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1 Table of contents

1 Table of contents 2
2 Zusammenfassung 4
3 Abstract 5
4 Introduction 6
4.1 Bipolar disorder and schizophrenia: psychosis spectrum disorder diseases? 6
4.2 Schizophrenia 7
4.2.1 Clinical presentation and diagnosis of schizophrenia 7
4.2.2 Treatment of schizophrenia 8
4.3 Bipolar disorder 9
4.3.1 Clinical presentation and diagnosis of bipolar disorder 11
4.3.2 Treatment of bipolar disorder 11
4.3.3 Alda-scale 13
4.4 Biomarkers 13
4.5 Lipidomics 14
4.5.1 Omics 14
4.5.2 Lipids 15
4.5.3 Lipidomic analysis 17
5 State of research 20
5.1 Lipidomics in schizophrenia and bipolar disorder 20
5.2 Lipidomics and antipsychotics 24
6 Question and objective 26
6.1 Disease effects 26
6.2 Impact of medication intake 27
6.3 Lithium response 27
7 Methods 28
7.1 Data collection 28
7.2 Data preparation 29
7.3 Data analysis 29
7.3.1 Subgroups 29
7.3.2 Matching 30

Table of contents

7.3.3 Workflow T-Test 32
7.3.4 Workflow Lipidr 32
8 Results 36
8.1 Baseline characteristics 36
8.2 Lipid classes 38
8.3 Disease effects 39
8.3.1 Bipolar disorder 39
8.3.2 Schizophrenia 41
8.3.3 Bipolar disorder vs. schizophrenia 44
8.4 Medication classes 46
8.4.1 Antipsychotics 47
8.4.2 Tranquilizers 50
8.4.3 Antidepressants 51
8.4.4 Mood stabilizers 53
8.5 Interaction of medication and disease 56
8.6 Individual drugs 56
8.6.1 Antipsychotics 57
8.6.2 Antidepressants 62
8.6.3 Mood stabilizers 65
8.7 Medication subgroups 69
8.7.1 Antipsychotics: receptor profiles 69
8.7.2 Antidepressants 71
8.8 Treatment response 74
8.9 Multiple vs. single drug use 75
8.9.1 Quetiapine 76
8.9.2 Aripiprazole 76
8.9.3 Olanzapine 76
8.9.4 Risperidone 76
8.10 Effects by lipid class 79
9 Discussion 81
9.1 Disease effects 81

Table of contents

9.2 Medication effects 82
9.2.1 Antipsychotics 82
9.2.2 Antidepressants 84
9.2.3 Mood stabilizers 85
9.2.4 Lithium Lipidomics 86
9.3 Interaction of medication and disease 87
9.4 Multiple vs. single drug use 87
9.5 Effects by lipid classes 87
9.6 Sample size, significance and power 88
9.7 Matching 90
9.8 Limitations 91
10 Conclusion 91
11 List of abbreviations 93
12 Publication bibliography 95
13 List of figures 108
14 List of tables 112
15 Supplementary material 115
16 Affidavit 130
17 Confirmation of congruency 131

2 Zusammenfassung

Hintergrund: Ausgangspunkt dieser Arbeit ist die Untersuchung von potenziellen Unterschieden in Lipidprofilen von Patienten mit bipolarer Störung und Schizophrenie. Ausgehend davon soll der Einfluss verschiedener Medikamentenklassen und einzelner Medikamente, insbesondere Antipsychotika, auf das Lipidom betrachtet werden. In einem weiteren Schritt sollen potenzielle Lipid-Biomarker für das Ansprechen auf eine Lithium-Behandlung bei Patienten mit bipolarer Störung analysiert werden.

Methoden: Die Analyse umfasst insgesamt 622 Teilnehmer der laufenden, transdiagnostischen PsyCourse Studie aus Deutschland und Österreich: 192 Kontrollpersonen, 187 Patienten mit Schizphrenie (SCZ) und 243 Patienten mit bipolarer Störung (BP). Im Vergleich zur Kontrollgruppe wiesen Patienten mit SCZ und BP ein höheres Durchschnittsalter (44,9 bzw. 39,3 Jahre gegenüber 38,3 Jahre in der Kontrollgruppe) und einen höheren durchschnittlichen BMI auf (28,3 bzw. 28,4 kg/m^2 gegenüber 24,3 kg/m^2 in der Kontrollgruppe). Mittels LC-MS wurden Lipidintensitäten im Blutplasma gemessen, wobei 1.361 Lipidmerkmale erfasst und 395 Lipidverbindungen aus 16 Lipidklassen annotiert wurden. Die Lipidprofile von Patienten, die verschiedene Medikamente einnehmen, wurden mit denen von Kontrollgruppen verglichen, wobei eine Kombination statistischer Methoden, einschließlich t-Tests, Differenzialanalyse und Anreicherungsanalyse in lipidr angewendet wurde.

Ergebnisse: Im Rahmen dieser Analyse wurden signifikante Unterschiede in den Lipidprofilen von Patienten mit SCZ und BP und gesunden Kontrollpersonen festgestellt. Bezüglich der Medikamentenklassen führten Antipsychotika zu den größten Veränderungen im Lipidom mit einer hohen Anzahl von signifikant veränderten Lipidspezies und -klassen, darunter dCer, PC, TAG und DAG. Ähnliche Ergebnisse zeigten sich auch in der Schizophrenie-Kohorte, deren Population sich signifikant mit der Antipsychotika-Kohorte überschnitt. Innerhalb der Antipsychotika und auch der Antidepressiva gab es sowohl gemeinsame Effekte auf bestimmte Lipidklassen (TAG, PC, dCer), als auch unterschiedliche Effekte (CAR, FA, DAG) der einzelnen Medikamente in den Klassen. Im Falle von Lithium zeigten sich signifikante Veränderungen bei mehreren Lipidklassen sowie einzelner Lipidspezies, darunter CAR, LPE, LPC und dCer. Wird Lithium mit anderen Phasenprophylaktika zu einer einzigen Kategorie zusammengefasst, weist die Gruppe der Phasenprophylaktika nur wenige signifikante Veränderungen auf. Dies deutet auf unterschiedliche Effekte der einzelnen Medikamente hin bei gleichzeitig fehlendem Veränderungen, die der Klasse der Stimmungsstabilisierer gemein sind.

Fazit: Die Ergebnisse dieser Arbeit verdeutlichen den signifikanten Einfluss von Medikamenten auf das Lipidom und das Potenzial von Lipid-Biomarkern für eine personalisierte Behandlung von BP und SCZ. Allerdings müssen Einschränkungen wie die geringe Kohortengröße für einige Subgruppen sowie fehlende Daten zur Dosierung beachtet werden. Weitere Studien mit größeren Kohorten und longitudinalen Daten könnten diese Erkenntnisse validieren und das Verständnis für die Rolle des Lipidoms beim Ansprechen auf eine Behandlung vertiefen.

3 Abstract

Background: The starting point of this study is the investigation of potential differences in lipid profiles of patients with bipolar disorder (BP) and schizophrenia (SCZ). Based on this, the influence of different medication classes and individual medications, especially antipsychotics, on the lipidome will be examined. In a further step, potential lipid biomarkers for the response to lithium treatment in patients with bipolar disorder will be analyzed.

Methods: The analysis includes a total of 622 participants from the ongoing transdiagnostic PsyCourse study in Germany and Austria: 192 controls, 187 patients with SCZ, and 243 patients with BP. Compared to the control group, patients with SCZ and BP had a higher average age (44.9 and 39.3 years vs. 38.3 years in the control group) and a higher average BMI (28.3 and 28.4 kg/m2 vs. 24.3 kg/m2 in the control group). Lipid intensities in blood plasma were measured using LC-MS, detecting 1,361 lipid features and annotating 395 lipid compounds belonging to 16 lipid classes. The lipid profiles of patients taking different medications were compared to those of control groups, applying a combination of statistical methods, including t-tests, differential analysis, and enrichment analysis in lipidr.

Results: The results of this analysis revealed significant differences in the plasma lipid profiles of patients with BP and SCZ taking medication belonging to different classes. There were similarities and differences in affected lipid classes between SCZ and BP cohorts. Considering the medication classes, the overall impact on the plasma lipidome was largest for antipsychotics, with a high number of altered lipid species and classes, including dCer, PC, TAG and DAG. Several of these changes were also reflected in the schizophrenia cohort, which was also taking antipsychotics more frequently than the other groups. Both antipsychotics and antidepressants shared common effects (TAG, PC, dCer), but also had distinct effects (CAR, FA, DAG) for each class. In the case of lithium, several lipid classes and peaks were significantly altered, with potential biomarkers including CAR, LPE, LPC, and dCer. When lithium is grouped together with the other mood stabilizers as a single category, the mood stabilizer group shows few significant alterations, indicating strong effects of individual drugs but no common trend.

Conclusion: The findings of this thesis highlight the significant impact of medication on the lipidome and the potential for lipid biomarkers to personalize treatment for BP and SCZ. However, limitations such as the relatively small sample size and the lack of data on dosing need to be taken into consideration. Further studies with larger sample sizes and longitudinal data are needed to validate these findings and improve our understanding of the lipidome's role in treatment response.

4 Introduction

4.1 Bipolar disorder and schizophrenia: psychosis spectrum disorder diseases?

Psychosis is a broad term that refers to a mental state characterized by a loss of contact with reality, including delusions and hallucinations. The term psychosis, first used by the Austrian medical doctor Ernst von Feuchtersleben in 1845, has undergone changes over time to reflect the scientific and social contexts (Gaebel and Zielasek 2015). In 1899, German psychiatrist Emil Kraepelin was the first to propose a fundamental dichotomous distinction of psychosis between “manic-depressive insanity” and “dementia praecox” (Rybakowski 2021; Kendler 2021). Today “dementia praecox” is known as schizophrenia (SCZ) and “manic-depressive insanity” closely matches the definition of bipolar disorder (BP) (Rybakowski 2019). This fundamental dichotomous distinction was a milestone in psychiatric systematology and can nowadays still be found in psychiatric diagnosis systems like the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) (American Psychiatric Association 2022) and ICD-11 (World Health Organization 2022).

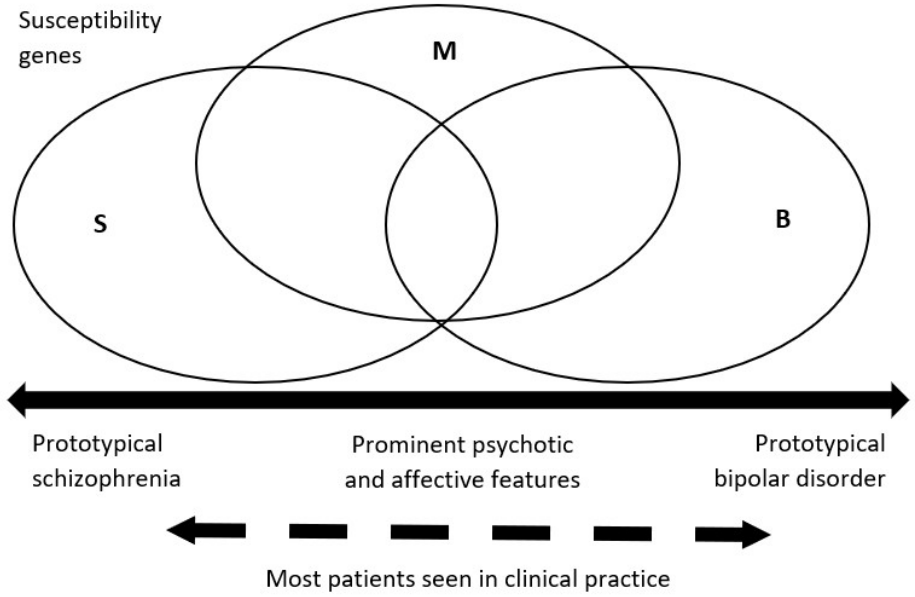

Figure 1: Psychosis Spectrum Disorder: while there are features that are characteristic for either schizophrenia (S) or bipolar disorder (B), there is a considerable overlap in symptoms (M) (Reproduced with permission from Elsevier, ©2004. Murray et al. 2004)

Even though the dichotomy proposed by Emil Kraepelin is still valid today, more recent findings show a highly polygenic nature (O'Donovan and Owen 2016) of these diseases as well as an overlap in clinical symptoms, such as hallucinations, delusions, and mood symptoms, as shown in figure 1 (Budde et al. 2019; Yuji Yamada et al.). While neurocognitive impairment has long been considered a key feature of SCZ, recent studies show that it also plays an important role in bipolar disorder. Furthermore, similarities in familial patterns, risk genes, outcome, and treatment response can be observed (Yuji Yamada et al.). This leads to a growing movement demanding a modern spectrum diagnostic approach (Guloksuz and van Os 2018). Despite these findings, SCZ and bipolar disorder are considered separate entities in the current DSM-5 (American Psychiatric Association 2022).

4.2 Schizophrenia

SCZ is a mental health disorder that affects approximately 1% of people worldwide, with a great variation between sites (Keshavan et al. 2020; Stępnicki et al. 2018; McGrath et al. 2008). Women are affected slightly more often than men. (McGrath et al. 2008) SCZ typically has an onset in late adolescence or early twenties, with females experiencing slightly later onset (Gogtay et al. 2011). It is characterized by symptoms such as hallucinations, delusions, disorganized speech, poor hygiene, decreased motivation, difficulty expressing emotions, and decreased interest in socializing with friends and family. People with SCZ may also experience symptoms of mania, depression, or anxiety (Borelli and Solari 2019).

SCZ is widely considered to be a neurodevelopmental disorder that begins early in life (Jaaro-Peled and Sawa 2020; Rund 2018). Although the heritability of SCZ is high, with genetic and environmental factors being shared, the concordance rate of monozygotic twins is only approximately 33%, indicating a significant environmental contribution to the development of the disorder. Several studies have shown that cognitive and neuro-motor skills are delayed in childhood among individuals who later develop SCZ (Jaaro-Peled and Sawa 2020). Disorders of cognitive functioning in SCZ patients have been documented in numerous studies, with cognitive functions affected to a greater or lesser extent. Working memory, executive function, and attention are particularly affected. Moreover, people with SCZ seem to be impaired in their ability to perceive emotions and understand the thoughts and intentions of other people (Rund 2018).

As mentioned before, environmental and genetic factors play a role in the development of SCZ. Various environmental risk factors have been linked to the development of SCZ, such as pregnancy and birth complications, childhood trauma, migration, social isolation, urbanicity, and substance abuse (Vilain et al. 2013; Stilo and Murray 2019). These factors can act alone or in combination, and can influence the likelihood of an individual developing SCZ over time. However, none of these risk factors on their own is sufficient to cause SCZ, and most show only a modest effect, resulting in a twofold increase in risk (Stilo and Murray 2019). Brain structural and functional changes, as well as neurochemical disturbances, involving dopamine, have been found in people with SCZ. The genetic basis of SCZ is complex, and it is widely accepted that the disorder is largely polygenic, meaning that multiple genes are involved in its development (Jauhar et al. 2022). Large-scale genome-wide association studies (GWAS) have identified more than a hundred loci, each of which makes a small contribution to illness risk. Despite these findings, an important fraction of the heritability of SCZ remains unexplained (Foley et al. 2017).

4.2.1 Clinical presentation and diagnosis of schizophrenia

The diagnosis of SCZ has long been challenging due to the complexity of symptoms that overlap with other mental health disorders, particularly affective disorders. This is evidenced by the concept of schizoaffective disorder, which describes patients who exhibit both affective and psychotic symptoms (Malhi et al. 2008).

The DSM-5 (Diagnostic and Statistical Manual of Mental Disorders) is a standardized diagnostic tool used in the United States and in research settings world-wide to classify and describe mental health disorders, including those on the schizophrenic spectrum (American Psychiatric Association 2022). The first edition of what is now commonly referred to as the DSM-1 was published in 1952 (Cooper and Blashfield 2016), and since then, there have been multiple revisions leading up to the most recent edition, the DSM-5, which was published in 2013. While there were expectations that the DSM-5 would shift towards a classification that wasn't solely based on symptoms, this was not ultimately realized (Paulzen and Schneider 2014). Instead, it continues to use a categorical approach with some attempts to incorporate dimensional aspects (Paulzen and Schneider 2014).

This thesis is exclusively focused on the DSM diagnostic system, as it was the basis for defining diagnoses in the datasets used, which is also why the ICD classification system is not taken into account.

According to the DSM-5, SCZ is defined by Criterions A to F. For Criterion A (characteristic symptoms) to be fulfilled, two (or more) of the following have to be present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3) (Tandon et al. 2013; American Psychiatric Association 2022):

1. Delusions
2. Hallucinations
3. Disorganized speech (e.g., frequent derailment or incoherence)
4. Grossly disorganized or catatonic behavior
5. Negative symptoms (i.e., diminished emotional expression or avolition)

Furthermore patients have to experience a social/occupational dysfunction (Criterion B), the symptoms have to last for at least 6 months (Criterion C) and a schizoaffective or mood disorder must have been excluded (Criterion D) (Tandon et al. 2013).

4.2.2 Treatment of schizophrenia

SCZ is characterized by a combination of positive and negative symptoms, cognitive dysfunction, affective and motor disturbances. As this can result in functional impairment and poor quality of life an early diagnosis as well as an effective treatment are crucial. Current treatment guidelines recommend long-term treatment with antipsychotic medications and psychological interventions (Krogmann et al. 2019; DGPPN 2019).

4.2.2.1 Pharmacological treatment

Antipsychotics that modulate dopamine to varying degrees are currently the only approved treatment for SCZ. While many antipsychotics have been developed to reduce acute symptoms, they are mostly effective against positive symptoms. Residual symptoms, such as negative symptoms and cognitive dysfunction, which persist for most of a patient's life in many cases, are relatively undertreated (Krogmann et al. 2019).

Antipsychotics, which are used among other things in the treatment of SCZ, can be divided into three groups, in line with the chronology of their development (Maric et al. 2016) (Abou-Setta et al. 2012).

- First generation antipsychotics (FGA): dopamine antagonists, also known as conventional or typical antipsychotics (including pimozide, haloperidol, fluphenazine)
- Second generation antipsychotics (SGA): also known as atypical antipsychotics, including dopamine-serotonin antagonists (risperidone, paliperidone) and multitarget antipsychotics (clozapine, olanzapine, ziprasidone, quetiapine, asenapine, iloperidone)
- Third generation antipsychotics (TGA): dopamine-functionally selective (aripirazole, brexpiprazole, cariprazine). "Functionally selective" in this context refers to the ability of a drug, such as aripiprazole, to produce specific functional effects at a receptor, in this case the D2 receptor, based on the activity of that receptor. Aripiprazole is considered functionally selective because it has both functional antagonist activity under hyper-dopaminergic conditions and functional agonist properties under hypo-dopaminergic conditions. (Araújo et al. 2012)

FGAs are linked with extrapyramidal side effects, tardive dyskinesia, and hyperprolactinemia. SGAs gained popularity over FGAs due to fewer neurological and cognitive side effects, but they have cardiometabolic side effects. TGAs act as serotonin-dopamine activity modulators and have fewer side effects than FGAs and SGAs (Sabe et al. 2022).

Antipsychotics can prevent relapse in SCZ, but they have significant side effects and may not be equally efficient for all patients. A Cochrane review found that 24% of patients still experienced relapse within a year of begin of drug treatment (Bighelli et al. 2021).

4.2.2.2 Psychosocial interventions

According to German treatment guidelines, individuals with schizophrenia should receive structured psychoeducation in a group setting as part of a comprehensive treatment plan. Family members and trusted individuals should also be included in the psychoeducational intervention. Additionally, specific psychotherapeutic family interventions should be offered to families with individuals experiencing first psychotic episodes. Cognitive remediation should be provided to individuals with cognitive impairments in order to improve cognitive and psychosocial functioning (DGPPN 2019).

These recommendations are consistent with the findings of Bighelli et al., who reported that family interventions, family psychoeducation and cognitive-behavioral therapy are effective in reducing relapse rates in patients with schizophrenia (Bighelli et al. 2021).

The treatment of schizophrenia should be integrated into a comprehensive treatment plan that is tailored to the individual and adapted to the specific phase of the illness. This plan should involve a multidisciplinary team and be conducted in close proximity to the patient's home. The plan should be created with the participation of the patient and all those involved in the treatment process (DGPPN 2019).

4.3 Bipolar disorder

BP is a chronic and recurrent illness that affects more than 1% of the world's population, with similar rates regardless of nationality, ethnic origin, or socioeconomic status (Grande et al. 2016). The

disorder typically begins in adolescence or early adulthood and is characterized by fluctuations in mood state and energy, which are shown in figure 2. Patients experience recurrent episodes of pathologic mood states, characterized by manic or depressive symptoms, which are interspersed by periods of relatively normal mood (euthymia) (Grande et al. 2016; McCormick et al. 2015).

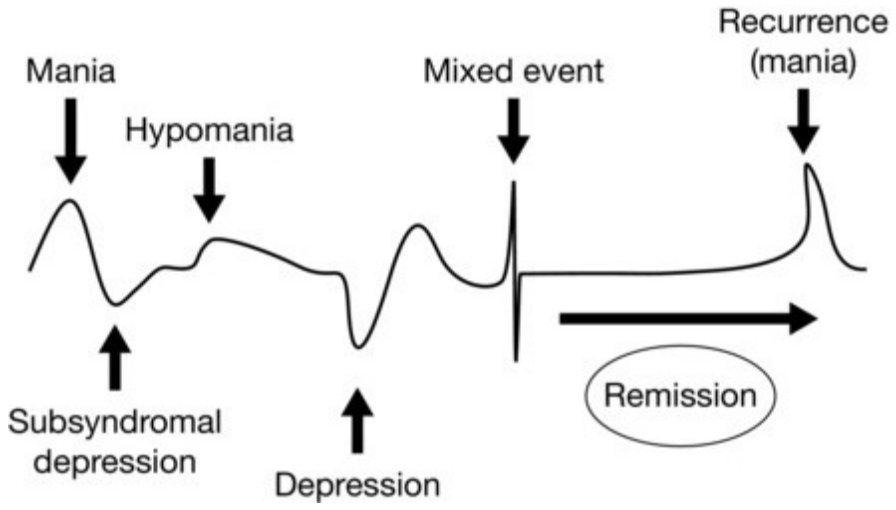

Figure 2: Mood range and associated mood diagnosis in BP (Reproduced with permission from Wolters Kluwer Health, ©2015. McCormick et al. 2015)

The symptoms of BP can be extremely disabling and can have significant impact on both the patients and their caregivers. This mental illness is a major contributor to disability in young people and can result in cognitive and functional impairments, as well as increased mortality rates, particularly due to suicide (McCormick et al. 2015). Individuals with bipolar disorder are at a significantly elevated risk of suicide compared to the general population. In fact, bipolar disorder has the highest rate of suicide among all mental health conditions, with an incidence that is estimated to be 20-30 times higher than that of the general population (Miller and Black 2020). According to Volavka, both schizophrenia and bipolar disorder are associated with a higher risk of violence compared to the general population. The evidence suggests that the risk of violence is higher in bipolar disorder than in schizophrenia, with most incidents occurring during the manic phase (Volavka 2013). Furthermore individuals with BP commonly have other medical and psychiatric conditions that coincide with their diagnosis (McCormick et al. 2015). Álvarez Ruiz et al. reported a substantial comorbidity between bipolar disorder and eating disorders, particularly bulimia nervosa and binge eating disorder, in their review (Álvarez Ruiz and Gutiérrez-Rojas 2015). Another review by Leo et al. found that the comorbidity rates between migraine and bipolar disorder are significantly higher than the estimated prevalence rates of the individual conditions in the general population (Leo and Singh 2016). According to Rossom et al., individuals with serious mental illness (SMI) such as bipolar disorder, schizophrenia, or schizoaffective disorder have significantly higher estimated 10-year and 30-year cardiovascular risk compared to those without SMI. This increased risk was observed even in young adults and was found to be the highest among patients with bipolar disorder and schizoaffective disorder (Rossom et al. 2022).

