Plasma lipid alterations in young adults with psychotic experiences: A study from the Avon Longitudinal Study of Parents and Children cohort

Xiaofei Yin a,*, David Mongan b, Mary Cannon b, Stanley Zammit c, d, Tuulia Hyötyläinen e, Matej Orešić f, Lorraine Brennan a,1, David R. Cotter b,*,1

a Institute of Food and Health, UCD School of Agriculture and Food Science, University College Dublin, Belfield, Dublin, Ireland
b Department of Psychiatry, Royal College of Surgeons in Ireland, Beaumont Hospital, Dublin, Ireland
c MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, Cardiff, UK
d Centre for Academic Mental Health, School of Social & Community Medicine, University of Bristol, Bristol, UK
e School of Medical Sciences, Örebro University, Örebro, Sweden
f Turku Bioscience Centre, University of Turku and Åbo Akademi University, Turku, Finland

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ABSTRACT

Background: Psychotic experiences (PEs) are associated with an increased risk of future psychotic and non-psychotic mental disorders. The identification of biomarkers of PEs may provide insights regarding the underlying pathophysiology.

Methods: The current study applied targeted lipidomic approaches to compare plasma lipid profiles in participants from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort who did (n = 206) or did not (n = 206) have PEs when aged approximately 24 years.

Results: In total, 202 lipids including 8 lipid classes were measured by using ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry (UHPLC-QTOF-MS). Eight lipid clusters were generated. Thirteen individual lipids were nominally significantly higher in the PEs group compared to the control group. After correction for multiple comparisons, 9 lipids comprising 3 lysophosphatidylcholines (LPCs), 2 phosphatidylcholines (PCs) and 4 triacylglycerols (TGs) remained significant. In addition, PEs cases had increased levels of TGs and LPCs with a low double bond count.

Conclusions: These findings indicate plasma lipidomic abnormalities in individuals experiencing PEs. The lipidomic profile measures could aid our understanding of the underlying pathophysiological mechanisms.

1. Introduction

Psychotic experiences (PEs) are common in the general population (Yung et al., 2007) with as many as 5.8% of adults (18 years and older) (McGrath et al., 2015) and 17% of children reporting PEs (Kelleher et al., 2012). Furthermore, evidence has accumulated that PEs are associated with the subsequent onset of a wide array of common mental disorders, such as depressive disorders and anxiety disorders (Yung et al., 2007; Varghese et al., 2011), and psychotic disorders (Downs et al., 2013; Werbeloff et al., 2012). Early identification and intervention of people with psychosis significantly improves their clinical outcomes (Larsen et al., 2011). The identification of PEs primary relies on clinical interviews, for example the face-to-face, semi-structured Psychosis-Like Symptom (PLIKS) interview, which assesses current (past 6 months/1 year) self-reported and interviewer-rated PEs (Sullivan et al., 2020). Identifying the molecular signature of PEs can help to provide improved insights into their pathophysiological basis.

Currently, our understanding of the pathophysiology underlying psychosis remains limited although evidence for inflammatory contributions is increasingly supported (Mongan et al., 2020; Osimo et al., 2021; Cotter et al., 1995). Genetic (Sekar et al., 2016) and environmental (Croft et al., 2019) contributions are also well described. Accumulated research has also suggested that perturbations of lipid metabolism are implicated in neuropsychiatric disorders, including schizophrenia (Schneider et al., 2017; Misiak et al., 2017), bipolar disorder (Hamazaki et al., 2015) and major depressive disorder (Müller

* Corresponding authors.
E-mail addresses: xiaofei.yin@ucdconnect.ie (X. Yin), drcotter@rcsi.ie (D.R. Cotter).
1 These authors contributed equally to this study as joint senior authors.

