		
	Hydroxyacetic acid		
	2,3-dihydroxybutanoic acid		
	Glycerate 3-phosphate	Glycolysis	
	Fructose	Glycolysis, fructose & mannose metabolism	
	Glyceraldehyde-3-phosphate	Glycolysis, pentose phosphate pathway	
	Dihydroxyacetone phosphate	Inositol phosphate metabolism	
	Ribose 5-phosphate	Pentose phosphate pathway	
	Gluconic acid		
	Glucose 6-phosphate	Glycolysis	
	Fructose 6-phosphate	Glycolysis	

	Maltose		
	Inositol	Inositol phosphate metabolism	
	Sorbitol	Fructose & mannose metabolism	
	Methyl phosphate		
	Galactose oxime		
	Fumaric acid	TCA cycle	
	Succinic acid		
	Taurine		Antioxidant defence
Other metabolites	Adrenaline		Inhibitory neurotransmitter
	Noradrenaline		Inhibitory neurotransmitter
	MHPG		
	Dopamine		Dopamine hypothesis
	HVA		Metabolic stress
	5-HT		
	IAA		
	NA5HT	Tryptophan metabolism	
	5-HIAA		
	Melatonin	Tryptophan metabolism	
	5-HTP	Tryptophan metabolism	
	N-acetylserotonin	Tryptophan metabolism	
	Kynurenine	Tryptophan metabolism	
	KYNA		
	Uric acid		
	Allantoin	Purine metabolism	
	Benzoic acid		
	Hydroxylamine	Nitrogen metabolism	
	Imidazolelactic acid		
	Cyclohexylamine		
	Hippurate		
	Catechol		
	NO_x	Nitrogen metabolism and others	

	Folate	1 carbon metabolism
	Vitamin B6	
	Vitamin D	
	Vitamin E	
	Tocopherol-α	
	Tocopherol-γ	
	Biopyrrins	
	tele-methylhistamine	
	TMAO	
	6-deoxy-mannofuranose	

Note: Pathways obtained from KEGG

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