4.3.1 Clinical presentation and diagnosis of bipolar disorder

In clinical practice, accurately diagnosing BP can be challenging due to the similarity of its onset to that of unipolar depression, which is often marked by a depressive episode. Additionally, there are presently no biomarkers that can be used to diagnose this disorder, underscoring the importance of clinical evaluation. The identification of hypomanic episodes and a thorough evaluation over time are vital in distinguishing BP from other conditions (Grande et al. 2016).

The diagnosis of bipolar I disorder according to the DSM-5 requires the occurrence of a manic episode, while hypomanic or major depressive episodes are no absolute prerequisite. A manic episode is defined by Criterions A to D. Criterion A states that during a manic episode patients experience "abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently goal-directed behavior or energy, lasting at least 1 week" (Kaltenboeck et al. 2016; American Psychiatric Association 2022). They have to experience at least 3 of the following symptoms (Criterion B) (Kaltenboeck et al. 2016; American Psychiatric Association 2022):

1. Inflated self-esteem or grandiosity
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep)
3. More talkative than usual or pressure to keep talking
4. Flight of ideas or subjective experience that thoughts are racing
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli)
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation
7. Excessive involvement in pleasurable activities that have a high potential for painful consequences

Like people suffering from SCZ, patients with BP in a manic episode also encounter an impairment in social or occupational functioning (Criterion C). A hypomanic or major depressive episode, which may precede or follow a manic episode, is characterized by depressed mood, loss of interest or pleasure in almost all activities, sleep disturbance, psychomotor changes (agitation or retardation) etc (Kaltenboeck et al. 2016).

Individuals with bipolar II disorder show no manic episodes, but protracted depressive episodes and one or more hypomanic episodes (Phillips and Kupfer 2013).

4.3.2 Treatment of bipolar disorder

BP has a prevalence of 1-4%, depending on the used criteria, causes high direct and indirect costs, leads to a reduced life expectancy of more than 10 years for patients compared to the general population and is one of the leading causes for disability (Harrison et al. 2016). Consequently, effective treatment of BP is a central goal of modern psychiatry.

The treatment of BP —like that of SCZ— typically involves two distinct phases, acute and maintenance. During the acute phase, the focus is on managing the symptoms of the current mood episode, whether it be manic, hypomanic, or depressive. In contrast, the maintenance phase is geared towards preventing the recurrence of future acute episodes. These two phases have distinct treatment needs, and different medications have shown varying levels of effectiveness depending on the illness phase (Bobo 2017).

4.3.2.1 Pharmacological treatment

4.3.2.1.1 Mania

Acute mania can be treated with a range of medications including mood stabilizers such as lithium and valproic acid, as well as atypical antipsychotics like aripiprazole and risperidone (DGBS e.V. und DGPPN e.V. 2019; Kato 2019). In case of inadequate response to monotherapy, olanzapine or Risperidone can be used in addition to existing phase prophylaxis with lithium or valproate (DGBS e.V. und DGPPN e.V. 2019). There is no significant difference between monotherapies, but a combination of a mood stabilizer and an antipsychotic is more effective than mood stabilizer monotherapy (Kato 2019).

4.3.2.1.2 Depression

Limited options exist for treating acute bipolar depression. German treatment guidelines recommend a monotherapy with quetiapine, with alternative treatment options including olanzapine, carbamazepine, and lamotrigine (DGBS e.V. und DGPPN e.V. 2019). For tricyclic antidepressants and venlafaxine their potential for rapid cycling and manic switch should be considered (Kato 2019; DGBS e.V. und DGPPN e.V. 2019).

4.3.2.1.3 Maintenance

Lithium is the first-line treatment for maintenance treatment of BP, with lamotrigine, quetiapine, valproic acid, olanzapine, aripiprazole, and long-acting injectable risperidone as other options. Combination of lithium or valproic acid with atypical antipsychotics may also be effective (DGBS e.V. und DGPPN e.V. 2019; Kato 2019). Benzodiazepine use should be minimized due to limited data suggesting potential worsening of the course of BD (Kato 2019).

4.3.2.2 Psychosocial interventions

Psychotherapy in the treatment of bipolar disorder is used during acute episodes, maintenance and stabilization, and most importantly, to prevent new episodes of the illness. Psychotherapy is often combined with other treatments such as occupational therapy, sports or exercise, art therapy, or bodywork. However, it is important to note that psychotherapy is typically seen as a complement to medication, not as a substitute (DGBS e.V. und DGPPN e.V. 2019; Bobo 2017). In the case of mild manic and hypomanic episodes, cognitive behavioral therapy, psychoeducation, or family-focused treatment can be offered to achieve positive effects on the duration and intensity of symptoms. Psychotherapy should be offered for the treatment of acute depressive episodes in the context of bipolar disorder. For prophylactic treatment, extensive and interactive group psychoeducation is recommended. Manualized, structured cognitive behavioral therapy should be recommended for prophylactic treatment of bipolar disorder in the case of current stability and largely euthymic mood. Group psychoeducation is also recommended for prophylactic treatment of manic episodes, while psychoeducation and psychotherapy are recommended for prophylactic treatment of depressive episodes in bipolar disorder (DGBS e.V. und DGPPN e.V. 2019).

Overall, the treatment of BP requires a comprehensive and individualized approach that takes into account the patient's symptoms, medical history, and preferences (DGBS e.V. und DGPPN e.V. 2019).

While medication is often the first-line treatment, non-pharmacological interventions can be helpful adjuncts and may be particularly useful as recurrence prophylactic treatment (DGBS e.V. und DGPPN e.V. 2019).

4.3.3 Alda-scale

Assessing treatment response in SCZ and BPD are an important aspect of clinical management of the two disorders. While few standardized measures of treatment response exist for SCZ, only one widely adopted psychometric tool for measuring the long-term treatment response to mood stabilization with lithium in BP exists: the Alda-scale (Lee et al. 2020; Grof et al. 2002; Tighe et al. 2015).

The Alda-scale includes two subscales (Scott et al. 2020)

- Subscale A: measure of global treatment response
    - Values: 0 (no change or worsening) to 10 (complete response, no recurrences in the course of adequate treatment, no residual symptoms, and full functional recovery)
- Subscale B: five confounding factors (B1-B5) that affect treatment response
    - Number (B1) and frequency (B2) of episodes before treatment; duration of (B3) and adherence (B4) with treatment and use of additional medications (B5)
    - Each confounding factor is rated from 0 to 2
    - Subscale B = B1 + B2 + B3 + B4 + B5
- Total score (TS) = subscale A – subscale B
    - If the TS is negative, it is recalibrated as TS = 0
    - Dichotomous score (Nunes et al. 2020)
        - TS ≥ 7: responder
        - TS < 7: non-responder

4.4 Biomarkers

Biomarkers are measurable biological indicators that can be used to diagnose or track disease progression, treatment response, and overall health status (Diamandis 2010). In many instances, clinically used biomarkers are easier and less expensive to measure than the final clinical endpoint, and they are typically measured over a shorter duration (Aronson and Ferner 2017). The underlying concept behind the use of biomarkers for diagnosis of a disease is that a specific observation or measurement can act as a proxy of a biological process and signify the presence of a disease. One well-known example for a biomarker is the fasting blood glucose level, which is commonly used to diagnose and monitor diabetes. The prostate-specific antigen (PSA) is another important biomarker for the detection and monitoring of prostate cancer (Diamandis 2010).

To determine the significance of a biomarker, it is essential to comprehend the pathophysiological connection between the biomarker and the pertinent clinical endpoint. Effective biomarkers should be quantifiable with low variability, should have a considerable signal-to-noise ratio, and should promptly and dependably modify in response to changes in the condition or its treatment (Aronson and Ferner 2017).

Identifying effective biomarkers for SCZ and other psychiatric conditions like BP has been of great interest for many years. Biomarkers could lead to a more reliable and objective diagnosis, as well as identifying individuals at risk for developing the disease. They could also be useful for predicting treatment response and measuring disease outcome. Recent findings include elevated MBP and NDEL1 gene expression in early psychosis patients and elevated cytokine levels in individuals at risk for developing psychotic disorder (Davison et al. 2018). Similar efforts are also underway in BP, where the identification of objective biomarkers that distinguish it from unipolar depression could significantly aid in diagnosis and the development of personalized treatments. By providing biological targets for treatment development, such biomarkers can help improve treatment efficacy and patient outcomes while at the same time reducing harm from unwanted side effects by preventing unnecessary treatments (Phillips and Kupfer 2013).

Advances in technology have led to the use of Omics methods such as genomics, transcriptomics, proteomics, and metabolomics in the search for biomarkers in various mental health disorders (Davison et al. 2018).

4.5 Lipidomics

4.5.1 Omics

The field of Omics refers to the study of biological molecules and their functions at various levels in a comprehensive fashion, including the entire DNA sequence but not limited to genes and their regulatory elements (genome), all epigenomic modifications (epigenome), all RNA transcripts (transcriptome), all proteins (proteome), and all metabolites (metabolome). Omics approaches use high-throughput techniques that allow for the analysis of large quantities of genes, transcripts, proteins, or other molecular species in a single procedure or a combination of procedures. The goal is to understand complex biological processes holistically and in an unbiased fashion. By taking an integrative approach that combines multiple of these holistically queried layers of biology, “multi-omics” data can highlight the interrelationships of the involved biomolecules and their functions (Morrison et al. 2006; Schneider and Orchard 2011; Subramanian et al. 2020).

Metabolomics studies metabolites and metabolic networks, including lipids, and lipidomics is a distinct discipline within the field of metabolomics that considers the entire collection of chemically distinct lipid molecular species in a cell, an organ, or a biological system. The goal of these subgroups is to provide a system-level understanding of correlations and dependencies between molecular components and their functions (Subramanian et al. 2020; Schneider and Orchard 2011; Han and Gross 2022). The classification of lipidomics in the area of all Omics methods is shown in figure 3.

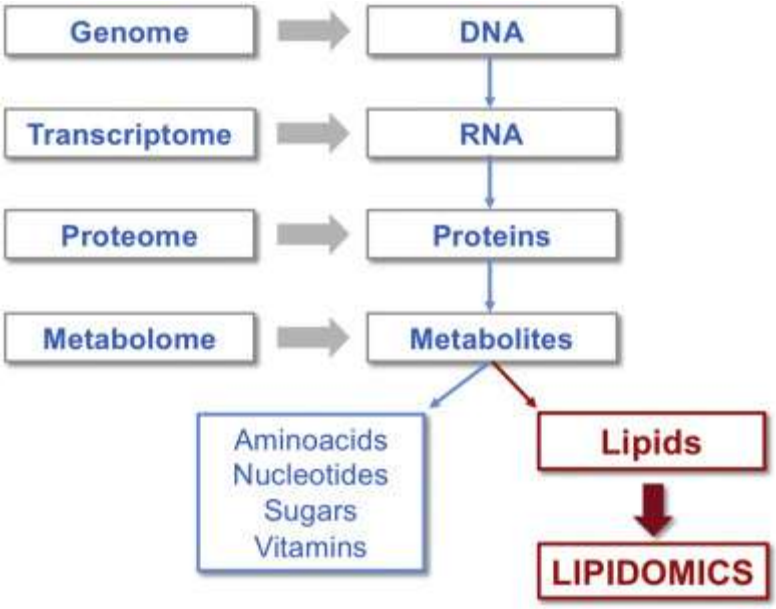

Figure 3: Classification of lipidomics in the area of all Omics methods (Reproduced with permission from Advanced Drug Delivery Reviews, ©2020. Wu et al. 2020)

4.5.2 Lipids

Lipids are a diverse group of molecules that are insoluble in water but soluble in non-polar organic solvents. They can be hydrophobic or amphiphilic, and the latter can form cellular membranes due to their hydrophilic headgroup and hydrophobic region (Cockcroft 2021). This allows lipids to self-assemble into complex structures in an aqueous environment (Cockcroft 2021; Lauwers et al. 2016). Lipids play a crucial role in many biological processes, including energy metabolism, cell signaling, and membrane structure (Wu et al. 2020; Züllig et al. 2020; Shevchenko and Simons 2010).

In terms of energy metabolism, lipids serve as a major source of energy for the body, with triglycerides being the primary storage form of energy. (Singh et al. 2009). Lipids are stored in the form of lipid droplets. These organelles are made up of a neutral lipid core surrounded by a phospholipid monolayer, and are primarily composed of triglycerides (TAGs) and cholesterol esters. Lipid droplets are formed in the endoplasmic reticulum (ER) and can be mobilized by hormones through a process of lipolysis, where lipases remove fatty acids from the TAGs for energy use (Cockcroft 2021).

Additionally, lipids are involved in cell signaling pathways, acting as signaling molecules, and are essential for proper cellular communication (Züllig et al. 2020; Shevchenko and Simons 2010; Cockcroft 2021). One example of where lipid signaling plays a role is in T cell responses, with selective lipid metabolites acting as metabolic rheostats to regulate intracellular signaling processes (Lim et al. 2022). Lipid metabolism also plays a significant role in cancer, with enhanced synthesis or uptake of lipids contributing to rapid cancer cell growth and tumor formation (Snaebjornsson et al. 2020). Additionally, lipids have been found to play important roles in regulating aging and longevity, with many genetic pathways linked to lipid metabolism and lipid signaling. Lipids are also known to act as signaling molecules, actively modulating lifespan and health span (Mutlu et al. 2021).

Introduction

Lipids play a crucial role in the formation of cell membranes and are involved in several cellular functions, including regulating membrane proteins, cellular architecture, and creating subcompartments in membranes. Membrane rafts, defined as dynamic, sterol- and sphingolipid-enriched protein assemblies, play a vital role in this process. Lipid-protein interactions and the specific binding of proteins with different lipid species in membranes remain largely uncharacterized. Nonetheless, increasing evidence suggests that specific protein-lipid interactions have possible structural and regulatory implications (Shevchenko and Simons 2010).

Lipids are also a crucial part of the brain's structure and function, with the brain having a unique lipidome that changes with age, gender, neuronal activity, stress, and trauma (Lauwers et al. 2016). Lauwers et al. show that the presynaptic terminal, which is essential for neurotransmitter release, is a membrane-remodeling machine that is sensitive to changes in lipid composition. The study highlights the importance of synaptic trace lipids, such as PtdInsPs (phosphatidylinositolphosphates), in providing specific membrane landmarks and working together with more abundant lipids to define bulk membrane properties. These findings suggest that the cooperation between lipid and protein molecules underlies presynaptic activity (Lauwers et al. 2016). Yu et al. investigated the lipidome composition of the prefrontal cortex gray matter in cognitively healthy individuals and individuals with autism, schizophrenia, and Down syndrome. The findings suggest that the cortical aging process involves substantial lipidome changes, and a clear increase in predicted membrane fluidity over the lifespan is observed. Additionally, all three cognitive disorders are accompanied by significant lipid concentration changes, which include shared and disease-specific pathway alterations. Lipidome changes in schizophrenia overlap with genetic variants linked to the disease, indicating the potential role of lipidome changes in its etiology (Yu et al. 2020).

Lipids have been shown to be involved in numerous essential biological processes, making them potentially valuable biomarkers for a variety of diseases. Changes in lipid profiles have been associated with numerous diseases, including metabolic disorders, cardiovascular diseases, and cancer. Therefore, a better understanding of the role of lipids in various diseases and the development of sensitive methods for lipid profiling can provide valuable insight into disease pathogenesis and potentially lead to the development of new therapeutic approaches (Shevchenko and Simons 2010; Wu et al. 2020; Züllig et al. 2020). One case that exemplifies the contribution of lipidomics to the understanding of the pathophysiology of a disease is Krabbe disease. The accumulation of lysosphingolipid psychosine in Krabbe disease has been proposed as a potential mechanism for the disruption of cellular membrane organization and neurotoxicity. The “psychosine hypothesis” has refined the understanding of the pathophysiology of Krabbe disease by showing how the disruption of sphingolipid metabolism can lead to the elevation of a toxic lysosphingolipid that disrupts “lipid rafts” and vesicular transport, which are critical for the function of glia and neurons (Spassieva and Bieberich 2016).

However, their potential goes beyond just biomarkers. Lipids may play a crucial role in the pathophysiology underlying mental health disorders, which could significantly advance our understanding of these complex conditions.

4.5.3 Lipidomic analysis

The analysis of lipids involves several stages, including the preparation of samples, the generation of mass spectrometric data, and the analysis of data using chemometrics, which are displayed in figure 4 (Wu et al. 2020).

Figure 4: The lipidomics workflow (Reproduced with permission from Springer nature, ©2019. Züllig et al. 2020)

4.5.3.1 Sample preparation

Lipids are typically not found in their free form within cells and are instead embedded in a matrix. To extract lipids from different sources, a variety of extraction methods have been developed. Lipids can be extracted from plasma, tissue, cells, or cell culture supernatants, with blood samples being particularly useful due to their high lipid content and their easy availability. In lipidomic research, both plasma and serum samples are commonly used for lipid analysis (Wu et al. 2020).

However, standardized protocols for sample preparation are crucial to ensure the reproducibility and comparability of lipid data (Lipidomics Standards Initiative Consortium 2019; Köfeler et al. 2021). It is worth noting that there is no one-size-fits-all extraction protocol for lipid analysis, as each lipid category and class has its own unique characteristics that may require specific extraction methods (Köfeler et al. 2021). While for polar lipids like glycerophospholipids, the Bligh and Dyer protocol may be slightly more suitable due to its higher proportion of methanol, the Folch protocol with its higher content of nonpolar chloroform in the organic phase is more effective in increasing the solubility of nonpolar lipids like triglycerides (TG) (Köfeler et al. 2021). Therefore, it is crucial to carefully select an appropriate protocol based on the lipid sample being studied to obtain reliable and comparable lipid data (Köfeler et al. 2021).

4.5.3.2 Data acquisition

Mass spectrometry (MS) is a powerful analytic technique used in lipidomics for the detection, identification, and quantification of lipids (Meikle et al. 2021; Wu et al. 2020). There are various setups for conducting lipidomics analysis, with direct infusion and LC/MS being two frequently used approaches. Direct infusion involves the infusion of an organic plasma extract directly into the spectrometer, without prior chromatographic separation, and is often described as "shotgun" lipidomics (Wu et al. 2020; Meikle et al. 2021). On the other hand, LC/MS involves the incorporation of liquid chromatography (LC) separation coupled with mass spectrometry, providing an additional dimension of characterization and potential sensitivity for low abundance lipids (Meikle et al. 2021). Internal standards are often included to account for variation in extraction recovery, matrix effects, ionization, and fragmentation efficiencies (Meikle et al. 2021; Khoury et al. 2018). Mass spectrometry can be used for targeted and non-targeted lipidomics, and the initial step involves sample preparation and lipid extraction (Meikle et al. 2021; Wu et al. 2020; Khoury et al. 2018). Targeted lipidomics focuses on known lipids and accurately determines their relative abundances, while non-targeted lipidomics screens all lipid species in a sample without preselection, resulting in a high

number of mass signals. Non-targeted lipid analysis requires chemometric methods to reveal relevant signals and database searches to identify unknown mass signals. The non-targeted approach allows the quantification of unknown but relevant lipids, making it a powerful tool for the identification of novel lipid biomarkers and mediators (Wu et al. 2020).

Mass spectrometry instruments consist of an ion source, analyzer, and detector system for producing gaseous ions, resolving the ions into their characteristic mass components, and detecting and recording the relative abundance of each resolved ion species (Khoury et al. 2018). There are five types of mass spectrometry methods available for lipid identification and quantification, including electrospray ionization MS, matrix-assisted laser desorption/ionization (MALDI) MS, gas chromatography/mass spectrometry (GC-MS), non-aqueous capillary electrophoresis (NACE), and MALDI imaging (Wu et al. 2020). Separation methods like gas chromatography (GC) and liquid chromatography (LC) are available for different lipid classes, with LC being the most frequently used separation method due to its high separation efficiency and selectivity. Although NACE has excellent separation efficiency, it is less sensitive than LC and GC (Wu et al. 2020). Figure 5 illustrates an extracted-ion chromatogram with the corresponding MS/MS spectrum.