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Lipids show high concentration in central nervous system and play an important role in central nervous system as modulators of the redox state and inflammation (Gui et al., 2018). Previous studies have demonstrated alterations in phospholipids, such as phosphatidylcholines (PCs) and sphingomyelins (SMs) in individuals with schizophrenia (Weber-Fahr et al., 2013; Castillo et al., 2016). Lipidomic approaches have been used to map dysregulated lipids involved in disease pathogenesis and to uncover potential molecular biomarkers that can be used as indicators of pathological abnormalities. For example, a case-control study by McEvoy and colleagues reported significant down-regulation of several n-3 and n-6 PUFA compositions in phosphatidylcholine (PC) and phosphatidylethanolamine (PE) lipid classes in the blood plasma of first episode of schizophrenia, compared to controls (McEvoy et al., 2013). Essential polyunsaturated fatty acids, lipid-peroxidation metabolites, phosphatidylcholines (PCs) and lysophosphatidylcholines (LPCs), glutamate, 3-methoxy-4-hydroxyphenylglycol, and vitamin E were reported from a systematic review as potential metabolite signatures of schizophrenia, some of which converge on signalling and inflammatory/anti-inflammatory processes (Davison et al., 2018). However, these latter studies mainly focused on populations who had already developed psychotic disorders and comprehensive studies on identifying molecular signatures which precede psychotic disorders are needed.

In our previous studies, the alterations of circulating lipid including LPCs and PCs were observed from childhood (age 11–12) and adolescence (age 18) in relation to the reporting of psychotic disorder (PD) or PEs in the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort (O’Gorman et al., 2017; Madrid-Gambin et al., 2019). Results showed phospholipid metabolites such as LPCs (LPC(16:1), LPC(18:1), LPC(18:2), LPC(20:3)) and PCs (PC(34:2), PC(36:4)) were significantly elevated in blood from 11-year-old children with outcomes of PD at age 18. Furthermore, similar phospholipid alterations were also found in 12-year-old children who were identified as experiencing PEs at age 18. In the current study we have extended these analyses to subjects in the ALSPAC cohort at age 24 who reported PEs compared to control subjects who did not report PEs. The objective was to apply a lipidomic approach to investigate plasma lipid alterations and identify potential molecular signatures/biomarkers associated with PEs.

2. Materials and methods

2.1. Study cohort

The study comprised individuals from the ALSPAC cohort, which is a prospective birth cohort study (Boyd et al., 2013; Fraser et al., 2013; Northstone et al., 2019). The study originally recruited 14,541 pregnancies to women who were resident in Avon, UK, and who were expected to deliver between 1st April 1991 and 31st December 1992. Of those pregnancies, 13,988 children were survived for at least 12 months. When the oldest children were approximately 7 years of age, an attempt was made to bolster the initial sample with eligible cases who had not joined the study originally. Additional children were enrolled, and the total sample size is 15,454 pregnancies with 14,901 children alive at 1 year of age. Follow-up of the children included questionnaires, clinical assessment visits and biological sample collection. Study data were collected and managed using REDCap, research electronic data capture tools (Harris et al., 2009; Harris et al., 2019). Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the local Royal College of Surgeons in Ireland (RCSI) Research Ethics Committee. Consent for biological sample was collected in accordance with the Human Tissue Act (2004). Informed consent for use of questionnaire and clinic data was obtained following recommendations of the ALSPAC Ethics and Law Committee at the time. The details of all the data can be found on the study website through a fully searchable data dictionary (http://www.bristol.ac.uk/alspac/researchers/access).

2.2. Measures of psychotic experiences, depressive disorder and generalised anxiety disorder

PEs were identified at age 24 through the face-to-face, semi-structured Psychosis-Like Symptom (PLIKS) interview (Zammit et al., 2013), conducted by trained psychology graduates in assessment clinics, and were coded according to the definitions and rating rules for the Schedules for Clinical Assessment in Neuropsychiatry, Version 2.0 (Organization, 1994). Interviewers rated PEs as not present, suspected or definitely psychotic. Participants were also assessed for the presence of depressive disorder (DEP) and generalised anxiety disorder (GAD) according to the ICD-10 criteria measured using the Computerised Interview Schedule (Revised) (CIS-R) (Lewis, 1994).