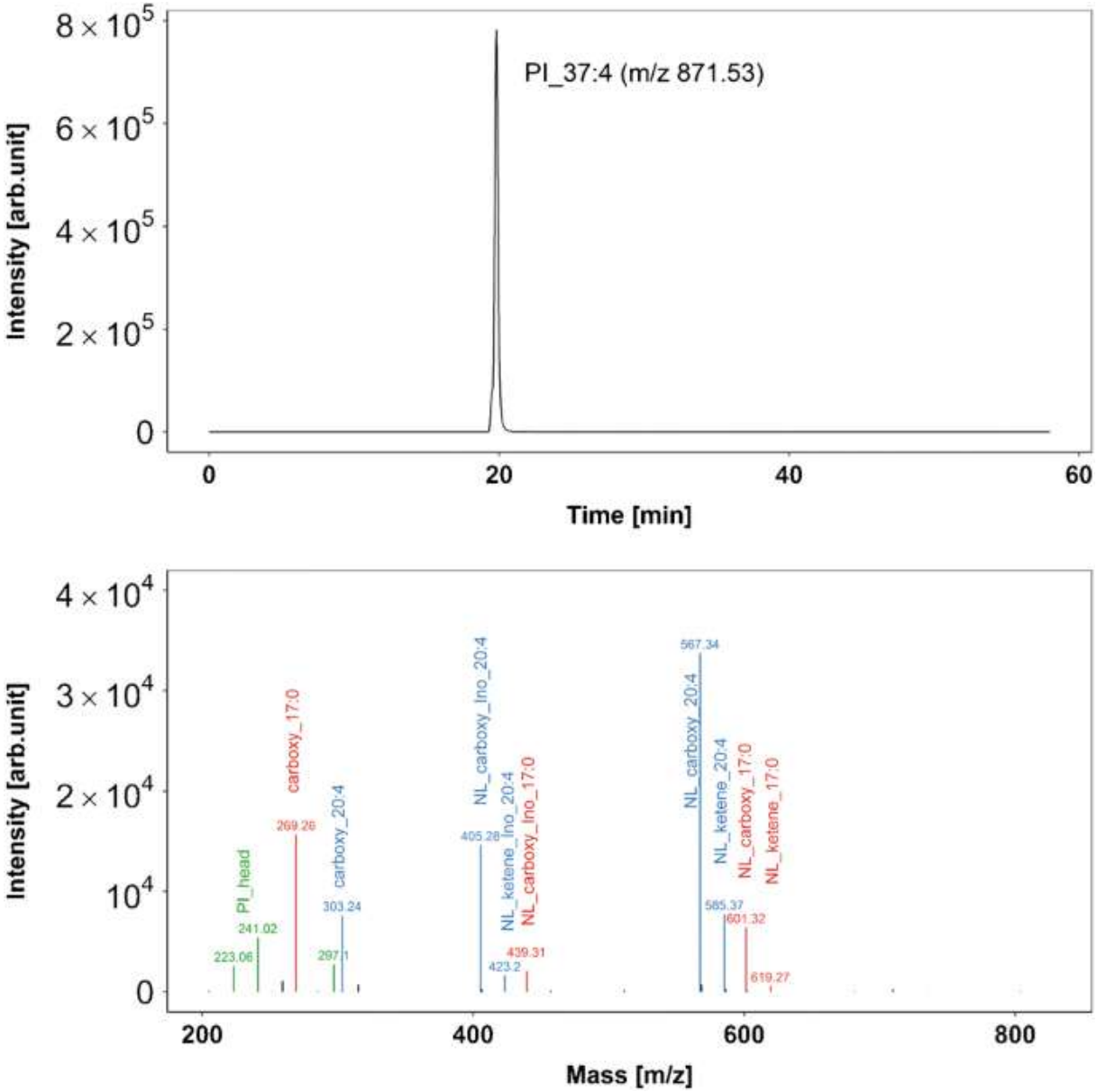

Figure 5: Upper panel: Extracted-ion chromatogram of glycerophosphoinositol, PI 37:4 (m/z 871.534 ± 5 ppm)
Lower panel: Corresponding MS/MS spectrum at a retention time of 19.82 min (CID fragmented). Blue fragments of 20:4 acyl chains, red fragments of 17:0 acyl chains, green fragments of PI head groups (Reproduced with permission from Springer nature, ©2019. Züllig et al. 2020)

4.5.3.3 Data processing

Several tools are available for MS-based lipidomics data analysis, such as LipidQA, LipidSearch, and LipidBlast (Triebl et al. 2017). However, there is no complete automation for "on-the-fly" data processing suitable for clinical lipidomics platforms (Meikle et al. 2021). Lipidr is an open-source R-based package that allows for data inspection, normalization, univariate and multivariate analyses, and visualization (Meikle et al. 2021). A major challenge in the field of lipidomics is the lack of uniform annotation for lipid species, which results in irreproducibility and difficulties in cross-study comparisons (Lipidomics Standards Initiative Consortium 2019; Liebisch et al. 2017). This problem is compounded by misidentifications, over-reporting, and reporting in arbitrary units rather than quantification of molecule numbers. Data repositories such as MetaboLights require the deposition of both raw data and experimental metadata in structured and accessible formats to allow for better

reproducibility and transparency of experimental results (Köfeler et al. 2021). The data format mzTab-M for metabolomics addresses these issues by capturing experimental metadata, summary information on small molecules across assays, MS features as a basis for quantitation, and evidence to support reporting of individual lipid or feature group identifications (Triebl et al. 2017; Köfeler et al. 2021; Meikle et al. 2021).

The analysis of lipids has emerged as a critical area of research in understanding various diseases, including mental disorders such as SCZ. Lipidomics, a metabolomics-based approach, enables the comprehensive analysis of lipids in biological systems, and recent technological advancements have significantly improved its applications in more complex biological samples. As many diseases exhibit notable changes in lipid profiles, lipidomics has become a valuable tool in scientific research. By exploring the biochemistry of lipids, lipidomics can provide insights into the specific roles of lipid molecular species in health and disease, and also aid in identifying potential biomarkers for preventive or therapeutic approaches in human health (Sethi et al. 2017).

5 State of research

5.1 Lipidomics in schizophrenia and bipolar disorder

The state of research on lipidomics in SCZ and BP is still relatively limited, but there has been a growing interest in recent years and various studies with heterogeneous results have been published. Table 1 gives an overview of studies assessing lipid alterations in patients with SCZ and BP mostly compared to healthy controls (CTL).

Table 1: Studies assessing lipid alterations in patients with SCZ and BP (Tkachev et al. 2023)

Study	Disease	Medication status	Sample size	Altered lipid classes
Cao et al., 2019	SCZ	pre- and post-treatment vs control	SCZ=225, CTL=175	CAR
Cao et al., 2020	SCZ	recently non-medicated (1 month)	SCZ=113, CTL=111	CAR, LPC, LPC_O
He et al., 2012	SCZ	medicated and non-medicated	SCZ=216, CTL=265	Only one lipid PC_O 38:6
Kriisa et al., 2017	SCZ	pre- and post-treatment vs control	SCZ=38, CTL=37	CAR
Leppik et al., 2020	SCZ	pre- and post-treatment vs control	SCZ=38, CTL=37	PC, PC_O, dSM
Liu et al., 2021	SCZ	medicated and non-medicated	SCZ=76, CTL=50	FFA, LPC, LPE, PC, PE, aspartic and lithocholic acid, carnitines
Solberg et al., 2016	SCZ	medicated	SCZ=55	total TAG, membrane PUFAs (blood cells, not blood plasma)

Tao et al., 2022	SCZ, BPD, MDD	medicated and non-medicated	SCZ=112, BPD=132, MDD=105, CTL=198	TAG, FFA
Tkachev et al., 2021	SCZ	medicated	SCZ=92	SCZ: Cer, TAG, PC, CAR, PC_O/PC_P, PE_O/PE_P
Tkachev et al., 2023	SCZ, BPD, MDD	medicated and non-medicated	SCZ=436, FEP=104, MDD=256, BPD=184, CTL=478	PC, PE, LPC, LPE, dSM, PC_O, PE_O
Wang et al., 2019	SCZ	medicated and non-medicated	SCZ=119 (28 FEP), CTL=109	PC, PE, LPC, LPE, dSM, PC-O, PE-O, FFA
Wang et al., 2020	SCZ	medicated and non-medicated	SCZ=119 (28 FEP), CTL=109	LPE_P, LPC_P, PE_P, PC_P
Wood et al., 2015	SCZ	medicated	SCZ=23, CTL=27	different lipids
Yan et al., 2018	SCZ	pre- treatment vs control and pre- vs post- treatment	SCZ=20, CTL=29	Cer, HexCer
Brunkhorst-Kanaan et al., 2019	BPD, MDD	medicated	MDD+BPD=67, CTL=405	different lipids
Guo et al., 2022	BPD	no information	BPD=24, CTL=30	FFA
Pomponi et al., 2013	BPD	medicated	BPD=42, CTL=57	different lipids
Ribeiro et al., 2017	BPDt	medicated	BPD=14, CTL=21	FFA
Saunders et al., 2015	BPD	medicated and non-medicated	BPD=27, CTL=31	FFA
Scola et al., 2018	BPD, MDD	medicated	BPD=87, MDD=34, CTL=31	different lipids including dSM, CAR, PE, LPE, TAG
Zhang et al., 2022	BPD	medicated	MDD=28, BPD=22, CTL=25	CAR

BPD bipolar disorder, CAR acylcarnitines, CTL controls, DAG diacylglycerides, dCer ceramides, dSM sphingomyelins, FFA free fatty acids, FEP first episode psychosis, HexCer hexosyl-metabolites of ceramides, LPE lysophosphatidylethanolamines, LPC lysophosphatidylcholines, LPC_O ether-linked lysophosphatidylcholines, LPC_P lysophosphatidylcholine plasmalogens, MAG monoacylglycerides, PC glycerophosphocholines, PC_O ether-linked phosphatidylcholines, PC_P phosphatidylcholine plasmalogens, PE phosphatidylethanolamines, PE_O ether-linked phosphatidylethanolamines, PE_P phosphatidylethanolamines plasmalogens, PI phosphatidylinositols, PG glycerophosphoglycerols, PS phosphatidylserines, PUFA polyunsaturated fatty acids, SCZ schizophrenia, TAG triglycerides

Lipidomics studies have identified potential diagnostic panels that could differentiate SCZ from healthy controls or major depressive disorder (Wang et al. 2022). In their review Zhuo et al. highlight the importance of lipidomics in the study of SCZ. Aberrations in specific lipid species, such as phospholipids and PUFAs, have been found to disrupt brain function and impair neurotransmitter systems (Zhuo et al. 2020). Liu et al. conducted a targeted metabolomics study using LC/MS to identify plasma lipid and amino acid biomarkers for SCZ. They analyzed plasma from 76 SCZ patients and 50 matched controls and identified one amino acid and 18 lipids or lipid-related metabolites, mainly from the classes FFA

(free fatty acids), LPC (lysophosphatidylcholines), LPE (lysophosphatidylethanolamines), PC (glycerophosphocholines) and PE (phosphatidylethanolamines), that were significantly differentially expressed between SCZ patients and controls. The identified biomarkers panel showed good diagnostic performance in discriminating SCZ patients from controls (Liu et al. 2021). When analyzing changes in blood plasma lipids in 92 SCZ patients during their inpatient treatment and their association with symptom improvement, Tkachev et al. found that short chain triglyceride species were increased in individuals with the least improvement in Positive and Negative Syndrome Scale scores (PANSS), suggesting a potential biomarker for treatment response in SCZ, even though this could not be replicated in a subsequent analysis (Tkachev et al. 2021; Tkachev et al. 2023). In a subsequent study Tchakev et al. analyzed the plasma lipidome composition of 980 individuals diagnosed with SCZ, MDD, BPD, or a first psychotic episode, as well as healthy controls, using LC/MS. They found 77 significantly altered lipids between those with SCZ and controls in all three sample cohorts, with consistent alterations also found in BPD and MDD (Tkachev et al. 2023). Based on lipidomics abnormalities Tao et al. identified transdiagnostic subtypes of mental health disorders (SCZ, BPD, MDD). Ten lipids were identified that classified patients and healthy controls. Two subtypes were found across patients with SCZ, BP, and MDD, with different clinical diagnosis, functional impairment, and brain white matter abnormalities (Tao et al. 2022). Cao et al. measured 29 acyl-carnitine levels in plasma samples from 225 subjects with SCZ and 175 age- and gender-matched healthy controls using LC-MS. The results showed significantly higher levels of C4-OH (C3-DC) and C16:1, but lower concentrations of several other acyl-carnitines in individuals with SCZ compared to healthy controls. Additionally, all detected acyl-carnitines were significantly different between pre- and post-treatment subjects (Cao et al. 2019). In another study Cao et al. recruited 113 recently non-medicated (1 month) patients with SCZ and 111 age- and sex-matched healthy subjects were recruited from China. LC/MS was used to analyze serum samples resulting in 11 metabolites, including LPC, LPE and CAR (acylcarnitines), separating patients and healthy controls (Cao et al. 2020). Leppik et al. used lipidomics to identify serum glycerophospholipids (GPLs) and sphingomyelins (SMs) associated with first-episode psychosis (FEP) before and after antipsychotic treatment. Results showed differences in lipid profiles between FEP patients and control subjects, with some changes after treatment, including alterations in PC, PC-O, dSM (Leppik et al. 2020). Kriisa et al. measured CAR levels in serum samples of antipsychotic-naïve FEP patients (n=38) and control subjects (n=37), and related to them inflammatory and metabolic biomarkers established in the same patient cohort. Seven months of antipsychotic drug treatment were also analyzed. The results showed increased levels of long-chain CAR and decreased levels of short-chain CAR in FEP patients compared to controls. Antipsychotic drug treatment reversed these levels back to those established for controls (Kriisa et al. 2017). Using targeted metabolomics, He et al. compared the levels of 103 metabolites in plasma samples from 216 healthy controls and 265 SCZ patients, including 52 without antipsychotic medication. They found that levels of four amino acids and one lipid (PC-O 38:6) were significantly altered in SCZ patients (He et al. 2012). Yan et al. used an untargeted lipidomic approach to analyze plasma lipidomic profiles of 20 SCZ patients pre- and post-antipsychotics treatment and 29 healthy controls. 47 lipids belonging to 9 lipid species were found to be dysregulated between naive SCZ patients and healthy controls, and 50 lipids belonging to 9 lipid

species were found to be dysregulated after antipsychotics treatment (Yan et al. 2018). Solberg et al. analysed lipid data from 55 patients with SCZ in an acute stage of the disease (T1) and after 5 years at a stable phase (T2). Serum lipid levels remained stable over time, with TAG significantly higher in patients compared to healthy controls at T1 and T2. Higher serum lipid levels were associated with more severe symptoms and poorer functioning at T2, and with more severe symptoms and poorer functioning at T1 (Solberg et al. 2016). Wood et al. investigated potential biomarkers of disease onset in SCZ by analyzing choline and ethanolamine plasmalogens in the plasma and platelets of 23 patients with SCZ and 27 controls. They found that plasma levels of both plasmalogens were decreased by 23 to 45% in patients with SCZ and that ethanolamine plasmalogens were also decreased in platelets (Wood et al. 2015). Wang et al. identified potential lipid biomarkers for SCZ using an untargeted LC-MS-based metabolic profiling approach on serum samples from 119 SCZ patients and 109 healthy controls. They found 51 significant lipid metabolites, with most PC, PE and LPC decreased in patients, while most LPE and dSM (sphingomyelins) increased (Wang et al. 2019). In a case-control study Wang et al. used a targeted LC-MS approach to measure the levels of 177 phospholipids and FFAs in serum samples. The results showed that 110 metabolites, including various types of phospholipids and dSM, were significantly altered in SCZ patients compared to controls indicating that phospholipid metabolism disturbances and lipid profile abnormalities are associated with SCZ (Wang et al. 2019; Wang et al. 2021).

In a study conducted by Zhang et al. female individuals with MDD (n=28), bipolar depression (n=22), and healthy controls (n=25) were assessed for clinical symptoms and underwent plasma lipid profiling using LC/MS. The results showed significant differences in lipid composition between patients with MDD and BP compared to controls and to each other, including alterations in dSM, CAR, PE, LPE and TAG. The study also identified potential diagnostic biomarkers that can distinguish MDD from HC, bipolar depression from HC, and MDD from bipolar depression (Zhang et al. 2022). Brunkhorst-Kanaan et al. conducted targeted and untargeted lipidomic analyses on 67 patients with unipolar or bipolar disorders and 405 healthy controls. The study found that ceramides and their hexosyl-metabolites were strongly increased in male patients with mood disorders, but not associated with the current episode or therapeutic improvement. The levels of long-chain ceramides were linearly associated with age, and patients receiving antidepressants had higher ceramide levels. There was no such association with lithium or antipsychotics except for olanzapine (Brunkhorst-Kanaan et al. 2019). Guo et al. performed lipid profiling on plasma samples from 24 female BPD patients and 30 healthy controls using LC/MS. Several lipid classes were found to be up or downregulated in BPD patients and were correlated with symptom severity. A set of nine lipid biomarkers was identified, providing a high accuracy (AUC = 0.994) for distinguishing BPD patients from healthy controls (Guo et al. 2022). Pomponi et al. measured fasting plasma levels of 15 FAs in 42 patients with BPD and 57 age- and gender-matched healthy controls using GC/MS. The study found that patients had significantly decreased levels of plasma docosahexaenoic acid compared to controls, but higher levels of all other FAs, including arachidonic acid, alpha-linolenic acid, and eicosapentaenoic acid (Pomponi et al. 2013). Ribeiro et al. compared the serum lipid profile of 14 bipolar disorder type I patients and 21 healthy controls using ultra-high performance LC/MS. They

found significant differences in 121 lipids between the two groups, with phosphatidylinositols being the most altered followed by glycerophospholipids, glycerolipids, and sphingolipids (Ribeiro et al. 2017). Saunders et al. conducted an observational, parallel group study comparing biomarkers between healthy controls (n = 31) and subjects with BPD (n = 27) during symptomatic and follow-up phases. The study found a large effect size of reduced unesterified eicosapentaenoic acid in the symptomatic BPD state, and altered n-3 polyunsaturated fatty acids ratios could indicate changes in polyunsaturated fatty acidsmetabolism concurrent with symptom improvement. However, no statistically significant difference was seen in any plasma polyunsaturated fatty acids concentration between the BPD and control groups after correction for multiple comparisons (Saunders et al. 2015). Scola et al. conducted a study in which they serum samples of 87 patients with BPD (31 euthymic, 22 depressive), 34 patients with MDD, and 31 non-psychiatric controls. They found no significant difference in total levels of fatty acids between the groups. They found a positive correlation between illness duration and omega-6 levels in BPD patients (Scola et al. 2018). Significant alterations in levels of free fatty acids, phosphatidylcholine, and ceramides have been found in post mortem gray and white matter of the prefrontal cortex in both SCZ and BP patients compared to healthy controls (Schwarz et al. 2008).

Taken together, it can be concluded that most studies to date have focused on a limited number of lipid classes, soley focused on a single mental health disorder and mostly evaluated in small sample sizes (rarely more than 100 individuals) (Tkachev et al. 2023; Wang et al. 2022). This emphasizes the importance of conducting more comprehensive and systematic evaluations of lipidome changes observed in specific disorders and their specificity to that disorder in cohorts with more patients with different diseases taking more lipid classes into consideration, ideally in an unbiased (i.e. untargeted) approach.

5.2 Lipidomics and antipsychotics

SCZ is primarily treated with typical or atypical antipsychotic drugs that control especially the positive symptoms of the disorder, but long-term use of these drugs often results in metabolic syndromes (Pereira et al. 2023; Kim et al. 2019). Whether the metabolic syndrome in SCZ is primarily a treatment effect, related to the behavioral changes inherent to the disorder or a common, coincident predisposition and medical condition is still unresolved (McEvoy et al. 2013). Although the exact mechanisms remain unclear, antipsychotic-induced lipid disturbances are a contributing factor to the link between antipsychotic treatment and metabolic and cardiovascular disease (Pereira et al. 2023). Analyzing the lipidomic effects of these drugs is crucial for advancing knowledge in the field (Correia et al. 2021). An overview over studies analyzing the effects of antipsychotics intake on lipid profils is shown in table 2.

Table 2: Studies assessing lipid alterations in patients with SCZ before and after treatment with antipsychotics

Study	Antipsychotics	Sample size	Lipid classes

Almeida et al., 2020	risperidone, olanzapine, quetiapine	SCZ=54	All treatments: dCer, PA, PC, PE, PI, PG, PS; only risperidone: DAG, CerP, TAG, dSM, PI_Cer
Kaddurah-Daouk et al., 2007	olanzapine, risperidone, aripiprazole	SCZ=50, CTL=16	SCZ: CE, DAG, FA, LPC, PC, PE, TAG olanzapine: TAG, PE, PC, CE, LPC risperidone: PE, PC, LPC, FA aripiprazole: PE
Tkachev et al., 2023	Information not available	FEP=92	CAR, LPC, PC, TAG, PE, PC
McEvoy et al., 2013	risperidone, aripiprazole	SCZ=20, FEP=20, CTL=29	PC, PE (only PC and PE were analysed)

CAR acylcarnitines, CE cholesteryl esters, CerP ceramide 1-phosphates, CTL controls, dCer ceramides, DAG diacylglycerides, dSM sphingomyelins, FA fatty acids, FEP first episode psychosis, LPC lysophosphatidylcholines, PC glycerophosphocholines, PE phosphatidylethanolamines, PI_Cer ceramide phosphoinositols, PG glycerophosphoglycerols, PS phosphatidylserines, SCZ schizophrenia, TAG triglycerides

Several studies have investigated the changes in lipid metabolism in SCZ patients and how they are affected by antipsychotic treatment. Almeida et al. evaluated lipidome changes in blood plasma samples of SCZ patients before and after 6 weeks of treatment with either risperidone (n = 23), olanzapine (n = 17) or quetiapine (n = 14). LC-MS/MS analysis showed changes in the levels of several lipid classes for all treatments, including Cer, PC, PE, PI (phosphoinositols), PG (glycerophosphoglycerols), and PS (phosphatidylserines). However, the treatment with risperidone also affected DAG (diacylglycerides), CerP (ceramide 1-phosphates), TAG, SM, and PI-Cer (ceramide phosphoinositols). Moreover, specific lipid profiles were observed that could be used to distinguish poor and good responders to the different antipsychotics (Almeida et al. 2020). Pereira et al. reviewed how antipsychotic medications affect lipid metabolism in individuals with schizophrenia. Antipsychotics are effective but increase the risk of metabolic disorders and premature cardiovascular death. The review highlights gaps in the understanding of how antipsychotics affect lipid metabolism at different levels and calls for further research in this area (Pereira et al. 2023). Kaddurah-Daouk et al. analysed 50 patients with SCZ and 16 healthy controls before and after treatment for 2-3 weeks, with olanzapine (n=20), risperidone (n=14), or aripiprazole (n=16). The authors found that olanzapine and risperidone affected a broader range of lipid classes than aripiprazole. Concentrations of TAG increased and FFA decreased with both olanzapine and risperidone but not with aripiprazole. PE concentrations, which were suppressed in patients with schizophrenia, were raised by all three drugs. A principal component analysis identified baseline lipid alterations that correlated with acute treatment response (Kaddurah-Daouk et al. 2007). Tkachev et al. analyzed 104 FEP patients before and after antipsychotic treatment and 92 controls in addition to the long-term patient analysis mentioned above. The study found that lipid alterations observed in long-term SCZ patients were also present in FEP patients treated with antipsychotics for less than a week. This included alterations in various lipid species belonging to CAR, LPC, PC, TAG, PE, and PC lipid classes (Tkachev et al. 2023). McEvoy et al. measured individual lipid species in 20 drug-naïve FEP SCZ patients, 20 non-adherent patients with chronic SCZ, and 29 control subjects using a lipidomics platform. The FEP group showed significant down-regulation of several n3

polyunsaturated fatty acids within the PC and PE lipid classes compared to controls. No differences were noted in n6 class PUFAs. The patients with chronic SCZ were not significantly different from controls. Drug treatment with risperidone and aripiprazole corrected the aberrant PUFA levels in FEP patients (McEvoy et al. 2013). Correira et al. evaluated the blood serum lipids of an animal model for SCZ and a normal control rat strain after long-term treatment (30 days) with typical haloperidol or atypical clozapine antipsychotics. The study also evaluated the effects of psychostimulants amphetamine or lisdexamfetamine on serum lipids. The study found greater lipid changes for clozapine compared to haloperidol. Clozapine treatment showed the greatest lipid variations for comparisons between antipsychotic-treated and control animals receiving vehicle. Haloperidol slightly increased polyunsaturated fatty acids and phospholipids. The study identified choline glycerophospholipids as an important lipid subclass to distinguish the effects of clozapine in normal control rats, as choline glycerophospholipids levels decreased after clozapine treatment. This effect was opposite to that observed in the animal model for SCZ treated with clozapine (Correia et al. 2021).

Antipsychotic drugs used to treat SCZ are effective in controlling positive symptoms, but long-term use can lead to metabolic syndromes, and studies investigating whether these metabolic disorders are primarily a treatment effect or a predisposition have yielded inconsistent results, highlighting the need for further research. Lipidome analysis suggests changes in lipid metabolism in patients treated with antipsychotic drugs with some but not all lipids being affected by medication (Tkachev et al. 2023), and specific lipid profiles have been identified as potential biomarkers for treatment response, but the exact mechanisms behind these changes remain unclear, and further research is necessary to fully understand the influence of antipsychotic treatment on circulating lipids.

6 Question and objective

6.1 Disease effects

The starting point of this analysis is to investigate potential differences in lipid profiles among patients with BP, SCZ, and healthy controls. Specifically, the study aims to identify the specific lipid classes and peaks that show significant alterations in these patient groups. Furthermore, the analysis will explore whether similar lipid species are affected when comparing SCZ to BP, or if there are specific alterations unique to each disorder.

These results have the potential to provide valuable insights into the underlying mechanisms and pathways involved in these diseases. Additionally, a deeper understanding of the extent of overlap and differences between BP and SCZ could shed light on whether they represent distinct disease entities or a spectrum disorder. The identification of potential markers that can differentiate between these disorders or indicate a psychosis spectrum disorder would have significant clinical implications for accurate diagnosis and treatment strategies.

6.2 Impact of medication intake

In a second step this thesis will investigate the impact of medication intake on lipid profiles. Specifically, the second part of this study takes into account all medication types that patients may be taking, such as antipsychotics, antidepressants, mood stabilizers, and tranquilizers.

By analyzing changes in individual lipid peaks and lipid classes, this study aims to determine whether medication intake alters the lipidome and whether the induced changes are similar for drugs from the same medication class. This analysis has the potential to shed light on the mechanisms of action of different medications, as well as to help interpret lipidomic data from patients.

If specific medications have a significant impact on lipid profiles, they need to be taken into consideration as a covariate when analyzing lipid profiles from patients taking this specific medication. Moreover, if the changes in lipid profiles induced by different medications are similar, it suggests that they may act through similar mechanisms, while different changes in lipid profiles for each medication class would indicate distinct mechanisms of action.

Therefore, this thesis seeks to address the following questions: Does medication intake alter the lipidome? Are the induced changes similar for drugs from one medication class, or are there different changes in the lipid profile for each medication class? By answering these questions, this study aims to provide valuable insights into the complex relationship between medication intake and lipid profiles.

6.3 Lithium response

This thesis will specifically emphasize the analysis of the effects on the lipidome and treatment response related to lithium, a widely used mood stabilizer in patients with BP. Since its introduction, Lithium has been one of the primary mood stabilizers used for long-term maintenance treatment in patients with BP and the first-line treatment recommended in the current treatment guidelines of the Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN 2019). In addition to its effectiveness in preventing manic episodes and reducing the risk of relapse, lithium has also been proven to reduce the risk of suicide attempts (Fountoulakis et al. 2022; Hou et al. 2016; Song et al. 2017). However, not all patients respond to lithium treatment in the same way, with about 20% to 30% of patients experiencing sustained improvement, while 30% have only partial response and over 40% have no response at all (Hou et al. 2016). The lack of a clear understanding of lithium's mechanism of action complicates efforts to identify molecular targets for its response variability. Identifying patients who are likely to respond to lithium before treatment could significantly reduce the duration of untreated illness (Papiol et al. 2022; Idemoto et al. 2021). The identification of biomarkers that predict response to lithium treatment in patients with BP holds great promise for improving the management of this complex and often debilitating condition.

Given the current limitations in predicting patient response to lithium treatment for BP, this issue is being addressed in this thesis through the search for potential markers of treatment response. Although several biomarkers have been proposed, the use of lipidomics for this purpose has not yet been explored. Therefore, this thesis aims to investigate the lipid profiles of patients taking lithium

and compare them to those of patients not taking lithium, in order to identify potential differences that may indicate a biomarker for response. Additionally, associations between lipid profiles and changes in the Alda-scale will be examined, in an effort to establish a response lipid profile.

Through a rigorous analysis of lipid profiles, this thesis will explore potential associations between specific lipid classes and lithium response. By identifying the lipid profile changes associated with positive treatment outcomes, this thesis aims to lay the foundation for a predictive biomarker for lithium response.

7 Methods

7.1 Data collection

The data analyzed in this thesis was obtained from the transdiagnostic PsyCourse study, which is a multicenter study conducted across 18 clinical sites in Germany and Austria. The study focuses on the affective-to-psychotic continuum and combines longitudinal deep phenotyping and dimensional assessment of psychopathology with an extensive collection of biomaterial, including blood plasma samples, at four time points over an 18 months period. (Budde et al. 2019). The study includes approximatley 1800 individuals at baseline, including patients with DSM-4 diagnoses of a range of affective and psychotic disorders, as well as healthy controls. Lipidomic data was obtained from 622 individuals included in the PsyCourse study. This thesis focuses on the analysis of this subset of individuals. Among these individuals, there were 430 patients, including 187 with SCZ and 243 with BP, as well as 192 controls (chapter 8.1 Baseline characteristics).

Medication data was collected for each individual in the PsyCourse Study (Budde et al. 2019), which included information on the following medication classes/groups: antidepressants, antipsychotics, mood stabilizers, and tranquilizers. Additionally, the most commonly used antipsychotics, antidepressants, and mood stabilizers in this dataset were included in the analysis individually. These included, among others, aripiprazole, bupropion, clozapine, escitalopram, haloperidol, lamotrigine, lithium, mirtazapine, olanzapine, paliperidone, quetiapine, risperidone, sertraline, valproic acid, venlafaxine, and ziprasidone. More information can be found in The PsyCourse Codebook, which contains a list of all deep-phenotyping variables (Heilbronner et al. 2021).

Liquid chromatography coupled with untargeted mass spectrometry (LC-MS) was utilized to measure blood plasma lipid intensities in both negative and positive ionization modes at the Max-Planck Institute for Evolutionary Anthrophology, Leipzig, Germany, and Skolkovo Technical University, Moscow, Russia, in collaboration with the laboratory of Prof. Philipp Khaitovitch. The approach allowed for the reproducible detection of 1,361 lipid features, out of which 394 lipid compounds were annotated based on their retention time, mass-to-charge properties, and LC-MS2 fragmentation patterns for a subset of compounds. These annotated lipids belonged to 16 lipid classes and were consistent with previously reported blood plasma lipidome components (Tkachev et al. 2023; Burla et al. 2018; Bowden et al. 2017; Wang et al. 2021; Kaddurah-Daouk et al. 2007).

7.2 Data preparation

The original dataset from the PsyCourse study contained a total of 757 plasma lipidome measurements from 622 individuals. However, since this thesis centered around a cross-sectional analysis, only one timepoint per individual was considered. In cases where an individual had multiple measurements at different timepoints, the measurement with less information about the individual, like sex, age, bmi, medication, was discarded. If both timepoints had the same amount of information, the first measurement was used for the analysis.

Furthermore, lipids of a known association with fasting status (n = 30), of which 27 were annotated as free fatty acids, were discarded from the analysis (Tkachev et al. 2023). This left a total of 365 annotated lipids and 1280 detected features for further analysis.

After discarding the lipids associated with fasting status, the remaining data was centered and scaled using the scale function in R 4.2.1 (R Core Team 2022). Any lipid intensities with a standard deviation greater than 3 were considered outliers and were set to NA (not available) to ensure that they did not significantly influence the analysis. This is a common technique in data preprocessing to remove extreme values that could skew the results of statistical analyses.

However, before statistical tests could be performed on the data, normality criteria had to be met (Kim and Park 2019). To assess normality, skewness (measure of symmetry of the distribution) and kurtosis (measure of heaviness of the distribution tails) were calculated for each peak (representative of one lipid species) in the data. Peaks with an absolute value for skewness greater than 1 and an absolute value for kurtosis greater than 5 were discarded from the analysis (Hair J et al. 2010; Byrne 2010). This step was necessary to ensure that the data met the assumptions of normality required for many statistical tests.

7.3 Data analysis

7.3.1 Subgroups

To address the various research questions, a total of 29 subgroups were analyzed. Of these, three subgroups assessed the diagnosis, with one comparing patients with SCZ to controls, another comparing patients with BP to controls, and a third comparing patients with BP to patients with SCZ.

25 subgroups were based on medication intake, including antipsychotics, antidepressants, mood stabilizers, tranquilizers, tricyclic antidepressants (TCA), selective serotonin reuptake inhibitors (SSRIs), and selective norepinephrine reuptake inhibitors (SNRIs), the receptor profiles ZPR (ziprasidone, paliperidone, risperidone) and CO (clozapine, olanzapine), and individual drugs such as aripiprazole, bupropion, clozapine, escitalopram, haloperidol, lamotrigine, lithium, mirtazapine, olanzapine, paliperidone, quetiapine, risperidone, sertraline, valproic acid, venlafaxine, and ziprasidone. These subgroups were designed to assess whether lipid profiles were similar within medication classes, which would suggest a shared mechanism of action.

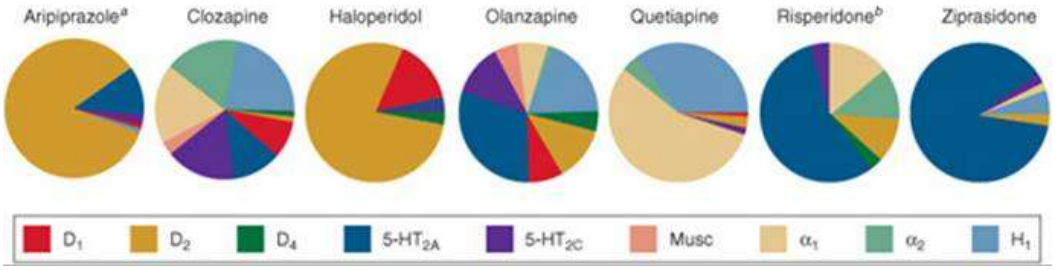

Figure 6: Profiles for receptor binding of second-generation antipsychotics and haloperidol. [a]Partial agonist activity at D_2 receptors, whereas all others are D_2 antagonists. [b]Paliperidone data are unavailable but would be expected to be similar to risperidone. (D, dopamine receptor; H_1, histamine receptor; 5-HT, serotonin receptor; Musc, muscarinic receptor; α_1 and α_2, receptors.) (Chisholm-Burns 2010)

While many classes of drugs have consistent mechanisms of action, such as benzodiazepines and SSRIs, antipsychotics have a wide range of mechanisms of action. Figure 6 shows receptor binding profiles of second-generation antipsychotics and haloperidol (Chisholm-Burns 2010). To address this variability, two subgroups of antipsychotic medications based on their receptor profiles were considered. The goal was to identify common effects on lipid composition that might be related to shared mechanisms of action among medications with similar receptor profiles.

Another subgroup examined the treatment response to lithium by evaluating Alda-scores (Lee et al. 2020; Grof et al. 2002; Tighe et al. 2015).

To analyze and compare the subgroups, a workflow as depicted below was established and then applied to each of the cohorts. This allowed for a systematic and consistent approach to analyzing the data and addressing the research questions.

7.3.2 Matching

The workflow for the analysis involved the first step of matching the cohort using the match.it package in R (ref), which offers various methods of matching. The choice of matching method depended on the size of the cohort. In order to achieve the best performance, for cohorts with less than 300 individuals, nearest neighbor matching was used, while for cohorts with more than 300 individuals, optimal full matching was used. Supplementary table S1 delineates which strategy was used for which analysis.

For the Alda subgroup it was not feasible to perform matching within the group, since only 81 individuals were included in this subgroup. Furthermore, matching outside the group was not possible since the treatment response information was only available for individuals with an Alda-score.

Nearest neighbor matching involves pairing each treated unit with a control unit that has the closest propensity score. Any remaining control units are excluded from the analysis. This method has been shown to effectively balance covariates in the treatment groups due to the balancing properties of the propensity score. (Rosenbaum and Rubin 1983) Nearest neighbor matching was used for the following cohorts: tranquilizers, TCA, SSRI, SNRI, receptor profiles ZPR (ziprasidone, paliperidone, risperidone) and CO (clozapine, olanzapine), aripiprazole, bupropion, clozapine, escitalopram,

haloperidol, lamotrigine, lithium, mirtazapine, olanzapine, paliperidone, quetiapine, risperidone, sertraline, valproic acid, venlafaxine and ziprasidone.

Optimal full matching assigns each treated and control unit to a subclass, where each subclass contains one treated unit and one or more control units or one control unit and one or more treated units. This method minimizes the sum of the absolute within-subclass distances in the matched sample, and weights are computed based on subclass membership. These weights function like propensity score weights and can be used to estimate a weighted treatment effect that is ideally free from confounding by the measured covariates. (Stuart and Green 2008; Hansen 2004) Optimal full matching was used for the following cohorts: antipsychotics, antidepressants, mood stabilizers, SCZ and BP.

In order to perform the matching, several covariates were taken into account including age, sex, BMI, and diagnosis. By taking these covariates into consideration, the matching process aimed to reduce the influence of confounding variables and increase the validity of the results obtained.

To ensure the quality control of the matching process, the match.it package provides various tools. One of these is a function that computes the standard pairwise and standard mean distance for each of the covariates, as well as an overall score. This allows for an assessment of how well the matching algorithm performed in terms of achieving balance between the matched groups across the selected covariates.

Another feature offered by the package is the ability to visualize the distribution of propensity scores for the matched individuals. This allows for a graphical representation of how well the propensity scores were balanced between the matched groups. Figure 7 shows the exemplary distribution of propensity scores for the matched lithium cohort.

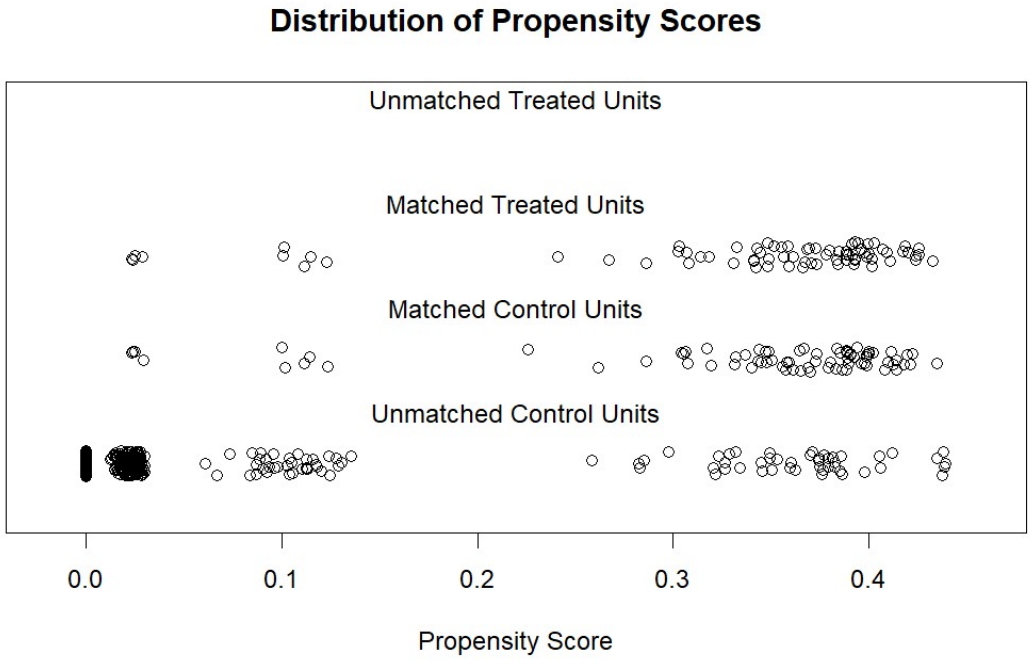

Figure 7: Exemplary distribution of propensity scores for the matched lithium cohort of 152 individuals

Both of these features were utilized for each of the cohorts to ensure that proper matching was performed and that the matched groups were as similar as possible across the selected covariates.

7.3.3 Workflow T-Test

In the first part of the workflow, a two-sided t-test was conducted for several variables in the cohorts, including antipsychotics, antidepressants, mood stabilizers, tranquilizers, BP, SCZ, the dichotomous version of the Alda-score (Lee et al. 2020; Grof et al. 2002; Tighe et al. 2015), the two receptor profiles ZPR and CO as well as for aripiprazole, clozapine, haloperidol, lithium, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone. A two-sided t-test can only be performed on a binary variable, so the dichotomous version of the Alda-score was used for this test. Additionally, a linear model was applied to the continuous version of the Alda-score to find peaks that showed a significant association with the Alda-score.

In statistical analysis, conducting multiple hypothesis tests increases the risk of obtaining false positive results. To address this issue, a correction for multiple testing was performed using the Benjamini-Hochberg correction (Lee et al. 2020; Grof et al. 2002; Tighe et al. 2015). This method adjusts the p-value threshold for statistical significance to control the overall false positive rate by taking into account the number of tests performed (Andrade 2019).

After applying the correction, a list was created for each of the cohorts that included all significant peaks that remained after the Benjamini-Hochberg correction.

7.3.4 Workflow Lipidr

For the second part of the analysis, a software package called lipidr in R was utilized. This package is designed specifically for analyzing and mining lipidomics datasets, and includes a range of features for data import, normalization, and analysis. One key feature of lipidr is its ability to import data from various sources, including public lipidomics datasets. The package also includes uni- and multivariate analysis capabilities, and results are displayed using interactive visualizations (Mohamed et al. 2020b). In lipidr only annotated peaks can be analysed, as only peaks with annotation can be imported.

7.3.4.1 Preprocessing and quality control

After the data preprocessing steps, lipidr generates various plots of samples and measured lipids for quality control. Box plots are used to visualize the distribution of samples within each subgroup, an example of which is shown in figure 8 for the risperidone subgroup, and intensity distributions within different lipid classes, which is illustrated in figure 9 likewise for the risperidone subgroup, is also plotted.

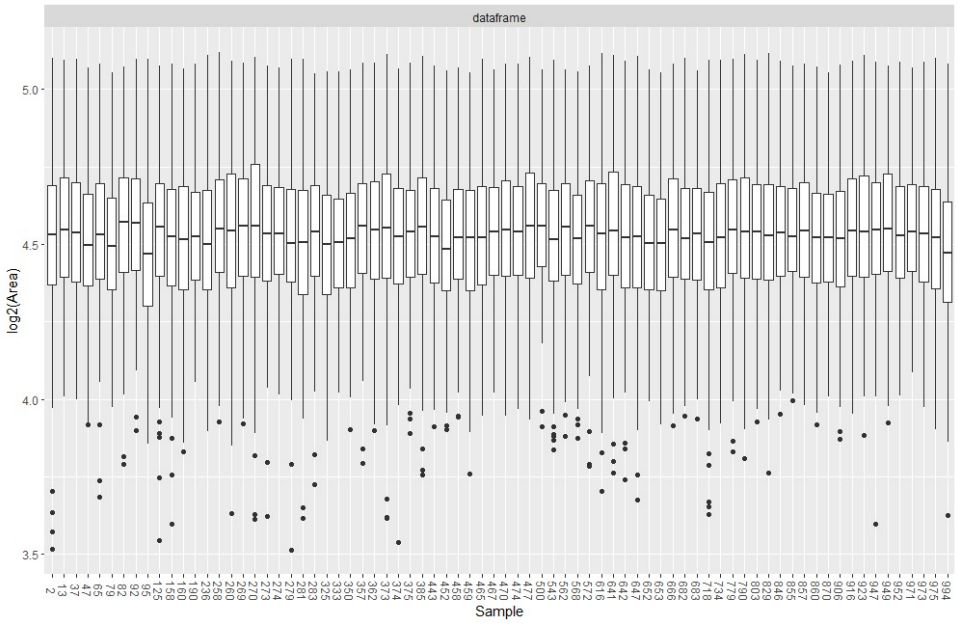

Figure 8: Distribution of samples for the risperidone subgroup. The sample number is plotted on the x-axis, the log2(Area) is shown on the y-axis

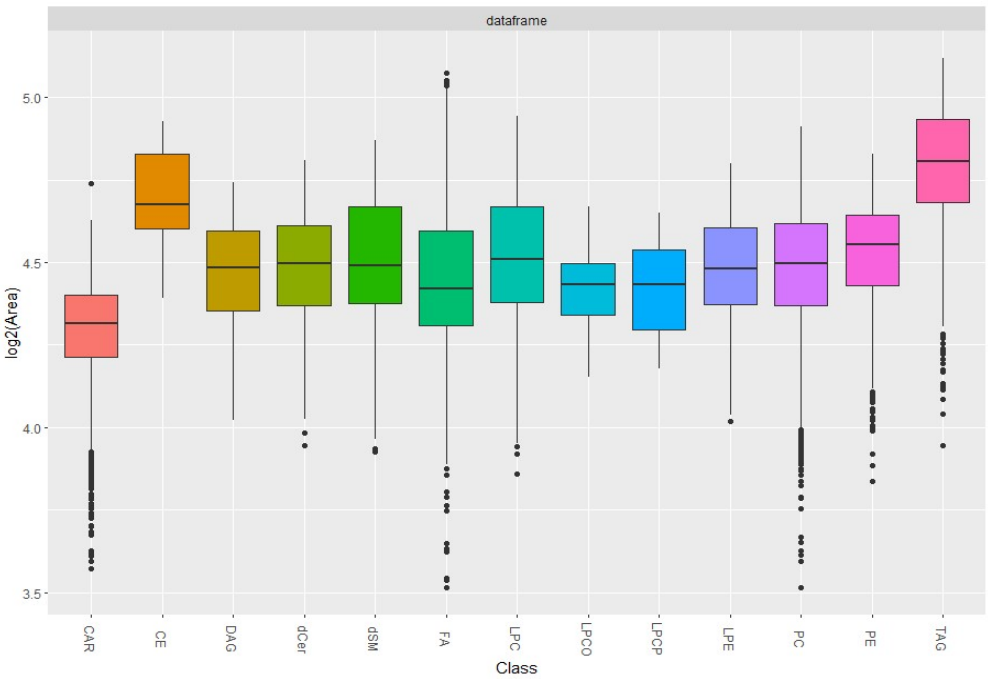

Figure 9: Intensity distribution of lipid classes for the risperidone subgroup. The lipid class is plotted on the x-axis, the log2(Area) is shown on the y-axis. TAG triacylglycerols, FA fatty acyls, PC phosphatidylcholines, dSM sphingomyelins, dCer ceramides, LPC lysophosphatidylcholines, CAR acylcarnitines, PE phosphatidylethanolamines, LPE lysophosphatidylethanolamines, DAG diacylglycerols, LPCO ether-linked lysophosphatidylcholines, CE cholesteryl esters, LPCP lysophosphatidylcholine plasmalogens

In the next step, multiple transitions were summarized into a single value by taking the average intensity. Following this, a Probabilistic Quotient Normalization (PQN) is applied. The PQN method employs a comparison of the quotient distributions between the sample and a reference spectrum to calculate a dilution factor for each sample (Karaman 2017; Dieterle et al. 2006). This dilution factor is then utilized to normalize the samples.