2.3. Study design

We undertook a nested case-control study from the ALSPAC cohort and chose to assess all available plasma samples from 24-year-old adults. 3866 individuals were interviewed with the PLIKS at age 24 (Sullivan et al., 2020). Of those 3866 individuals, participants with suspected or definite PEs and with available plasma samples were selected as cases (n = 206). Among the cases, there were 148 individuals with PEs only, 13 individuals with PEs and DEP, 28 individuals with PEs and DEP and GAD, and 17 individuals with PEs and GAD. Age-matched individuals without suspected or definite PEs, depressive disorder, and anxiety disorder were then randomly selected as controls to match the cases (n = 206). Demographic characteristics of the study population are presented in Table 1.

2.4. Plasma sample collection

Fasting plasma samples were collected from the participants into heparin Sarstedt S-Monovette tubes (Sarstedt, Nümbrecht, Germany). Following collection, plasma samples were stored on ice for a maximum of 90 min until processed, and then centrifuged and stored at −80 °C until further analyses.

Table 1

|                  | Controls | PEs |
|------------------|----------|-----|
| Participants, n  | 206      | 206 |
| Age (years)      | 24       | 24  |
| Gender, n        | 97(M)/109| 78 (M)/128|
| BMI (kg/m²)      | 24.01 ± 3.66 | 25.94 ± 6.33 |
| Whether or not in education, employed or in a training scheme | 191(Y)/13 | 167(Y)/30 |
| Alcohol use (AUDIT-C score) | 5.36 | 5.29 |
| Any illicit substance use in past 12 months | 38(Y)/168 | 78 (Y)/126 |
| Smoking          | 132(Y)/74 | 154(Y)/47 |
| Frequency of use of cannabis in past year | None | 157 |
| Some (once or twice) | 39 | 44 |
| Monthly or weekly | 7 | 26 |
| Daily            | 3 | 22 |
| Medication use for hallucinations or delusions | 206(N) | 19(Y)/187 |

Abbreviations: ALSPAC, Avon Longitudinal Study of Parents and Children; BMI, body mass index. PEs, psychotic experiences. BMI expressed as Mean ± SD. AUDIT-C: The Alcohol Use Disorders Identification Test. The illicit substance included nitrous oxide, inhalants, sedatives/sleeping pills, hallucinogens, opioids.

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2.5. Lipidomic analysis

Plasma samples were analyzed using an ultra-high-performance liquid chromatography-quadrupole time-of-flight mass spectrometry method (UHPLC-QTOF-MS) to obtain global profiling of lipids. Samples were prepared following the previously reported Folch procedure with minor changes (Folch et al., 1957). The sample processing, data acquisition, and quantification of lipids were performed as previously described (O’Gorman et al., 2017; Lamichhane et al., 2021). The protocol is described in detail in the Supplementary Methods.

Lipidomic data were pre-processed with an open-source software, MZmine 2 (Piuskal et al., 2010). The processing steps included import of mzML files, crop filtering, mass detection, chromatogram deconvolution, isotopic peak grouper, join aligner, peak list row filter, gap filling and identification of lipids using a custom database search. Peak areas were normalised using internal class-specific standards for identified lipids and closest internal standard (based on retention time) for the unknown lipids, followed by calculation of the concentrations based on lipid-class calibration curves. The dataset was filtered, allowing the signal to be missing in a maximum of 50% of the samples at each batch. Missing values that remained were then imputed with feature-wise half-the-minimum. All lipids that were present in more than 75% of samples were considered for statistical analysis. Quality control was performed throughout the sample run by including blanks, pure standard samples, extracted standard samples and pooled plasma samples. Relative standard deviation (% RSD) for lipid concentrations in pooled plasma sample was on average 24.66%.

2.6. Statistical analysis

Cluster analysis of lipidomic data was performed using the Mclust R package (version 5.4.5), which used Gaussian mixture modelling fitted via the expectation-maximisation (EM) algorithm for model-based clustering (Scrucca et al., 2016). The model performance was evaluated by the Bayesian Information Criterion (BIC), and generally, the model with the highest BIC is chosen (Dickens et al., 2021). The highest BIC achieved by Mclust from the lipidomic dataset in control subjects was used to determine both the model type and the number of clusters into which the variables should be divided. Prior to clustering, the data were log10-transformed. The lipidomic clusters were generated for control group. The sum value of the lipids in each cluster was calculated and estimated the significant difference between healthy controls and PEs cases using the generalised linear model (GLM) in SPSS 24.0. at a significance threshold of $P < 0.05$.