7.3.4.2 Data analysis

7.3.4.2.1 Differential analysis

After the data normalization and scaling, a differential analysis was performed using a function in lipidr that is based on the limma package (Ritchie et al. 2015), which is commonly used for analyzing microarray data but can also be applied to lipidomics data (Mohamed et al. 2020a; Olund Villumsen et al. 2021; Buas et al. 2021). The analysis aimed to identify lipids that showed significant changes in abundance between the different sample groups. A list of lipids with significantly altered levels for each comparison was generated, along with a volcano plot visualizing the results of the differential analysis. An exemplary volcano plot displaying the results of the differential analysis comparing patients with SCZ vs. controls is displayed in figure 10.

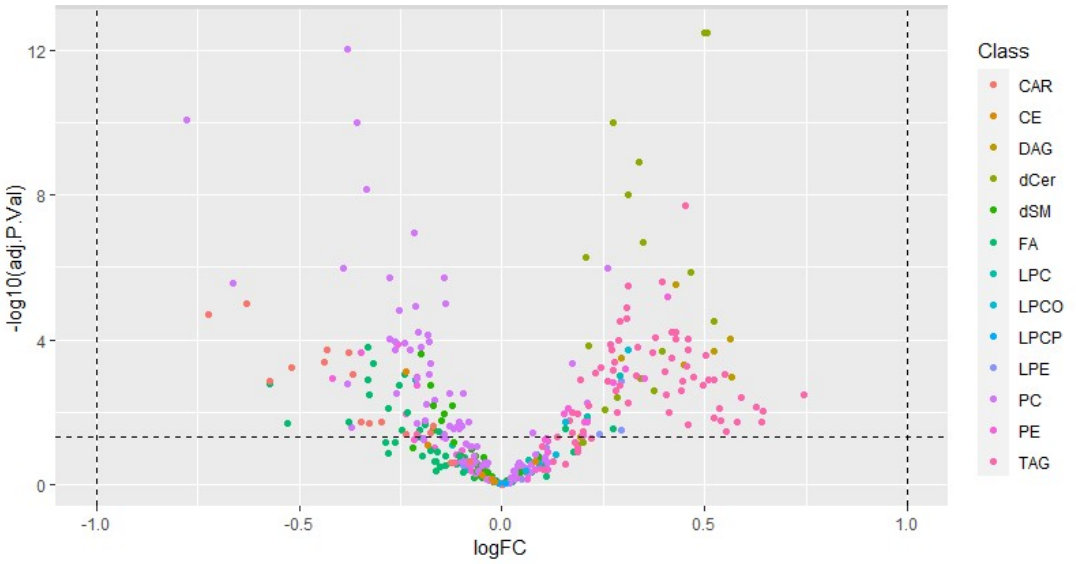

Figure 10: Volcano plot displaying the results of the differential analysis comparing patients with SCZ vs. controls (Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

7.3.4.2.2 Enrichment analysis

Lipidomic data analysis poses unique challenges due to the diverse characteristics of each lipid species, including lipid class, shape, chain length, degree of unsaturation, hydroxyl groups, and fatty acid composition, which can all significantly impact cellular function. Despite the similarities to genomics and metabolomics data, there is a lack of analysis tools specifically designed for lipidomics (Lin et al. 2021). To address this issue, Lipidr includes a lipid set enrichment analysis (LSEA) based on the Gene Set Enrichment Analysis (GSEA) method. GSEA is commonly used to evaluate expression data at the gene set level using prior biological knowledge, such as published information about biochemical pathways or co-expression networks (Subramanian et al. 2005).

7.3.4.2.3 Visualization

In the final step of the analysis, the lipid set enrichment analysis results generated in lipidr were visualized using the ggplot2 package outside of lipidr. The main objective of the visualization was to compare the effects of different medications on the lipidome. To achieve this, two types of plots were selected. The first type displays all lipid classes for a single medication class or drug in one plot, as shown in figure 11, while the second type shows the effects of different medication classes and individual drugs on a single lipid class in one plot, which is visualised in figure 12.

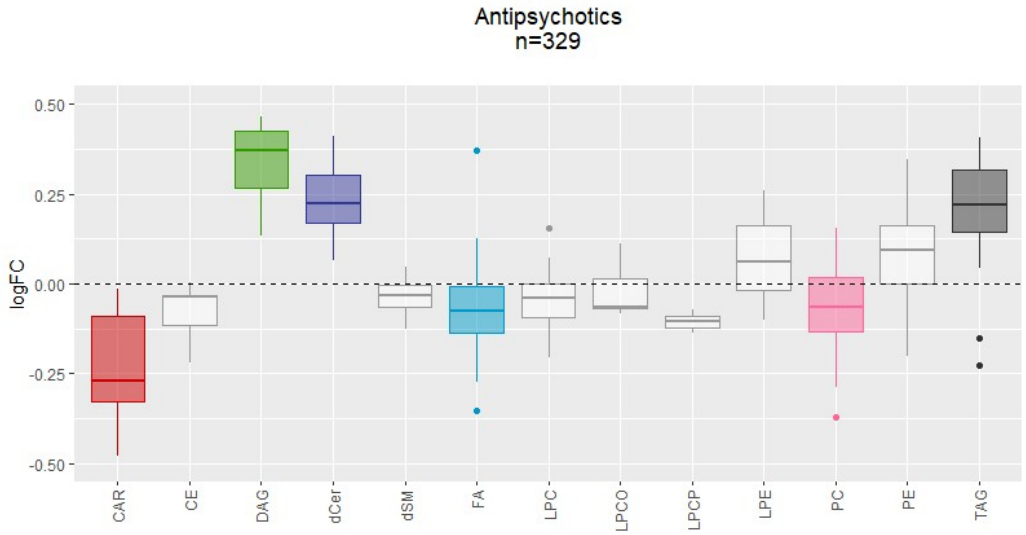

Figure 11: Vertical boxplot comparing the effect size of antipsychotics on different lipid classes (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

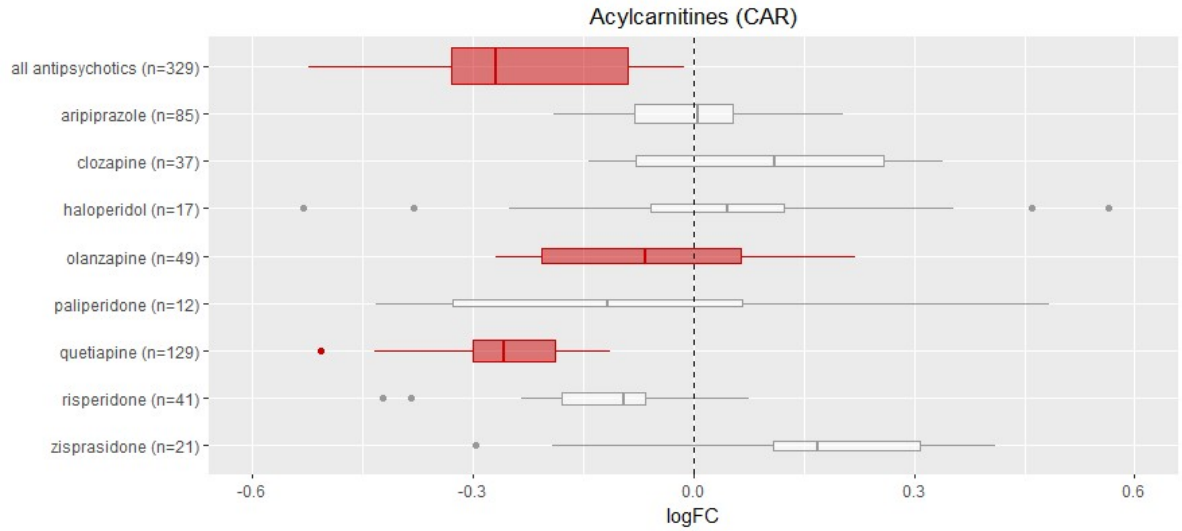

Figure 12: Horizontal boxplot comparing the effect sizes of different medications on acylcarnitines levels (multiple hypothesis testing correction was applied and the whiskers of medication classes/individual drugs that significantly (p<0.05 after Benjamini-Hochberg correction for multiple testing) alter adjusted p-values of acylcarnitine expression are coloured red; the size of the whiskers corresponds to the size of the subgroup)

8 Results

8.1 Baseline characteristics

The analysis includes a total of 622 individuals from 12 different clinics in Germany and Austria. Sample collection took place between 2011 and 2017. The group consists of 192 controls, 187 patients with SCZ, and 243 patients with BP (191 with BP I, and 53 with BP II).

Patients with BP had a significant higher average age (44.9 $\pm$ 13.4 years) than patients with SCZ (39.3 $\pm$ 12.8 years, p=1.149E-05) and controls (38.3 $\pm$ 16.1, p=5.002E-06). Compared to the control group, patients with BP and SCZ had a significantly higher average BMI (28.3 $\pm$ 6.2 kg/m^2 and 28.4 $\pm$ 6.3 kg/m^2 vs. 24.3 $\pm$ 4.6 kg/m^2 for controls, p=1.382E-13 [BP vs. controls], p=9.507E-12 [SCZ vs.

controls]). The percentage of female participants was higher in the control group (56.8%) compared to patients with BP (46.5%) and SCZ (29.9%).

Drug intake varied between the groups, with the highest percentage of medication intake observed in the SCZ group, followed by the BP group, while the control group mostly did not take any medication at all.

Regarding medication classes, antipsychotics were the most commonly used drugs for the treatment of SCZ, with 92.5% of patients taking them at the time of biosampling for lipidomics and the second most commonly used drugs in BP, with of 64.2% patients taking them at the time of study inclusion. In patients with SCZ, the specific drugs most frequently used were aripiprazole (25.1%), clozapine (19.3%) and risperidone (18.7%). Quetiapine (35.0%), aripiprazole (15.6%) and olanzapine (9.5%) were the most commonly used drugs in patients with BP.

In the BP group, mood stabilizers were the most frequently prescribed medication class (69.5%), with lithium (31.7%) and valproic acid (26.3%) being the most commonly used mood stabilizers. Antidepressants were also frequently used in the BP group (47.7%), with SNRIs (16.9%) and SSRIs (17.7%) being the most commonly prescribed. Tranquilizers were used in a smaller percentage of patients in both the BP (9.9%) and SCZ (19.8%) groups.

Table 3 presents the baseline characteristics of the individuals included in the analysis, including age, BMI, gender distribution, and medication intake among the three groups: BP, SCZ, and controls.

In summary, the medication intake varied between the groups, with antipsychotics being the most commonly used medication class in SCZ, while mood stabilizers were the most frequently prescribed in BP. Clozapine, risperidone, and aripiprazole were the most commonly used antipsychotics, and lithium and valproic acid were the most commonly used mood stabilizers. The control group mostly did not take any medication at all.

Table 3: Baseline characteristics of the individuals included in the analysis

	Bipolar disorder (n=243)	**SCZ (n=187)**	**Controls (n=192)**
Age [years], mean (sd)	44.9 (13.4)	39.3 (12.8)	38.3 (16.1)
BMI [kg/m^2], mean (sd)	28.3 (6.2)	28.4 (6.3)	24.3 (4.6)
Female, % (n)	46.5 (113)	29.9 (56)	56.8 (109)
Male, % (n)	53.5 (130)	70.1 (131)	43.2 (83)
Medication intake			
Antipsychotics, % (n)	64.2 (156)	92.5 (173)	0 (0)
Aripiprazole, % (n)	15.6 (38)	25.1 (47)	0 (0)
Clozapine, % (n)	0.4 (1)	19.3 (36)	0 (0)
Haloperidol, % (n)	1.2 (3)	7.5 (14)	0 (0)
Olanzapine, % (n)	9.5 (23)	13.9 (26)	0 (0)
Paliperdinone, % (n)	1.2 (3)	4.8 (9)	0 (0)

Quetiapine, % (n)	35.0 (85)	23.5 (44)	0 (0)
Risperidone, % (n)	2.5 (6)	18.7 (35)	0 (0)
Zisprasidone, % (n)	5.3 (13)	4.3 (8)	0 (0)
Antidepressants, % (n)	47.7 (116)	26.2 (49)	0 (0)
SNRI, n (%)	16.9 (41)	7.5 (14)	0 (0)
Venlafaxine, % (n)	8.2 (20)	7.0 (13)	0 (0)
SSRI, n (%)	17.7 (43)	12.3 (23)	0 (0)
Escitaloprame, % (n)	5.3 (13)	1.6 (3)	0 (0)
Sertraline, % (n)	8.2 (20)	8.0 (15)	0 (0)
TCA, n (%)	3.7 (9)	2.7 (5)	0 (0)
Mirtazapine, % (n)	5.3 (13)	3.7 (7)	0 (0)
Bupropione, % (n)	7.8 (19)	1.1 (2)	0 (0)
Mood stablizers, % (n)	69.5 (169)	6.4 (12)	2.1 (4)
Lamotrigine, n (%)	11.9 (29)	1.1 (2)	1.0 (2)
Lithium, n (%)	31.7 (77)	2.1 (4)	0 (0)
Valproic acid, n (%)	26.3 (64)	3.7 (7)	0 (0)
Tranquilizers, % (n)	9.9 (24)	19.8 (37)	1.0 (2)

8.2 Lipid classes

The untargeted lipidomic analysis identified lipid species belonging to the lipid classes of triacylglycerols (TAG), fatty acyls (FA), phosphatidylcholines (PC), sphingomyelins (dSM), ether-linked phosphatidylcholines (PC_O), phosphatidylcholine plasmalogens (PC_P), phosphatidylethanolamines plasmalogens (PE_P), ceramides (dCer), lysophosphatidylcholines (LPC), acylcarnitines (CAR), phosphatidylethanolamines (PE), lysophosphatidylethanolamines (LPE), diacylglycerols (DAG), ether-linked lysophosphatidylcholines (LPC_O), cholesteryl esters (CE), and lysophosphatidylcholine plasmalogens (LPC_P). Among these 16 lipid classes, TAG were the most abundant (71 lipid species), followed by FA (56 lipid species) and PC (46 lipid species). Table 4 presents the number of lipid species per lipid class for all lipid classes included in the analysis.

Table 4: Number of different lipid species per lipid class included in this analysis

TAG	FA	PC	dSM	PC_O	PC_P	PE_P	dCer	LPC	CAR	PE	LPE	DAG	LPC_O	CE	LPC_P
71	56	46	32	31	26	26	20	19	18	18	9	7	7	6	2

8.3 Disease effects

The initial part of the results centers on the analysis of differences between patients with SCZ and BP compared to healthy controls. It also examines the distinctions and variations that exist between these two psychiatric conditions.

8.3.1 Bipolar disorder

In the matched cohort for BP, a different type of matching called full matching was applied. Out of the 243 patients with BP in the dataset, 230 were matched based on age, gender, and BMI to 182 control individuals. The average age of the matched patients was 44.8 years, their average BMI was 28.3 kg/m^2 and 47.8% (n=110) of them were female. Differences in age, BMI, and gender distribution between the two groups can be attributed to the matching process. A summary of the baseline characteristics is displayed in table 5.

Table 5: Baseline characteristics of the matched BP cohort

	BP (n=230)	**Controls (n=182)**
Age [years], mean (sd)	44.8 (13.4)	38.3 (16.0)
BMI [kg/m^2], mean (sd)	28.3 (6.2)	24.3 (4.6)
Female, % (n)	47.8 (110)	57.7 (105)

In the matched BP cohort, a two-sided t-test revealed 282 significantly altered peaks, with 81 of them annotated. The most significantly altered annotated lipid species were FA 25:0 (corrected p-value=1,15E-07), PC 36:4 (corrected p-value=1,40E-07) and LPE 20:4 (corrected p-value=2,69E-07), which are shown in table 6. The lipid classes with the highest number of significantly changed lipid species were FA and TAG. However, when considering the size of the lipid classes, LPEs were the most affected, with 55.6% of the LPEs being significantly altered, followed by FAs at 35.7% (see supplemental material, table S3).

Table 6: Two-sided t-test for the matched BP cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction

Peak	**Lipid species**	**P-value**	**Adjusted p-value**
gpeakneg2021	NA	6.69E-12	3.59E-09
gpeakneg3319	NA	8.52E-12	3.59E-09
gpeakpos5479	NA	3.61E-12	3.59E-09
gpeakneg2732	NA	1.37E-10	4.33E-08
gpeakneg1661	FA 25:0	4.54E-10	1.15E-07
gpeakneg4797	PC 36:4	6.66E-10	1.40E-07
gpeakneg2333	LPE 20:4	1.49E-09	2.69E-07
gpeakpos5175	NA	4.15E-09	5.82E-07
gpeakpos654	NA	3.76E-09	5.82E-07
gpeakneg2831	NA	6.75E-09	8.53E-07
gpeakneg2705	NA	1.35E-08	1.55E-06
gpeakneg3311	NA	1.85E-08	1.94E-06
gpeakneg1778	FA 27:4	6.31E-08	6.13E-06
gpeakneg2753	NA	7.12E-08	6.42E-06
gpeakneg2153	NA	1.03E-07	8.64E-06
gpeakneg3330	NA	1.28E-07	1.01E-05
gpeakpos13367	NA	1.89E-07	1.40E-05
gpeakpos14292	NA	2.95E-07	2.07E-05
gpeakneg1838	NA	3.59E-07	2.38E-05
gpeakneg3016	NA	3.88E-07	2.45E-05

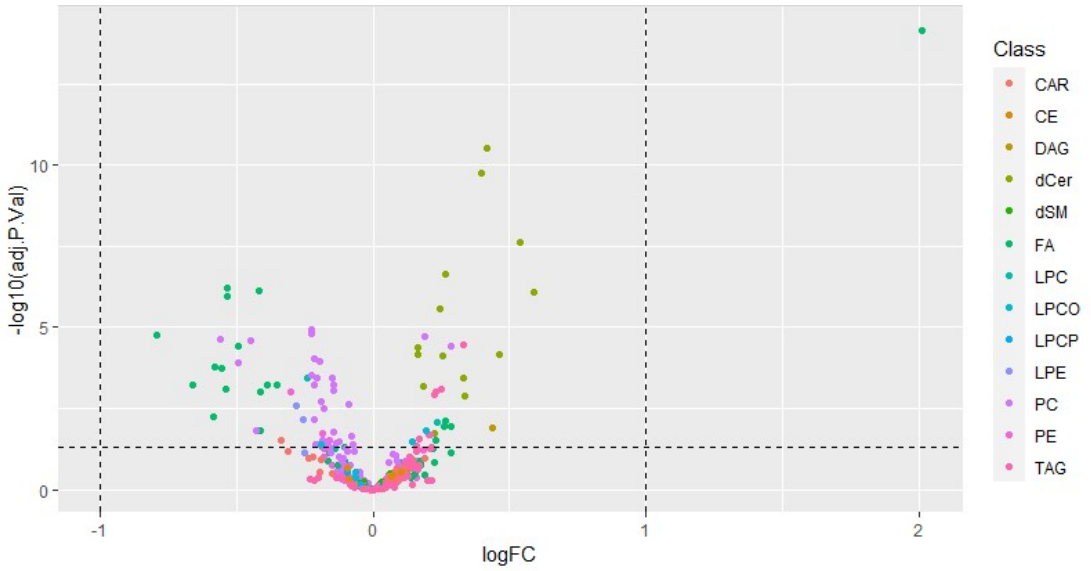

Figure 13: Volcano plot displaying the results of the differential analysis of the matched BP cohort in lipidr (86 significantly altered lipid species mostly belonging to the classes PC, FA and dCer; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

The differential analysis of the matched BP cohort in lipidr revealed 86 significantly altered annotated peaks, which are displayed in figure 13. The most significant alterations were found in dCer and FA, with 6 out of the 10 species with the lowest adjusted p-values belonging to dCer and the other 4 belonging to FA (table 7). Remarkably, 70.0% of the dCers and 67.4% of the PCs were significantly altered (see supplemental material, table S2). The most significantly altered annotated lipid species were FA 8:0 (adjusted p-value=7.26E-15), dCer 36:1 (adjusted p-value=3.13E-11) and dCer 36:2 (adjusted p-value=1.69E-10).

Table 7: Differential analysis for the matched BP cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

Lipid species	logFC	P-value	Adjusted p-value
FA 8:0	2.01051	1.99E-17	7.26E-15
dCer 36:1	0.41833	1.72E-13	3.13E-11
dCer 36:2	0.39513	1.39E-12	1.69E-10
dCer 42:4	0.53711	2.66E-10	2.42E-08
dCer 42:3	0.26637	3.15E-09	2.29E-07
FA 23:1	-0.53522	1.06E-08	6.41E-07
FA 11:1	-0.41639	1.49E-08	7.74E-07
dCer 40:3	0.58883	1.81E-08	8.24E-07
FA 23:0	-0.53410	2.86E-08	1.16E-06
dCer 40:2	0.24589	7.35E-08	2.67E-06
PCO 36:2	-0.22533	3.56E-07	1.18E-05
PCP 34:2	-0.22469	4.99E-07	1.51E-05
FA 27:3	-0.78951	6.28E-07	1.76E-05
PC 40:4	0.18784	7.41E-07	1.93E-05
PCP 34:3	-0.56108	9.27E-07	2.25E-05
PCP 35:2	-0.44809	1.10E-06	2.49E-05
TAG 56:5	0.33108	1.54E-06	3.29E-05
FA 12:3	-0.49584	1.84E-06	3.69E-05
PC 39:4	0.28549	1.93E-06	3.69E-05
dCer 34:1	0.16202	2.29E-06	4.17E-05

The enrichment analysis for the matched BP cohort resulted in four significantly altered lipid classes: dCer with an adjusted p-value of 3.88E-05, followed by PC, TAG and FA (table 8). The results of the enrichment analysis for all classes are shown in figure 14.

Lipid class	P-value	Adjusted p-value
dCer	5.79E-07	3.88E-05
PC	2.13E-05	0.00060
TAG	0.00019	0.00313
FA	0.00351	0.03918

Table 8: Results of the enrichment analysis of the matched BP cohort

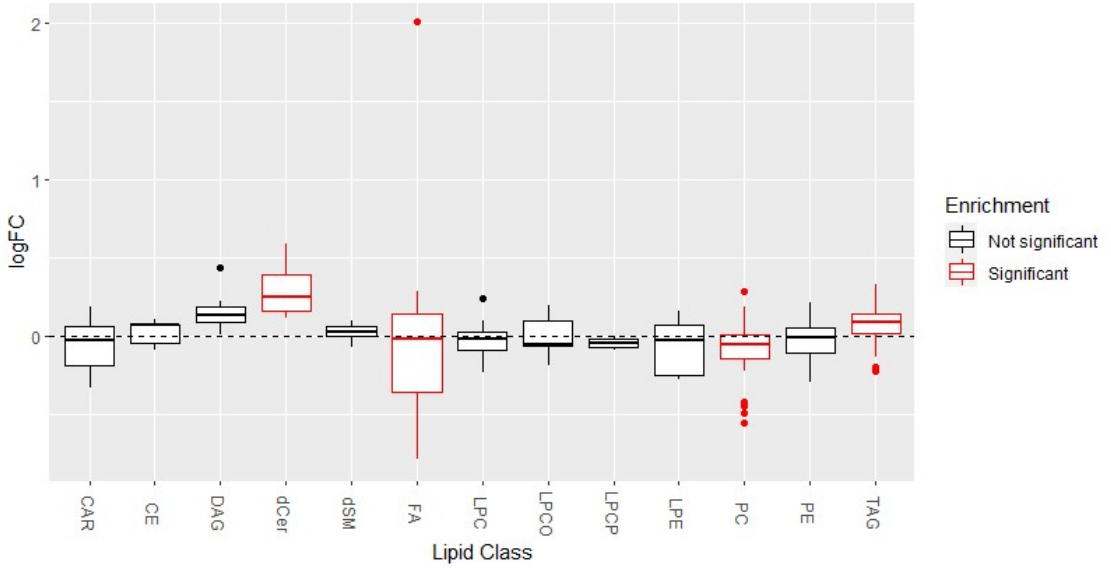

Figure 14: Boxplot showing the results of the enrichment analysis in the matched BP cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

The differential analysis of the BP cohort in lipidr showed the most significant alterations in annotated peaks belonging to dCer and FA, with a high percentage of significantly altered species in dCer and PC classes. Enrichment analysis of the matched BP cohort also showed significant alterations in lipid classes dCer and PC.

8.3.2 Schizophrenia

In the matched SCZ cohort, full matching was also applied, resulting in 178 individuals with SCZ matched based on age, gender, and BMI to 188 control individuals. The average age of the matched patients with SCZ was 39.3 years, their average BMI was 28.4 kg/m^2, and 30.3% (n=54) of them were female. As with the matched BP cohort, differences in age, BMI, and gender distribution between the two groups can be attributed to the matching process. Table 9 summarizes the baseline characteristics of the matched SCZ cohort.

Table 9: Baseline characteristics of the matched SCZ cohort

	SCZ (n=178)	Controls (n=188)
Age [years], mean (sd)	39.3 (12.9)	38.3 (16.0)
BMI [kg/m^2], mean (sd)	28.4 (6.3)	24.3 (4.6)
Female, % (n)	30.3 (54)	55.9 (105)

In the matched SCZ cohort, a two-sided t-test revealed 585 significantly altered peaks, with 149 of them annotated. The 20 peaks with the lowest adjusted p-values are shown in table 10. The most significantly altered annotated lipid species were LPE 20:4 (corrected p-value=4.56E-10), LPE 18:1 (corrected p-value=4.83E-10), and PC 38:4 (corrected p-value=2.85E-09). The lipid class with the highest number of significantly changed lipid species was TAG with 32 peaks, while the classes with the highest percentage of altered peaks were DAG (71.4%), CAR (66.7%), and dCer (65.0%). Other lipid classes with a notable number of altered peaks include dSM (43.8%) and PC (28.3%), for more details see supplemental material, table S3.

Table 10: Two-sided t-test for the matched SCZ cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction

Peak	Lipid species	P-value	Adjusted p-value
gpeakneg2732	NA	7.46E-14	5.11E-11
gpeakpos5479	NA	4.24E-13	1.78E-10
gpeakpos13367	NA	8.82E-13	2.78E-10
gpeakneg2333	LPE 20:4	1.81E-12	4.56E-10
gpeakneg2206	LPE 18:1	2.29E-12	4.83E-10
gpeakneg3670	NA	3.66E-12	6.60E-10
gpeakneg5259	NA	7.42E-12	1.17E-09
gpeakpos5175	NA	1.67E-11	2.35E-09
gpeakneg2537	NA	2.28E-11	2.85E-09
gpeakneg5055	PC 38:4	2.70E-11	2.85E-09
gpeakpos14834	NA	2.56E-11	2.85E-09
gpeakneg4244	PC_O 32:0	4.10E-11	3.99E-09
gpeakneg4360	PE 40:5	2.28E-10	2.06E-08
gpeakneg5161	PC_P 40:5	3.28E-10	2.76E-08
gpeakpos15025	NA	3.55E-10	2.80E-08
gpeakpos13191	NA	4.36E-10	3.24E-08
gpeakpos14292	NA	5.57E-10	3.91E-08
gpeakpos13266	NA	7.13E-10	4.74E-08
gpeakneg1904	NA	1.01E-09	6.40E-08
gpeakpos13860	NA	1.42E-09	8.55E-08

The differential analysis of the matched schizophrenia (SCZ) cohort in lipidr revealed 192 significantly altered peaks, which are visualized in figure 15. Of the 10 lipid species with the lowest adjusted p-value 5 belonged to dCer, 4 to PC, and 1 to TAG (table 11). The most significantly altered annotated lipid species were dCer 36:2 (adjusted p-value=3.20E-13), dCer 36:1 (adjusted p-value=3.20E-13), and PCP 34:2 (adjusted p-value=9.29E-13). Similarly to the BP cohort, dCer and PC were among the most significantly altered lipid classes, with 75% and 97.8% of their species significantly altered, respectively (see supplemental material, table S2).

Table 11: Differential analysis for the matched SCZ cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

Lipid species	logFC	P-value	Adjusted p-value
dCer 36:2	0.49994	1.76E-15	3.20E-13
dCer 36:1	0.50573	1.57E-15	3.20E-13
PCP 34:2	-0.38008	7.66E-15	9.29E-13
PCP 35:2	-0.77596	9.27E-13	8.43E-11
dCer 34:1	0.27268	1.55E-12	9.47E-11
PCP 36:2	-0.35630	1.56E-12	9.47E-11
dCer 40:2	0.33672	2.30E-11	1.19E-09
PCP 34:1	-0.33255	1.54E-10	6.99E-09
dCer 42:3	0.31215	2.31E-10	9.32E-09
TAG 56:5	0.45101	5.49E-10	2.00E-08
PC 37:2	-0.21781	3.43E-09	1.14E-07
dCer 42:2	0.34740	6.59E-09	2.00E-07
dCer 34:2	0.20643	1.93E-08	5.42E-07
PCP 37:4	-0.39229	4.05E-08	1.01E-06
PC 40:5	0.26059	4.17E-08	1.01E-06
dCer 38:1	0.46646	6.18E-08	1.40E-06
PC 36:4	-0.14408	8.71E-08	1.86E-06
PC 32:2	-0.27868	9.37E-08	1.89E-06
TAG 51:2	0.39307	1.30E-07	2.49E-06
PCP 34:3	-0.66408	1.48E-07	2.68E-06

The enrichment analysis of the matched SCZ cohort, which is visualized in figure 16, showed that TAG was the most significantly enriched class with an adjusted p-value of 3.41E-20, followed by PC, FA, CAR, dCer, and dSM (table 12).

Lipid class	P-value	Adjusted p-value
TAG	5.09E-22	3.41E-20
PC	8.13E-09	2.72E-07
FA	1.28E-07	2.86E-06
CAR	1.73E-07	2.90E-06
dCer	1.23E-05	0.00016
dSM	0.00148	0.01237

Table 12: Results of the enrichment analysis of the matched SCZ cohort

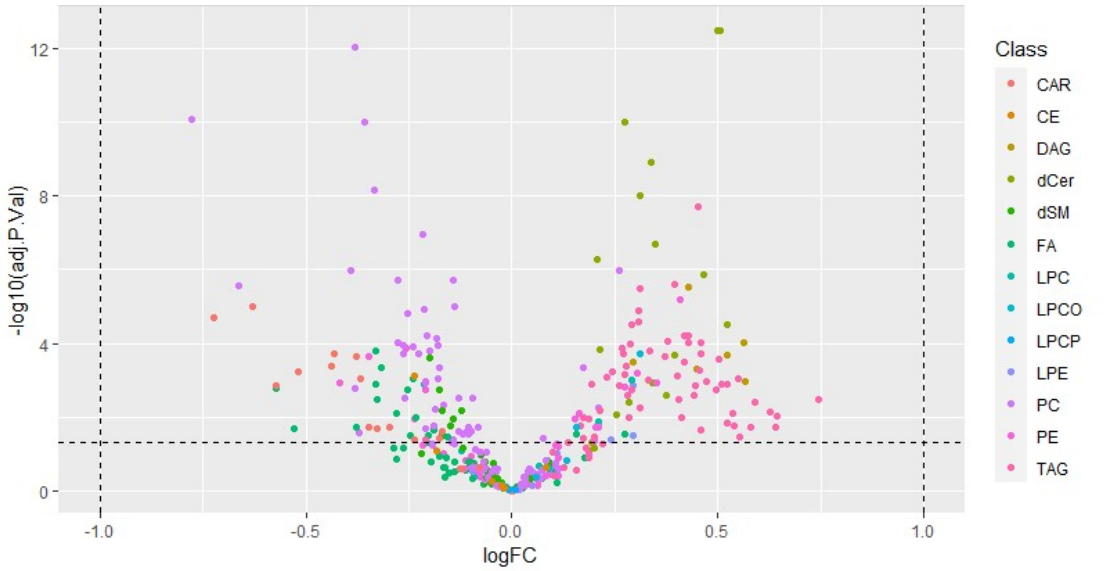

Figure 15: Volcano plot displaying the results of the differential analysis of the matched SCZ cohort in lipidr (192 significantly altered lipid species mostly belonging to the classes TAG, PC and FA; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

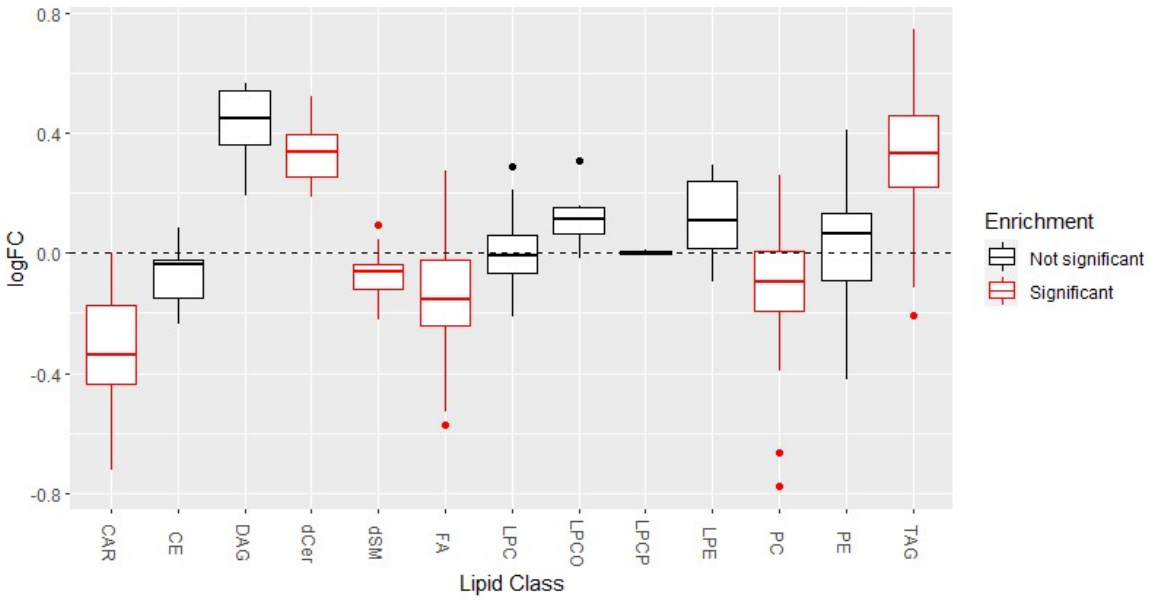

Figure 16: Boxplot showing the results of the enrichment analysis in the matched SCZ cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

8.3.3 Bipolar disorder vs. schizophrenia

In contrast to the previous matched BP cohort, in this subgroup, the patients with BP were matched against patients with SCZ (SCZ) instead of healthy controls. Full matching was applied, resulting in a total of 230 matched BP patients and 178 SCZ patients, with with similar age, BMI, and gender distribution in both groups. Table 13 provides an overview of the baseline characteristics of the matched BP and SCZ cohorts.

Table 13: Baseline characteristics of the matched BP vs. SCZ cohort

	BP (n=230)	SCZ (n=178)
Age [years], mean (sd)	41.4 (13.4)	43.3 (12.9)
BMI [kg/m^2], mean (sd)	28.2 (6.2)	28.5 (6.3)
Female, % (n)	47.8 (110)	50.3 (54)

In the matched BP vs. SCZ cohort, a two-sided t-test revealed 321 significantly altered peaks 321 significantly altered peaks, with 149 of them annotated. The most significantly altered annotated lipid species were FA 27:4 and FA 28:4, with corrected p-values of 6.19E-07 for both, and LPE 18:3 (corrected p-value=2.73E-05), which are displayed in table 14. The lipid class with the highest number of significantly changed lipid species was FA, followed by TAG. When considering the size of the lipid classes, FA had the highest percentage of altered peaks at 51.8%, followed by CAR at 50.0% (supplementary material, table S3).

Table 14: Two-sided t-test for the matched BP vs. SCZ cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction

Peak	Lipid species	P-value	Adjusted p-value
gpeakneg2153	NA	9.27E-12	1.17E-08
gpeakneg2021	NA	8.40E-10	5.31E-07
gpeakneg1778	FA 27:4	1.96E-09	6.19E-07
gpeakneg1860	FA 28:4	1.50E-09	6.19E-07
gpeakneg1823	NA	3.57E-09	9.02E-07
gpeakpos654	NA	3.73E-08	7.84E-06
gpeakneg1279	NA	7.60E-08	1.20E-05
gpeakneg1872	NA	6.96E-08	1.20E-05
gpeakneg4410	NA	1.57E-07	2.20E-05
gpeakneg2174	LPE 18:3	2.16E-07	2.73E-05
gpeakneg1723	FA 26:2	3.44E-07	3.95E-05
gpeakneg1722	FA 26:2	4.20E-07	4.42E-05
gpeakneg1964	NA	4.82E-07	4.69E-05
gpeakneg2660	LPC 18:3	5.65E-07	5.10E-05
gpeakneg1759	NA	6.32E-07	5.32E-05
gpeakpos14705	NA	8.05E-07	6.36E-05
gpeakpos8121	NA	1.55E-06	0.00012
gpeakpos5151	LPC_O 22:1	1.72E-06	0.00012
gpeakneg1661	FA 25:0	4.09E-06	0.00027
gpeakneg5223	NA	4.57E-06	0.00029

The differential analysis of the matched BP cohort against the SCZ cohort using lipidr revealed 139 significantly altered annotated peaks, with 5 out of the 10 species with the lowest adjusted p-values belonging to FA (see table 15). The most significantly altered annotated lipid species were FA 8:0 (adjusted p-value=2.56E-09), FA 25:0 (adjusted p-value=1.58E-05), and PE 36:1 (adjusted p-value=0.00024). FA and TAG were again the lipid classes with the highest number of significantly changed lipid species, but

Table 15: Differential analysis for the matched SCZ cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

Peak	Lipid species	P-value	Adjusted p-value
FA 8:0	1.74236	7.04E-12	2.56E-09
FA 25:0	-0.58585	8.67E-08	1.58E-05
PE 36:1	-0.38493	1.94E-06	0.00024
FA 22:6	0.41692	1.11E-05	0.00077
FA 25:2	-0.55720	1.91E-05	0.00077
FA 16:1	0.55268	1.69E-05	0.00077
CAR 14:2	0.56754	1.74E-05	0.00077
LPCO 22:1	-0.32057	1.59E-05	0.00077
TAG 46:4	-0.62498	1.45E-05	0.00077
TAG 46:3	-0.60391	2.31E-05	0.00084
FA 18:2	0.39686	3.01E-05	0.00099

this time CAR (72.2%) and DAG (71.4%) were also notable for their high percentage of altered peaks (see supplemental material, table S2). The results of the differential analysis are displayed in figure 17.

FA 17:2	0.56758	3.60E-05	0.00109
PCP 38:4	0.17766	5.51E-05	0.00154
FA 26:1	-0.56477	6.81E-05	0.00173
DAG 36:1	-0.49383	7.14E-05	0.00173
FA 23:0	-0.37339	0.00010	0.00203
FA 28:4	-0.69342	0.00010	0.00203
TAG 48:4	-0.45844	0.00011	0.00203
CAR 14:0	0.29212	9.32E-05	0.00203
FA 26:4	-0.24529	0.00012	0.00206

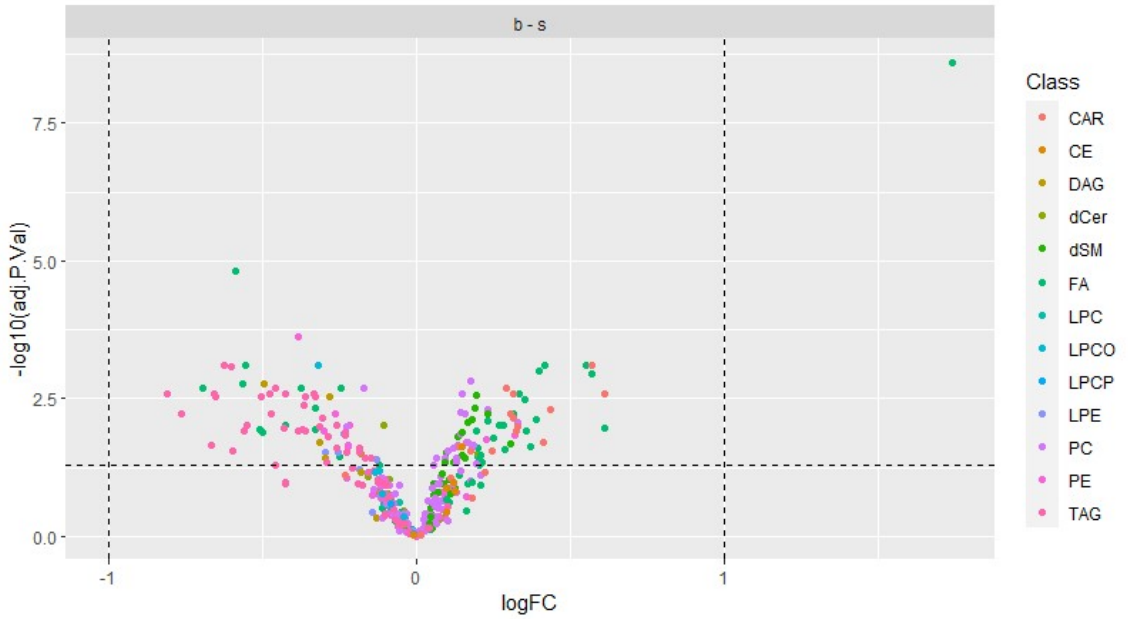

Figure 17: Volcano plot displaying the results of the differential analysis of the matched BP vs. SCZ cohort in lipidr (139 significantly altered lipid species mostly belonging to the classes TAG, FA and PC; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

In the matched BP vs. SCZ cohort, the most significantly enriched class was TAG with an adjusted p-value of 6.55E-14, followed by CAR and dSM (table 16). The enrichment analysis results of the matched BP vs. SCZ cohort in lipidr are presented in Figure 18 as a boxplot.

Lipid class	P-value	Adjusted p-value
TAG	9.78E-16	6.55E-14
CAR	2.04E-05	0.00068
dSM	0.00035	0.00581
FA	0.00068	0.00910
PC	0.00583	0.04950

Table 16: Results of the enrichment analysis of the matched BP vs. SCZ cohort

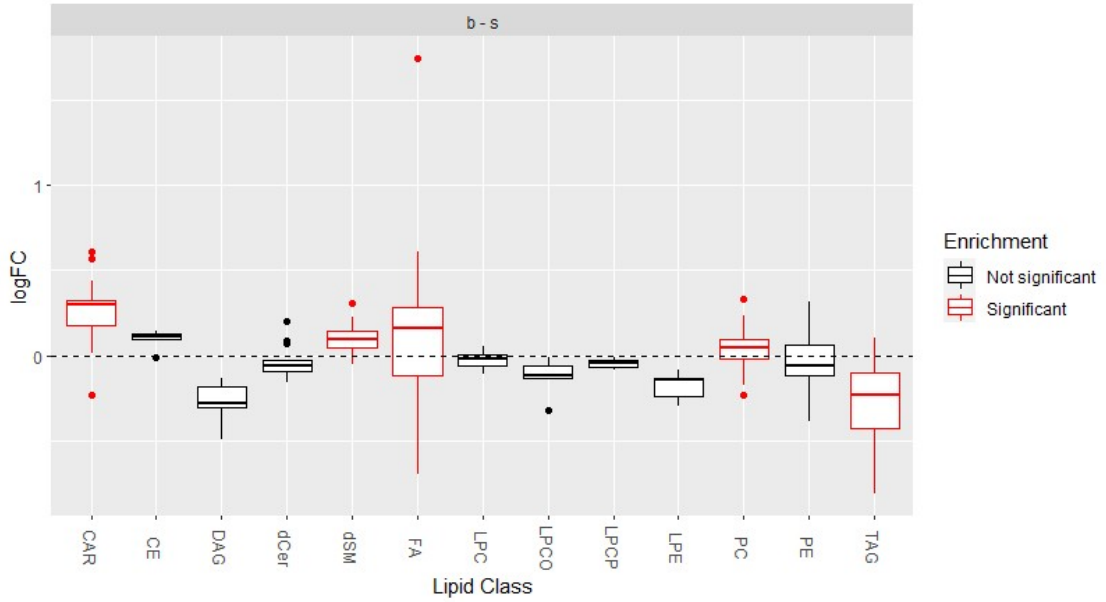

Figure 18: Boxplot showing the results of the enrichment analysis in the matched BP vs. SCZ cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

The differential analysis of the matched BP cohort against controls and the matched SCZ cohort against controls revealed that dCer and PC were among the most significantly altered lipid classes in both disorders. However, dCer was not significantly altered in the BP vs. SCZ analysis, suggesting that this lipid class alteration might be a feature shared by both diseases. In contrast, while TAG and FA were among the lipid classes most significantly altered in all three analyses, CAR and DAG were only notably altered in the BP vs. SCZ comparison. The differing results of the two BP analyses highlight the importance of carefully selecting appropriate control groups for lipidomic studies.