The log10-transformed lipid data were compared between PEs and control groups by GLM using SPSS 24.0. Lipids with $P$ value less than 0.05 were chosen in cluster analysis. $P$ values were adjusted for gender, BMI, smoking and alcohol use where appropriate. The Benjamini-Hochberg false discovery rate (FDR) was implemented to correct for multiple comparisons, and the FDR-adjusted $P$ values are FDR corrections for $P$ values calculated from GLM. In this study, the threshold of FDR q-value for significant difference was set at 0.05. The fold change of significantly differential plasma lipid between PEs and control groups was calculated and fold change with a cut-off of 1.2 was chosen.

3. Results

3.1. Description of study population

The study population characteristics are shown in Tables 1, and 206 PEs (78 males/128 females) and 206 controls (97 males/109 females) were included. BMI was significant difference between PEs and controls.

3.2. Lipidomic signatures of PEs at age 24

The final lipidomic datasets used for analysis included a total of 202 lipids including cholesterol esters (CEs), Ceramides (Cer), lysophosphatidylcholines (LPCs), phosphatidylcholines (PCs), phosphatidylethanolamines (PE), sphingomyelins (SMs) and triacylglycerols (TGs), and a phosphatidilysinolinositol (PI). The list of lipids is presented in Table S1.

The lipidomic data were analyzed using model-based clustering, which generated 8 lipid clusters. The description of each cluster is shown in Table 2 and Table S2. Of the 8 clusters, cluster 3, (which was dominated by LPCs, PCs, and TGs) was nominally significantly different between the control and the PEs group ($P$ value < 0.05). The individual lipids in cluster 3 were then assessed to identify differences between the groups. A total of 13 lipids were nominally significantly different between controls and cases (Table 3), 9 of which passed the significance at the selected FDR threshold of 0.05. These lipids comprised 3 LPCs ((18:0), (18:1), (18:2)), 2 PCs ((36:1), (36:3)) and 4 TGs ((18:1/18:1/ 18:1), (18:2/18:1/18:1), (54:2), (54:3)). All of these lipids showed elevated concentrations in PEs group compared to the control group. Of note TG (54:2) also displayed high fold change (> 1.2 in cases vs controls) (Fig. 1).

3.3. Lipidomic signatures of PEs at age 24 in males and females

The univariate analysis for individual lipids in cluster 3 was also performed separately on males and females. In males, two lipid classes including 4 PCs and 5 TGs altered significantly between control and PEs groups ($P$ value < 0.05), and their concentrations were all increased in PEs group (Fig. 2A). However, in this analysis none of these lipids passed the FDR threshold of 0.05. In females, 2 LPCs, 1 PC and 3 TGs displayed differences between controls and PEs cases (Fig. 2B), and LPC (18:1) and LPC (18:2) passed the FDR threshold of 0.05.

3.4. The relationship between psychotic disorder and acyl chain content

The qualitative evaluation of changes in different lipid species related to the acyl chain length and the level of saturation is shown in Fig. 3. For example, a downward sloping relationship was observed in LPCs in the ratio of PEs vs controls for longer carbon chain (> 18C) (Fig. 3A). Furthermore, a downward sloping relationship was also found.
The fold change of significantly differential plasma lipid between PEs and control groups in lipid cluster 3. *Fold change was higher than 1.20.

for the number of double bonds: LPCs with lower number of double bonds were higher in cases (Fig. 3B). With respect to the TGs the majority of the TGs with lower carbon numbers and lower double bond counts were at higher levels in the PEs group. In contrast, levels of several TGs containing polyunsaturated fatty acyl chains were lower in subjects with PEs than controls (Fig. 3C-D). However, for other lipid classes, no clear pattern with respect to the acyl chain length or double bonds was observed.