8.4 Medication classes

The subsequent part of this analysis investigates the impact of medication classes, including antipsychotics, antidepressants, mood stabilizers, and tranquilizers. It examines how the intake of these medications influences lipid profiles and any associated alterations, starting with an overview of the medication class effects followed by a detailed analysis of each of the medication classes.

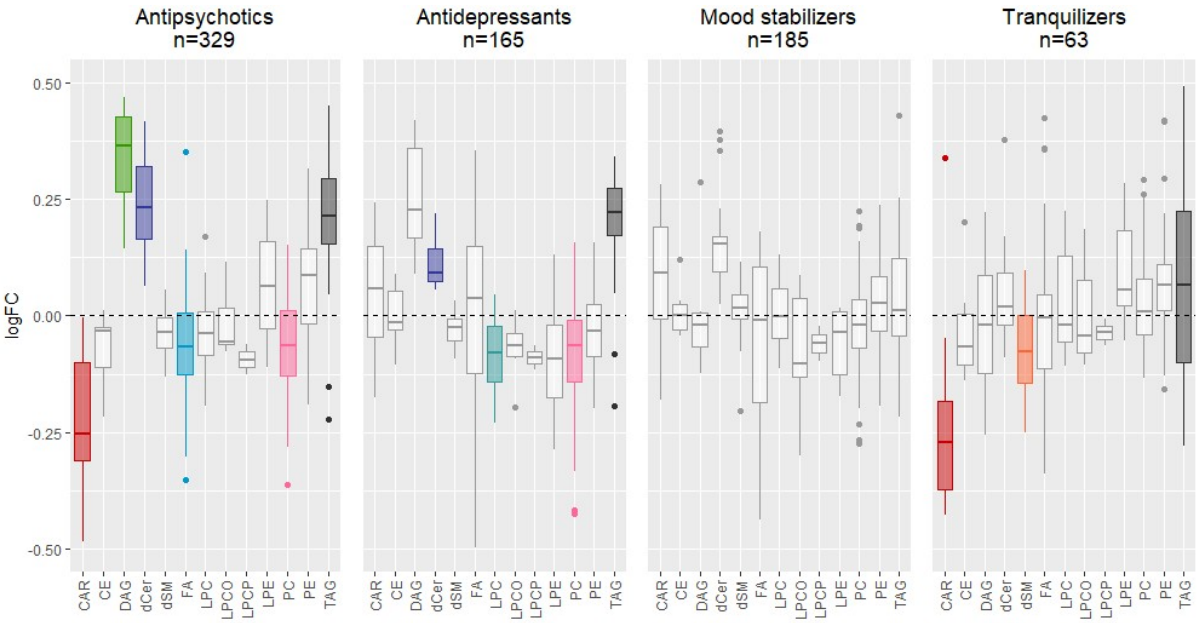

Figure 19: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antipsychotics, antidepressants, mood stabilizers and tranquilizers in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

Antipsychotics showed the most significant alterations with six lipid classes being affected, followed by antidepressants with four altered classes, tranquilizers with three altered classes, and mood stabilizers without any altered class. The lipid classes affected by most of the medication classes were TAG and dCer. TAG was enriched in all medication classes except mood stabilizers. Boxplots comparing the results of the enrichment analysis in the matched cohorts for antipsychotics, antidepressants, mood stabilizers, and tranquilizers are shown in figure 19. It is worth noting that TAG includes a large number of lipid species, which may give it greater statistical power to detect differences. dCer, PC, and CAR were altered in two medication classes. Interestingly, antipsychotics had the most profound effects on the lipidome, with over 150 individual peaks altered and six lipid classes affected.

8.4.1 Antipsychotics

As mentioned above, antipsychotics have been shown to have a significant impact on the plasma lipidome. In order to better understand the mechanisms behind these effects and attribute them to specific drugs, a total of 11 subgroups were analyzed in this chapter, including the overall class of antipsychotics, 8 individual drugs, and 2 classes of drugs sharing overlapping receptor profiles. Additionally, in 4 instances, sample numbers also permitted a differential analysis in those who were taking a specific drug as monotherapy vs. those taking it in combination with other drugs. The first part of this chapter focuses on the overall medication class of antipsychotics and their effects on the lipidome.

In the matched antipsychotics (AP) cohort, full matching was performed using age, gender, BMI and diagnosis. Out of the 316 individuals taking AP, 151 had been diagnosed with BP and 165 with SCZ. They were matched to 277 control individuals. The mean age of the matched AP cohort was 41.4 years, their mean BMI was 28.2 kg/m^2, and 39.6% (n=125) of them were female. As expected, there were significant differences in the distribution of diagnosis between the AP and control groups due to the matching process. Table 17 provides an overview of the baseline characteristics of the matched AP cohort included in the analysis.

	AP (n=316)	**Controls (n=277)**
Age [years], mean (sd)	41.4 (13.2)	43.3 (15.7)
Only BP	44.7 (13.1)	44.5 (13.1)
Only SCZ	39.1 (12.7)	42.6 (16.8)
BMI [kg/m^2], mean (sd)	28.2 (6.3)	28.5 (5.2)
Only BP	38.5 (6.3)	28.3 (6.2)
Only SCZ	28.6 (6.4)	25.0 (3.6)
Female, % (n)	39.6 (125)	51.3 (142)
Bipolar disorder, % (n)	47.8 (151)	27.8 (77)
Schizophrenia, % (n)	52.2 (165)	4.3 (12)

Table 17: Baseline characteristics of the matched antipsychotics (AP) cohort

In the matched AP cohort, a two-sided t-test revealed 465 significantly altered peaks, with 129 of them annotated. The 20 most significantly altered annotated lipid species, including PC_O 32:0 (p-value=1.25E-09), PC 38:4 (corrected p-value=1.78E-09), and LPE 20:4 (corrected p-value=5.51E-09), are shown in table 18. The lipid classes with the highest number of significantly changed lipid species were dCer and PC_O. Interestingly, FA had a much lower percentage of altered peaks compared to the other cohorts, with only 8.9% of its species being significantly altered (see supplemental material, table S3).

Peak	**Lipid species**	**P-value**	**Adjusted p-value**
gpeakneg2705	NA	4.25E-13	4.56E-10
gpeakneg2732	NA	1.08E-12	4.56E-10
gpeakneg3670	NA	8.36E-13	4.56E-10
gpeakneg4244	PC_O 32:0	3.95E-12	1.25E-09
gpeakneg5055	PC 38:4	7.05E-12	1.78E-09
gpeakneg2333	LPE 20:4	2.62E-11	5.51E-09
gpeakpos13367	NA	6.37E-11	1.15E-08
gpeakneg4960	PC_O 38:2	9.75E-11	1.54E-08
gpeakneg4360	PE 40:5	5.44E-10	7.63E-08
gpeakneg5259	NA	1.02E-09	1.29E-07
gpeakneg2206	LPE 18:1	3.14E-09	3.61E-07
gpeakneg4797	PC 36:4	6.10E-09	5.93E-07
gpeakpos5479	NA	5.83E-09	5.93E-07
gpeakneg4472	PC 33:1	6.68E-09	6.03E-07
gpeakpos14292	NA	1.02E-08	8.58E-07
gpeakneg2537	NA	1.14E-08	9.00E-07
gpeakneg2747	dCer 34:2	1.42E-08	9.99E-07
gpeakpos10030	NA	1.42E-08	9.99E-07
gpeakpos14586	NA	3.05E-08	2.03E-06
gpeakpos9257	NA	3.32E-08	2.10E-06

Table 18: Two-sided t-test for the matched AP cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction

The analysis of the matched AP cohort in lipidr revealed 153 significantly altered peaks. The most significantly altered annotated lipid species were dCer 36:2 (adjusted p-value=8.73E-13), PCP 34:2 (adjusted p-value=2.36E-11), and dCer 36:1 (adjusted p-value=2.52E-11), with 5 out of the 10 species with the lowest adjusted p-values belonging to dCer and 4 to PCP (table 19). The lipid classes with the highest number of significantly changed lipid species were PC, PE, and TAG, and the class with the highest percentage of altered lipid species was PE, with 17 out of 18 lipid species significantly altered, followed by PC, dCer, and TAG (see supplemental material, table S2). Figure 20 displays a volcano plot depicting the significant changes in lipid species found through differential analysis.

Table 19: Differential analysis for the matched AP cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

Lipid species	logFC	P-value	Adjusted p-value
dCer 36:2	0.37389	2.40E-15	8.73E-13
PCP 34:2	-0.28322	1.30E-13	2.36E-11
dCer 36:1	0.35462	2.07E-13	2.52E-11
PCP 35:2	-0.55427	2.40E-11	2.19E-09
PCP 36:2	-0.26227	5.38E-11	3.91E-09
PCP 34:1	-0.26864	1.50E-10	9.12E-09
dCer 40:2	0.23273	1.25E-09	6.51E-08
dCer 42:3	0.22139	3.99E-09	1.82E-07
dCer 34:1	0.16876	9.46E-09	3.83E-07
TAG 56:5	0.32220	2.19E-08	7.96E-07
DAG 36:2	0.31688	3.56E-07	1.18E-05
dCer 34:2	0.14899	4.20E-07	1.27E-05
dCer 40:3	0.41627	6.49E-07	1.58E-05
dCer 42:2	0.23258	6.15E-07	1.58E-05
PCP 34:3	-0.50407	6.33E-07	1.58E-05
PE 40:4	0.31645	1.19E-06	2.70E-05
PCO 36:2	-0.17526	1.68E-06	3.60E-05
PC 37:2	-0.14002	2.68E-06	5.43E-05
TAG 55:5	0.22930	2.83E-06	5.43E-05
CE 18:2	-0.21666	3.15E-06	5.73E-05

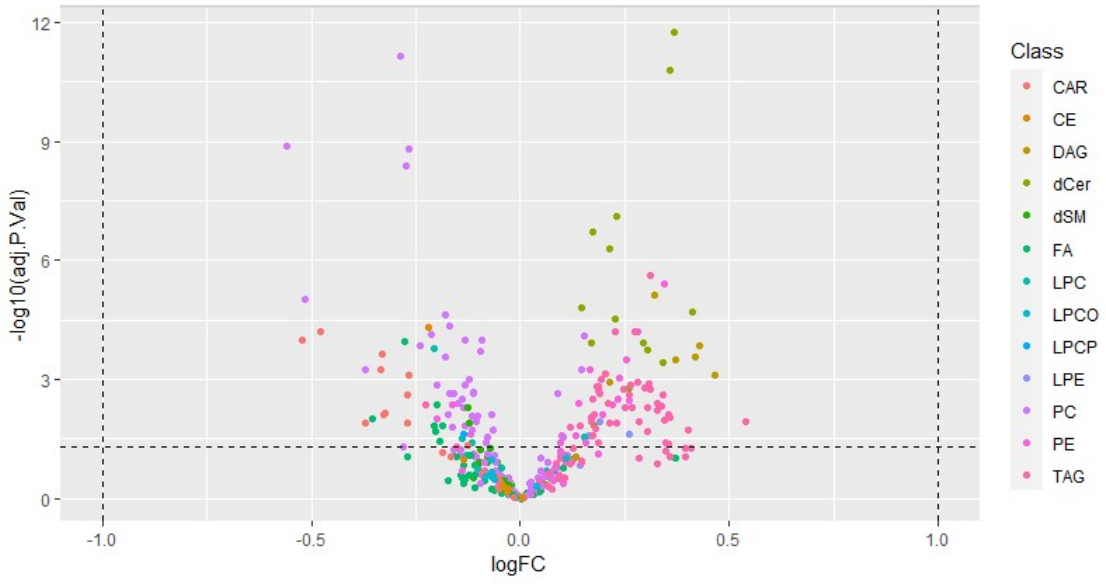

Figure 20: Volcano plot displaying the results of the differential analysis of the matched AP cohort in lipidr (153 significantly altered lipid species mostly belonging to the classes TAG, PC and PE; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

In the matched AP cohort, the most significantly enriched class was TAG with an adjusted p-value of 1.59E-17, followed by PC, CAR, dCer, FA and DAG (table 20). These results are visualized in figure 21 and are similar to those seen in the SCZ cohort (see chapter 8.3.2 Schizophrenia).

Lipid class	P-value	Adjusted p-value
TAG	2.38E-19	1.59E-17
PC	1.65E-10	5.52E-09
CAR	1.96E-08	4.38E-07
dCer	0.00012	0.00197
FA	0.00027	0.00359
DAG	0.00270	0.02259

Table 20: Results of the enrichment analysis of the matched AP cohort

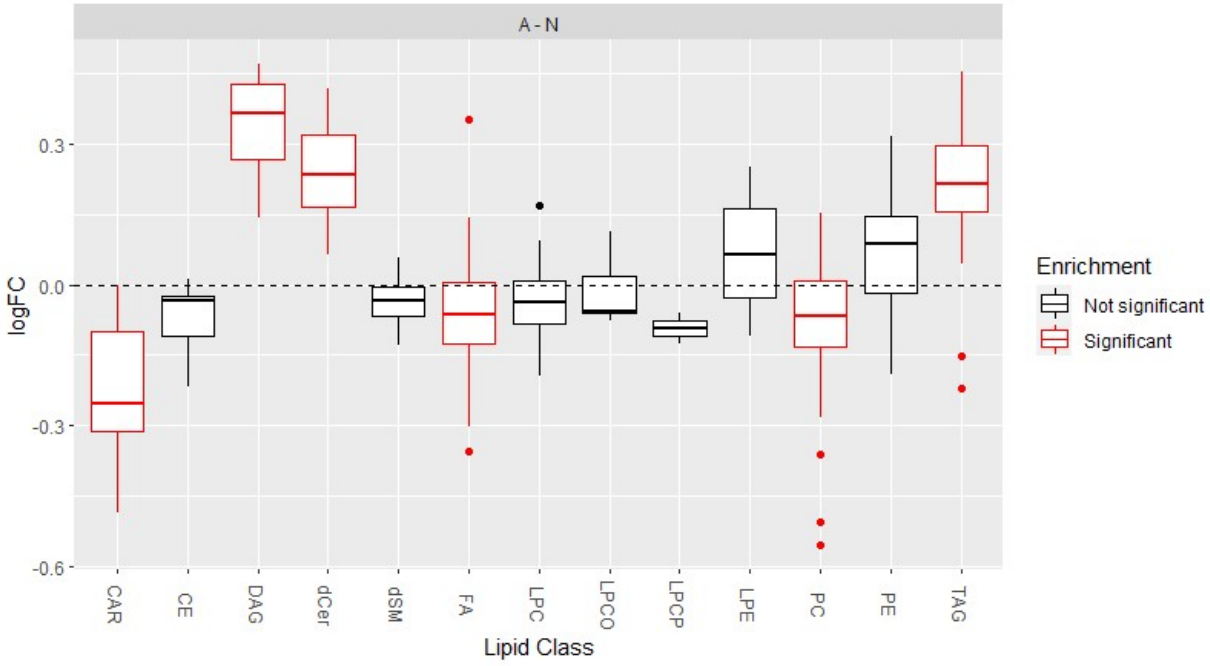

Figure 21: Boxplot showing the results of the enrichment analysis in the antipsychotics cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

The matched antipsychotics cohort displayed significant alterations in lipid species, with PE, PC and dCer being the classes with the highest percentage of altered lipid species. The most significantly enriched class was TAG, followed by PC and CAR, similar to the results seen in the SCZ cohort. However, as there is significant overlap between these cohorts, it is not possible to attribute these effects solely to the use of antipsychotics or the presence of SCZ.

8.4.2 Tranquilizers

The medication class tranquilizers had the smallest sample size compared to the other medication classes, with only 63 individuals taking tranquilizers in the entire cohort. 19.8% of SCZ patients and 9.9% of patients with BP were taking tranquilizers.

Nearest neighbor matching was applied to this cohort, matching each individual to the nearest neighbor in the control group based on age, sex, and BMI. This resulted in a matched cohort of 118 individuals, with 59 individuals taking tranquilizers ("T group") and 59 matched controls. Demographic data are outlined in Table 21.

	T (n=59)	Controls (n=59)
Age [years], mean (sd)	45.0 (14.2)	44.0 (13.8)
BMI [kg/m^2], mean (sd)	29.1 (6.0)	29.9 (7.1)
Female, % (n)	42.4 (25)	44.1 (26)
Bipolar disorder, % (n)	37.3 (22)	40.0 (23)
Schizophrenia, % (n)	59.3 (35)	59.3 (35)
Controls, % (n)	3.4 (2)	1.7 (1)

Table 21: Baseline characteristics of the matched tranquilizers (T) cohort

In the analysis of the tranquilizers cohort, there were no significant peaks in the t-test and no significantly altered lipid species in the differential analysis in lipidr. However, the enrichment analysis revealed that TAG was the most significantly enriched class with an adjusted p-value of 1.02E-07, followed by CAR and dSM, as shown in table 22.

Lipid class	P-value	Adjusted p-value
TAG	1.52E-09	1.02E-07
CAR	8.68E-08	2.91E-06
dSM	0.00076	0.01276

Table 22: Results of the enrichment analysis of the matched T cohort

8.4.3 Antidepressants

Compared to the medication class tranquilizers, the subgroup of individuals taking an antidepressant had a larger sample size, with 165 individuals taking antidepressants in the entire cohort. Among them, 47.7% of patients with BP and 26.2% of SCZ patients were taking antidepressants.

Optimal full matching was applied to the antidepressants (AD) cohort, matching 158 individuals taking antidepressants to 435 individuals not taking antidepressants. Demographic data are outlined in Table 23.

Table 23: Baseline characteristics of the matched antidepressants (AD) cohort

	AD (n=158)	Controls (n=435)
Age [years], mean (sd)	44.6 (14.4)	39.8 (14.2)
BMI [kg/m^2], mean (sd)	29.2 (6.2)	26.3 (5.9)
Female, % (n)	46.0 (200)	42.4 (67)
Bipolar disorder, % (n)	69.6 (110)	27.1 (118)
Schizophrenia, % (n)	30.4 (48)	29.7 (129)
Controls, % (n)	0 (0)	43.2 (188)

For the matched AD cohort, a two-sided t-test revealed 163 significantly altered peaks, with 49 of them annotated. The most significantly altered annotated lipid species were PC_P 34:0 (corrected p-value=0.0054), dCer 34:2, and PE 40:7 (both with corrected p-value=0.0056). Table 24 displays the 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction. The lipid classes with the highest number of significantly changed lipid species were TAG and PC_O. However, when considering the size of the lipid classes, LPEs were the most affected, with 33.3% of the LPEs being significantly altered, followed by LPC at 26.3% (see supplemental material, table S3).

Table 24: Two-sided t-test for the matched AD cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction

Peak	Lipid species	P-value	Adjusted p-value
gpeakneg2831	NA	6.76E-09	8.54E-06
gpeakneg5094	NA	1.69E-06	0.00107
gpeakpos10030	NA	5.83E-06	0.00213
gpeakpos9471	NA	6.74E-06	0.00213
gpeakpos14094	NA	1.45E-05	0.00366
gpeakpos13367	NA	1.78E-05	0.00376
gpeakneg4477	PC_P 34:0	2.98E-05	0.00537
gpeakneg2153	NA	4.82E-05	0.00561
gpeakneg2747	dCer 34:2	5.06E-05	0.00561
gpeakneg3319	NA	3.91E-05	0.00561
gpeakneg4321	PE 40:7	5.38E-05	0.00561
gpeakneg5055	PC 38:4	5.77E-05	0.00561
gpeakpos5346	NA	4.30E-05	0.00561
gpeakneg2636	NA	7.31E-05	0.00577
gpeakneg5259	NA	7.01E-05	0.00577
gpeakpos13880	NA	7.22E-05	0.00577
gpeakneg4797	PC 36:4	9.04E-05	0.00672
gpeakneg2319	LPE 20:5	0.00011	0.00747
gpeakneg2428	LPE 22:5	0.00017	0.00747
gpeakneg3680	PE_P 36:5	0.00013	0.00747

In the lipidr-based analysis, the matched AD cohort had 98 significantly altered annotated peaks. The peak with the lowest adjusted p-value was LPC 18:2 with a p-value of 0.00176. Table 25 shows the 20 lipid species with the lowest adjusted p-values after correction for multiple testing. The lipid classes with the highest number of significantly changed lipid species were TAG, PC and FA, and the class with the highest percentage of altered lipid species was PC, with 67.4% of its species significantly altered, followed by TAG (see supplemental material, table S2). The results of the differential analysis are visualized in figure 22 using a volcano plot.

Table 25: Differential analysis for the matched AD cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

Lipid species	logFC	P-value	Adjusted p-value
LPC 18:2	-0.22949	1.79E-05	0.00176
PCO 36:2	-0.18476	7.75E-06	0.00176
TAG 55:6	0.25191	1.84E-05	0.00176
TAG 56:5	0.27886	1.93E-05	0.00176
LPE 18:2	-0.28734	0.00010	0.00293
LPE 18:1	-0.27997	0.00010	0.00293
dCer 36:1	0.21841	7.87E-05	0.00293
PC 40:4	0.15282	6.48E-05	0.00293
PCO 42:7	-0.42415	6.06E-05	0.00293
TAG 50:3	0.23632	6.74E-05	0.00293
TAG 50:2	0.22353	9.58E-05	0.00293
TAG 51:2	0.26898	6.03E-05	0.00293
TAG 55:5	0.21521	0.00010	0.00293
dCer 36:2	0.20639	0.00014	0.00296
FA 11:1	-0.26716	0.00013	0.00296
PCP 34:1	-0.18157	0.00015	0.00296
PCP 36:2	-0.17330	0.00015	0.00296
PCO 42:4	-0.23202	0.00012	0.00296
PCO 42:3	-0.19874	0.00016	0.00302
PCP 44:7	-0.51438	0.00017	0.00305

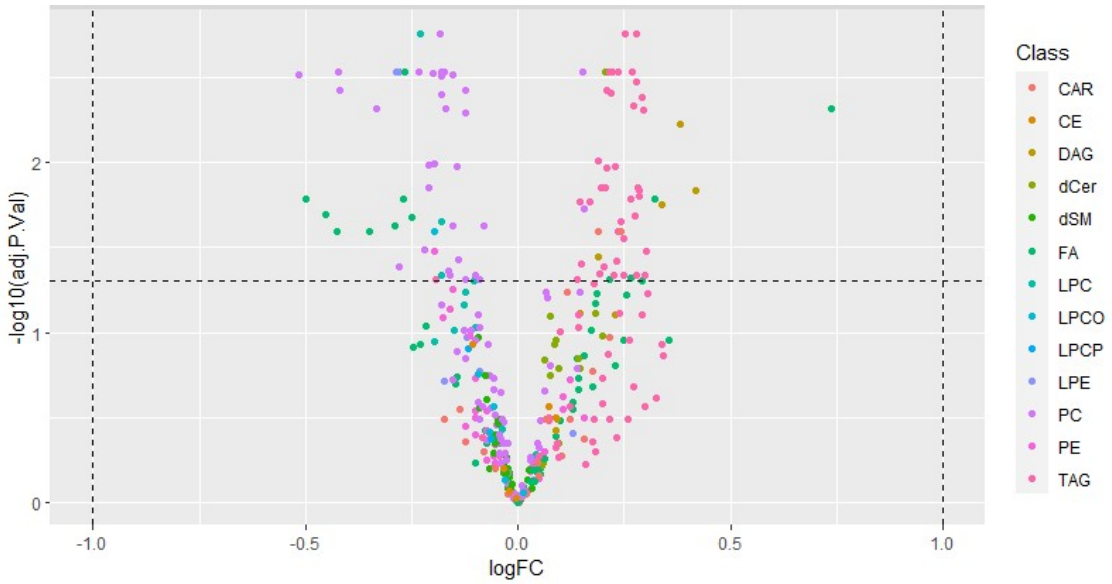

Figure 22: Volcano plot displaying the results of the differential analysis of the matched AD cohort in lipidr (98 significantly altered lipid species mostly belonging to the classes TAG, PC and FA; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

In the matched AD cohort, the most significantly enriched class was TAG with an adjusted p-value of 6.42E-20, followed by PC, LPC and dCer (table 26).