Table 3
Differential plasma lipids between control and PEs groups in lipid cluster 3.

| Lipid               | Controls       | PEs            | P value | FDR-adjusted |
|---------------------|----------------|----------------|---------|--------------|
| LPC(16:0)           | 21,308.38 ±    | 22,071.25 ±    | 0.0243  | 0.0996       |
|                     | 5708.86        | 6457.23        |         |              |
| LPC(18:0)           | 6424.38 ±      | 6681.36 ±      | 0.0059  | 0.0268       |
|                     | 2129.71        | 1950.11        |         |              |
| LPC(18:1)           | 6334.82 ±      | 6762.33 ±      | 0.0005  | 0.0069       |
|                     | 2256.17        | 2372.53        |         |              |
| LPC(18:2)           | 8664.92 ±      | 9316.65 ±      | 0.0010  | 0.0103       |
|                     | 3947.09        | 4137.52        |         |              |
| PC(36:1)            | 10,373.40 ±    | 11,072.48 ±    | 0.0030  | 0.0207       |
|                     | 2643.93        | 2395.22        |         |              |
| PC(36:1)_A          | 10,107.48 ±    | 10,883.44 ±    | 0.0316  | 0.1080       |
|                     | 3601.51        | 3782.91        |         |              |
| PC(36:1)_B          | 9934.64        | 10,733.65 ±    | 0.0356  | 0.1124       |
|                     | 3621.48        | 3833.90        |         |              |
| PC(36:3)            | 17,478.22 ±    | 18,622.60 ±    | 0.0004  | 0.0070       |
|                     | 5051.76        | 4977.97        |         |              |
| TG(18:1/18:1)       | 23,361.25 ±    | 27,328.40 ±    | 0.0032  | 0.0207       |
| 18:1/18:2           | 10,865.10      | 16,263.63      |         |              |
| TG(18:1/18:2)       | 10,821.73 ±    | 12,454.26 ±    | 0.0310  | 0.1080       |
| 18:1/18:2/18:2      | 5718.20        | 7319.98        |         |              |
| TG(18:2/18:1/18:1)  | 21,674.24 ±    | 24,820.70 ±    | 0.0035  | 0.0207       |
| TG(54:2)            | 9731.82 ±      | 12,083.61 ±    | 0.0050  | 0.0258       |
|                     | 5803.70        | 12,372.70      |         |              |
| TG(54:3)            | 5697.75 ±      | 6574.22 ±      | 0.0003  | 0.0069       |
|                     | 2456.53        | 3629.07        |         |              |

Abbreviations: LPC, lysophosphatidylcholine; PC, phosphatidylcholine; PEs, psychotic experiences; TG, triacylglycerol. PC(36:1)_A and PC(36:1)_B shows the same number of acyl chain carbons, but the different position of one double bond in the acyl chain. P values are adjusted for gender, BMI, smoking and alcohol use where appropriate. FDR adjusted P-values are subjected to FDR for multiple comparisons using the Benjamini–Hochberg procedure. Lipid levels (ng/mL) are expressed as Mean ± SD. Values in bold are lipids that remain significant (FDR-adjusted P value <0.05) following correction for multiple comparisons.

4. Discussion

Our findings indicate the presence of lipidomic alterations in individuals who report PEs at age 24 compared to those who do not, adding to the evidence base of dysregulated phospholipid levels in psychosis. Furthermore, the current study is broadly in line with findings from our previous lipidomic study in which we found altered levels of some LPCs and PCs (LPC(18:1), LPC(18:2), LPC(20:3), PC(34:2) and PC (36:4)) at age 12 to be associated with PD and PEs at age 18 (O’Gorman et al., 2017; Madrid-Gambin et al., 2019). Therefore, the current study adds to the current literature by demonstrating that perturbed lipid metabolism not only precedes psychosis (O’Gorman et al., 2017, Madrid-Gambin et al., 2019) but also occurs in association with it. The data also demonstrates the potential of plasma lipid metabolites, especially LPCs and PCs, as early biomarker candidates of PEs. Our data thus provides novel insights into the presence of a sustained lipid dysregulation among subjects who either have PEs or will develop them in future.

In the current study, 4 PCs with 36 and 38 of acyl chain carbons (PC (36:1), PC (36:1)_A, PC (36:1)_B, PC (36:3)), but different levels of saturation were found to be significantly elevated in the plasma of the PEs group at age 24. The current findings also showed 4 LPCs were significantly elevated among the PEs group, a finding which is broadly in line with the findings from our previous lipidomic study in the ALSPAC cohort at early age (O’Gorman et al., 2017; Madrid-Gambin et al., 2019). In the study of O’Gorman et al., the plasma signature of psychotic disorder (PD) at age 11 showed increased LPC(18:1), LPC(18:2), and LPC (20:3). Two of them (LPC(18:1), LPC(18:2)) were also significantly elevated in this current study at age 24. In addition, higher levels of LPCs (16:1, 18:1, 18:2 and 20:3) lipids were found in plasma samples from the 12-year-old children who went on to report definite PEs at age 18 (Madrid-Gambin et al., 2019). Some previously published lipidomic studies identified the elevated plasma levels of LPCs (16:0, 16:1, 18:1 and 22:4) in subjects with depression relative to healthy controls (Gui et al., 2018), and also elevated plasma levels of LPCs (16:0, 18:0, 18:1...
and 18:2) in first-episode neuroleptic naive individuals with schizophrenia as compared to healthy controls (Cai et al., 2012). Inconsistent findings have also been reported with reductions in LPCs observed in individuals with schizophrenia (Oresic et al., 2012; Wang et al., 2019). However, there is no simple interpretation of the LPC and PC changes observed in association with PEs or PD. Interestingly, LPCs are considered inflammatory lipids (Huang et al., 1999; Aiyar et al., 2007) which stimulate the release of basic fibroblast growth factor as well as the release of the cytokines GM-CSF, IL-6, and IL-8 (Aiyar et al., 2007). Dysregulation of inflammatory processes is now well described in psychosis (Mongan et al., 2020) with convincing evidence for raised inflammatory markers both preceding and in association with first onset psychosis (Khandaker et al., 2014; Schwarz et al., 2014; Perry et al., 2019). Our findings are therefore very much in keeping with this picture of raised inflammatory tone in psychosis and additionally suggest that LPCs may contribute to the pathophysiology though this mechanism.

A number of studies have reported positive associations between LPCs and metabolic disorders such as cardiovascular diseases (CVDs) (Lee et al., 2013; Stegemann et al., 2014) and obesity (Barber et al., 2012). An investigation from Western Australian Pregnancy Cohort Study showed plasma LPC(18:2) and LPC(C18:1) were significantly decreased in people with obesity at age 20 compared with individuals of normal BMI. Furthermore this analysis also showed a significant association between LPC(14:0) and PC(32:2) concentrations and homeostatic model assessment of insulin resistance in the normal-weight group (Rauschert et al., 2016). It is well known that people with psychosis are as high risk for developing obesity, type 2 diabetes, CVDs, and other metabolic syndromes. Perry et al. recently reported an association between insulin resistance and PEs at age 9 and 18 in the ALSPAC birth cohort. Furthermore, insulin resistance was also associated with inflammation markers. The interaction of metabolic risk factors and inflammation may increase the risks of PEs (Perry et al., 2019). Furthermore, Westman and colleagues analyzed mortality in all age groups of people with schizophrenia by specific CVDs in a national register study including 46,911 people who were admitted to hospital for schizophrenia in Sweden, and found CVDs were the leading cause of death in people who had schizophrenia (Westman et al., 2018). Rates of type 2 diabetes are estimated to be 2 to 3 times higher in schizophrenia than in the general population, with a prevalence of 10% to 15% (De Hert et al., 2009; Mitchell et al., 2013). In a systematic review and meta-analysis, data from 16 case-control studies implied that glucose homeostasis was altered from illness onset in schizophrenia, indicating that those persons with schizophrenia were at increased risk of diabetes (Pillinger et al., 2017). These comorbid disorders are hypothesized to arise from antipsychotic side effects, lifestyle factors and/or as a result of metabolic abnormalities that may co-occur with psychosis (Suvitaival et al., 2016). It is noteworthy that several lines of evidence imply the involvement of LPCs in the development of metabolic co-morbidities in psychotic people. For example, Suvitaival et al. observed the LPC (16:0, 18:0, 18:1) levels were inversely associated with 2-month changes in the insulin level among the subjects with first-episode psychosis (Suvitaival et al., 2016). Therefore, the identification of LPC lipids such as LPC(16:0), LPC(18:0), LPC(18:1), and LPC (18:2) found in the present study may be helpful to identify people with psychosis who are most vulnerable to develop metabolic co-morbidities, but with further assessment in clinical populations.

TGs, as the most abundant lipids in the human body, represent a major source of energy and constitute a critical component of the lipoprotein (Berglund et al., 2013). In our study, 5 TGs with 54 of acyl chain carbons in each were at a significant higher level in subjects with PEs. Furthermore, as seen in the acyl chain content TGs with more double bonds displayed diminished levels in PEs cases. A similar finding was observed from a population-based study in Finland, which analyzed serum samples from people with psychotic disorders (schizophrenia, other nonaffective psychosis, affective psychosis) and healthy controls. The lipid cluster containing TGs was most elevated in the schizophrenia group, compared to controls. The differences were most pronounced for TGs containing more saturated fatty acids, while the cluster containing TGs with polyunsaturated fatty acids did not differ between the groups (Oresic et al., 2011). In addition, several studies have revealed that there is a long-standing association between increased TG level and metabolic disorder such as obesity or CVDs (Nordestgaard and Varbo, 2014; Girona et al., 2011).
et al., 2019). For example, Robert et al. proposed non-fasting TG measurement as a marker for CVD risk (Rosenson et al., 2014). Furthermore, increased levels of TGs with low carbon number and double-bond count was previously reported in a subgroup of first-episode psychosis who rapidly gain weight (Suvitaival et al., 2016). Therefore, our study suggests the presence of altered TGs metabolism in association with PEs and further research is warranted in other larger prospective studies to elucidate the basis of this.

4.1. Limitations and strengths

Our study has several limitations. Firstly, while some of our subjects were also diagnosed with other mental health outcomes such as depression and/or generalised anxiety disorder, future research is needed to indicate whether these clinical presentations are associated with distinct lipidomic profiles and to assess the specificity of our findings in relation to psychosis. Secondly, a small number of our PEs cases also fulfilled criteria for PD but because the numbers were small and comparisons underpowered we were unable to consider the lipidomic profile of PD cases as a specific subgroup in this age 24 sample. Thirdly, the long-term outcome of these young adults who represent PEs is not known and good outcome and a broader phenotype is common (Guloksuz and Van Os, 2018). However, the present study has several strengths. Firstly, a major strength of this study is that the ALSPAC cohort includes both detailed longitudinal phenotyping and clinical assessments and biosampling. Secondly, this sample is of a large sample size. Thirdly, the participants of this study are young adults, and they were likely less subject to medication exposure and chronic illness compared to older clinical samples. Fourthly, the targeted metabolomics based on LC-MS covered a wide range of lipid profiling and made it possible to discovery any altered lipid in different lipid classes. Finally, we have been able to contextualise our results with those from a previous study from the same cohort at age 11 (O’Gorman et al., 2017), thus providing unique insights into the lipidomic profile associated with PEs from both a longitudinal and cross-sectional perspective.

5. Conclusion

In conclusion, our findings provide evidence for a disturbance of lipid metabolism including LPCs, PCs and TGs in adults with PEs. Although the mechanisms linking dysregulation of lipid metabolism with the pathophysiology of psychosis is not clear, the findings add further evidence for sustained metabolic dysfunction in psychosis and heighten the need to consider both neuropsychiatric and long-term cardiovascular outcomes when caring for subjects presenting with psychosis.

CRediT authorship contribution statement

DC, MC, and LB designed the study; TH and MO acquired the lipidomic data; S2 collected the data related to psychotic experiences; XY and LB carried out data analysis; XY, DM, DC, and LB drafted the manuscript. DC and LB contributed equally to this study as joint senior authors. All other authors contributed to the critical revision of the manuscript and have approved the final version to be published.

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Declaration of competing interest

DM, MC and DRC report a patent pending (UK Patent Application No. 1919155.0, “Biomarkers to predict psychosis”), and other authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.schres.2022.02.029.

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