Lipid class	P-value	Adjusted p-value
TAG	9.59E-22	6.42E-20
PC	1.02E-11	3.43E-10
LPC	0.00102	0.01706
dCer	0.00302	0.03370

Table 26: Results of the enrichment analysis of the matched AD cohort

8.4.4 Mood stabilizers

Compared to the medication class antidepressants, the mood stabilizers subgroup had a similar sample size, with 185 individuals taking mood stabilizers in the entire cohort. Among them, 69.5% of patients with BP, 6.4% of patients with SCZ, and 2.4% of controls were taking mood stabilizers.

In the mood stabilizer cohort, optimal full matching was used to match 176 individuals taking mood stabilizers to 417 individuals not taking mood stabilizers. The mean age of the mood stabilizer group was 44.7 years, while the control group had a significantly lower mean age of 39.6 years (p=4.414E-05). The mean BMI of the mood stabilizer group was 28.2 kg/m^2, while the control group had a significantly lower mean BMI of 26.6 kg/m^2 (p=0.0051). Among the mood stabilizer group, 38.1% were female, and a majority of 91.5% had BP, while only 6.3% had SCZ. It is important to note that these differences are a result of the matching method used. Table 27 provides the baseline characteristics of the matched M cohort.

Table 27: Baseline characteristics of the matched mood stabilizer (M) cohort

	M (n=176)	Controls (n=417)
Age [years], mean (sd)	44.7 (13.4)	39.6 (14.6)
BMI [kg/m^2], mean (sd)	28.2 (6.1)	26.6 (6.1)
Female, % (n)	38.1 (67)	45.6 (190)
Bipolar disorder, % (n)	91.5 (161)	16.1 (67)
Schizophrenia, % (n)	6.3 (11)	39.8 (166)
Controls, % (n)	2.3 (4)	44.1 (184)

For the matched mood stabilizers cohort, a two-sided t-test revealed 166 significantly altered peaks, with 45 of them annotated. The lipid species with the lowest corrected p-value after Benjamini-Hochberg correction was FA 25:0 with a corrected p-value of 2.48E-05. The 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction are shown in table 28. The lipid classes with the highest number of significantly changed lipid species were FA and PE_P. However, when considering the size of the lipid classes, LPC_Os were the most affected, with 28.6% of the LPC_Os being significantly altered, followed by LPC and FA (see supplemental material, table S3).

Table 28: Two-sided t-test for the matched M cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction

Peak	Lipid species	P-value	Adjusted p-value
gpeakpos654	NA	4.26E-12	5.38E-09
gpeakpos15331	NA	1.95E-08	1.23E-05
gpeakneg2021	NA	5.21E-08	2.19E-05
gpeakneg1661	FA 25:0	9.82E-08	2.48E-05
gpeakneg4797	PC 36:4	7.97E-08	2.48E-05
gpeakneg2753	NA	2.59E-07	5.45E-05
gpeakneg2367	NA	6.56E-07	0.00012
gpeakneg4669	PE_P 44:8	7.34E-07	0.00012
gpeakneg3311	NA	1.63E-06	0.00023
gpeakneg1778	FA 27:4	3.51E-06	0.00042
gpeakneg3016	NA	3.69E-06	0.00042
gpeakneg1774	NA	5.92E-06	0.00058
gpeakneg3721	NA	6.02E-06	0.00058
gpeakneg3319	NA	6.57E-06	0.00059
gpeakneg1722	FA 26:2	1.59E-05	0.00123
gpeakneg1823	NA	1.65E-05	0.00123
gpeakpos14925	NA	1.63E-05	0.00123
gpeakpos9471	NA	1.76E-05	0.00124
gpeakneg1793	FA 27:3	2.35E-05	0.00156
gpeakpos5151	LPC_O 22:1	2.73E-05	0.00172

In the matched mood stabilizers cohort, the differential analysis in lipidr revealed 40 significantly altered peaks, with the lowest adjusted p-values for FA 8:0, FA 11:1, and dCer 42:4 (table 29). It's worth noting that FA 8:0 had an extremely low adjusted p-value of 8.30E-41. However, this result should be interpreted with caution, as this peak has a very uncommon distribution, which is depicted in figure 23. Despite this, it met the normality criteria and was not excluded from the analysis.

Table 29: Differential analysis for the matched M cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

Lipid species	logFC	P-value	Adjusted p-value
FA 8:0	2,60207	2,28E-43	8,30E-41
FA 11:1	-0,39658	3,09E-09	5,63E-07
dCer 42:4	0,35402	4,39E-06	0,00053
LPCO 22:1	-0,30037	7,30E-06	0,00066
FA 23:0	-0,36564	1,82E-05	0,00094
dCer 40:3	0,39624	1,39E-05	0,00094
FA 12:3	-0,41786	1,67E-05	0,00094
dCer 43:3	0,37839	3,08E-05	0,00140
FA 23:1	-0,33904	3,86E-05	0,00156
PC 42:5	-0,26764	4,32E-05	0,00157
dCer 42:3	0,16385	7,10E-05	0,00222
PCO 40:3	-0,18351	7,30E-05	0,00222
FA 25:2	-0,42976	0,00011	0,00290
PCO 36:2	-0,15489	0,00011	0,00290
PC 39:4	0,22396	0,00012	0,00290
FA 25:0	-0,36421	0,00014	0,00325
FA 26:4	-0,21910	0,00020	0,00419
FA 26:1	-0,43892	0,00026	0,00520
dCer 40:2	0,14836	0,00043	0,00815
PCO 38:2	-0,19847	0,00060	0,01033

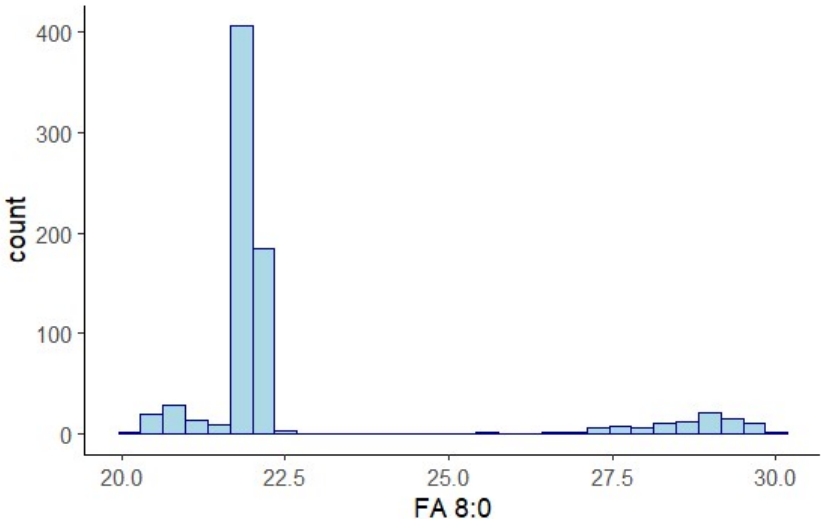

Figure 23: Histogram of the intensitiy distribution of FA 8:0

The lipid classes with the highest number of significantly changed lipid species were PC, FA, and dCer. However, when considering the percentage of altered lipid species within each class, dCer had the highest percentage, with 40% of its species significantly altered, followed by LPC_O at 28.6% and PC at 28.3% (see supplemental material, table S2). The results of the differential analysis of the matched M cohort are illustrated in Figure 24.

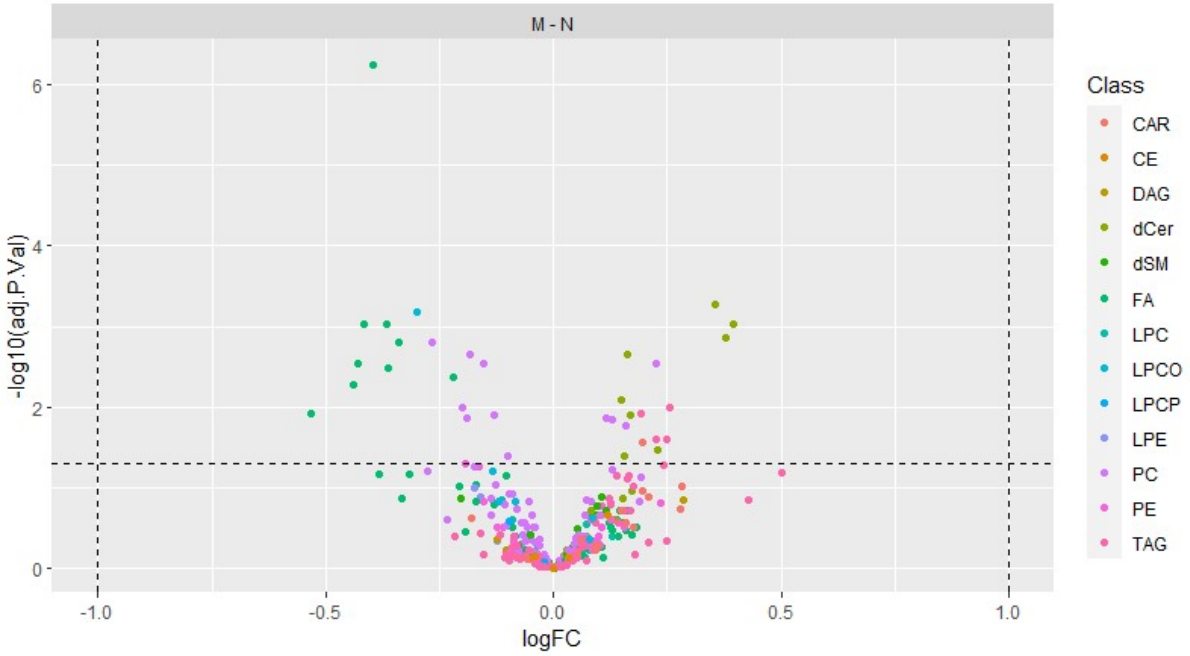

Figure 24: Volcano plot displaying the results of the differential analysis of the matched mood stabilizers cohort in lipidr (40 significantly altered lipid species mostly belonging to the classes PC, FA and dCer; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

In the matched mood stabilizers cohort, the enrichment analysis revealed that there was no significantly enriched lipid class.

8.5 Interaction of medication and disease

The antipsychotics cohort and the SCZ cohort showed the highest numbers of altered lipid species compared to all other cohorts. The alterations observed in both cohorts are also quite similar, which could be at least partially attributed to a significant overlap in population. However, it is difficult to completely distinguish between these effects since control individuals without a mental health diagnosis do not take antipsychotics, whereas almost all patients with SCZ take antipsychotics (92.5%). Notably, the effect sizes are slightly larger and the adjusted p-values are lower in the SCZ cohort when compared to the antipsychotics cohort. Figure 29 illustrates the comparison of enrichment analysis results in the matched cohorts for antipsychotics, BP, SCZ and BP vs. SCZ.

When comparing BP and SCZ cohorts that were matched against controls, some similarities in enriched dCers and decreased PCs and FAs were observed. However, differences in dSMs, TAGs, and CARs were present between the BP and SCZ cohorts.

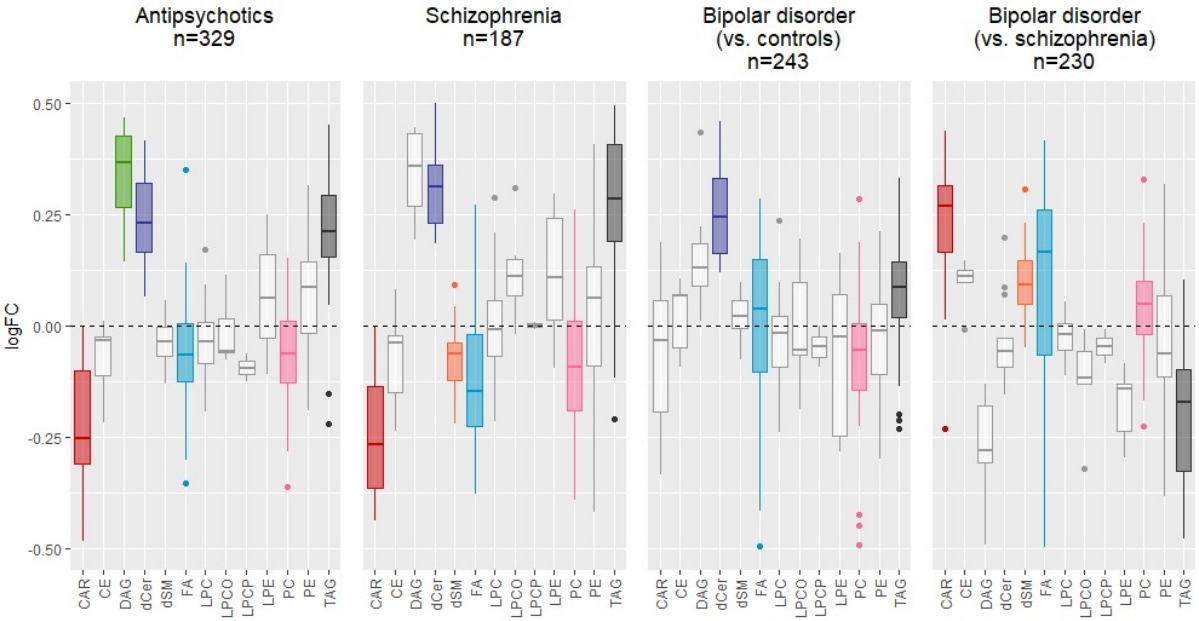

Figure 25: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antipsychotics, BP, SCZ and BP vs. SCZ in lipidr (the whiskers of significantly ($p<0.05$ after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

8.6 Individual drugs

The subsequent phase of this analysis delves deeper into the effects of medication intake by examining the impact of individual drugs within specific medication classes. However, due to the limited sample size in the subgroup of tranquilizers and insufficient representation of individuals taking the individual drugs, further analysis within this context is not conducted.

8.6.1 Antipsychotics

Table 30 shows the baseline charactertistics for each of the individual drugs from the medication class antipsychotics, including aripiprazole, clozapine, haloperidol, olanzapine, paliperidone, quetapine, risperidone and ziprasidone.

Cohort, n	Age, mean (sd)	BMI, mean (sd)	Females, % (n)	SCZ, % (n)	BP, % (n)
Aripiprazole, 162	40.1 (12.7)	30.8 (6.9)	35.2 (57)	56.8 (92)	34.6 (54)
Samples, 81	40.0 (12.6)	30.8 (7.1)	33.3 (27)	55.6 (45)	34.6 (28)
Controls, 81	40.2 (12.0)	30.8 (6.9)	37.0 (30)	58.0 (47)	34.6 (28)
Clozapine, 68	39.5 (12.3)	27.4 (5.8)	20.6 (14)	97.1 (66)	2.9 (2)
Samples, 34	38.6 (12.7)	28.1 (6.5)	20.6 (7)	97.1 (33)	2.9 (1)
Controls, 34	40.5 (11.9)	26.7 (5.1)	20.6 (7)	97.1 (33)	2.9 (1)
Haloperidol, 34	39.7 (10.9)	29.1 (5.3)	47.1 (16)	82.4 (28)	17.6 (6)
Samples, 17	41.1 (11.1)	29.0 (5.5)	47.1 (8)	82.4 (14)	17.6 (3)
Controls, 17	38.4 (11.0)	29.1 (5.3)	47.1 (8)	82.4 (14)	17.6 (3)
Olanzapine, 92	43.6 (14.5)	27.5 (5.1)	35.9 (33)	54.3 (50)	45.7 (42)
Samples, 46	42.3 (13.1)	27.4 (5.0)	32.6 (15)	54.3 (25)	45.7 (21)
Controls, 46	45.0 (15.9)	27.7 (5.3)	39.1 (18)	54.3 (25)	45.7 (21)
Paliperidone, 24	36.1 (10.5)	33.0 (8.7)	41.7 (10)	83.3 (20)	16.7 (4)
Samples, 12	38.5 (9.8)	34.3 (8.9)	41.7 (5)	75.0 (9)	25.0 (3)
Controls, 12	33.7 (11.1)	31.7 (8.6)	41.7 (5)	91.7 (11)	8.3 (1)
Quetiapine, 252	43.5 (13.2)	28.6 (6.5)	54.0 (136)	34.1 (86)	65.9 (166)
Samples, 126	42.7 (13.6)	28.8 (6.5)	52.4 (66)	34.1 (43)	65.9 (83)
Controls, 126	44.3 (12.9)	25.5 (6.5)	55.6 (70)	34.1 (43)	65.9 (83)
Risperidone, 76	38.3 (12.1)	29.7 (6.9)	34.2 (26)	84.2 (64)	15.8 (12)
Samples, 38	39.5 (13.6)	29.6 (6.8)	39.5 (15)	84.2 (32)	15.8 (6)
Controls, 38	37 (10.4)	29.9 (7.0)	28.9 (11)	84.2 (32)	15.8 (6)
Ziprasidone, 42	40.7 (11.1)	27.4 (5.3)	52.4 (22)	38.1 (16)	61.9 (26)
Samples, 21	42.5 (11.0)	28.5 (5.8)	52.4 (11)	38.1 (8)	61.9 (13)
Controls, 21	38.9 (11.2)	26.3 (4.6)	52.4 (11)	38.1 (8)	61.9 (13)

Table 30: Baseline characteristics of the matched cohorts for the individual drugs from the antipsychotics class

8.6.1.1 Aripiprazole

Aripiprazole, an atypical antipsychotic, did not show any significantly altered lipid species in both the t-test and the differential analysis in lipidr. The enrichment analysis of the matched aripiprazole cohort revealed that TAG was the most significantly enriched class with an adjusted p-value of 3.49E-22, followed by PC and FA (table 31).

Lipid class	P-value	Adjusted p-value
TAG	5.21E-24	3.49E-22
PC	1.67E-06	5.59E-05
FA	3.20E-05	0.00071

Table 31: Results of the enrichment analysis of the matched aripiprazole cohort

8.6.1.2 Clozapine

Clozapine, another atypical antipsychotic, also did not show any significantly altered lipid species in the t-test. However, the differential analysis in lipidr revealed 6 significantly altered lipid species belonging to the classes PE, PC, and LPCO (table 32), as displayed in Figure 26.

Table 32: Differential analysis for the matched AP cohort: 6 lipid species with significant adjusted p-values after correction for multiple testing

Lipid species	logFC	P-value	Adjusted p-value
PE 37:4	0.68702	0.00035	0.02697
PCP 34:3	-1.29171	0.00027	0.02697
PCP 34:2	-0.42616	0.00020	0.02697
PCO 34:2	-0.50809	0.00021	0.02697
LPCO 26:1	0.62127	0.00037	0.02697
LPCO 24:0	0.39427	0.00074	0.04507

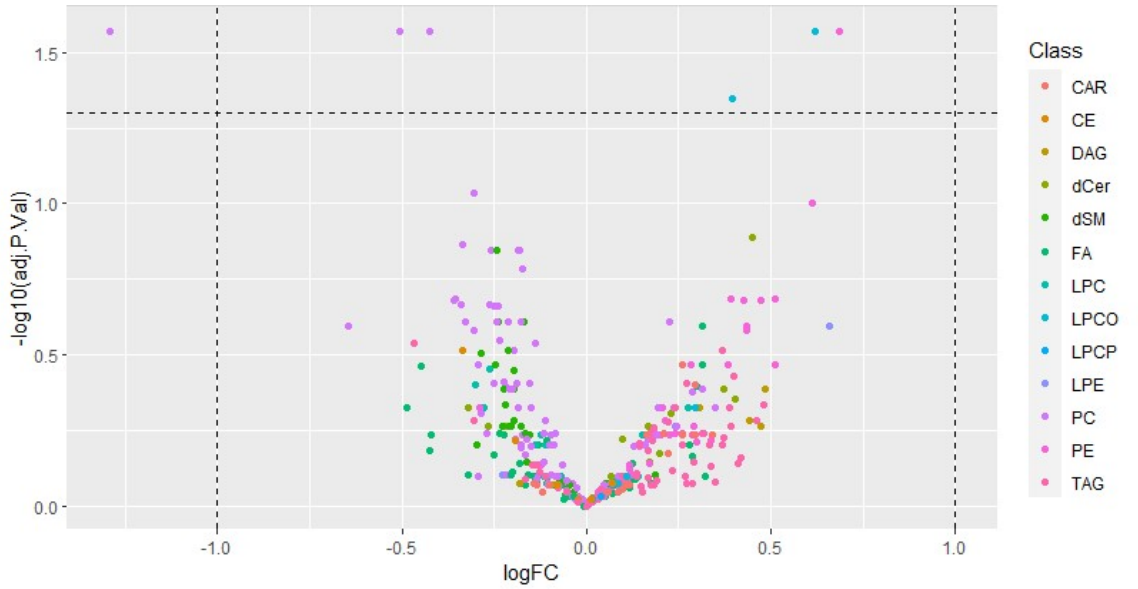

Figure 26: Volcano plot displaying the results of the differential analysis of the matched clozapine cohort in lipidr (6 significantly altered lipid species belonging to the classes PE, PC and LPCO; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

The enrichment analysis of the matched clozapine cohort showed that the most significantly enriched class was PC with an adjusted p-value of 3.11E-09, followed by PE, TAG and dSM (table 33).

Lipid class	P-value	Adjusted p-value
PC	4.64E-11	3.11E-09
PE	1.08E-06	3.61E-05
TAG	2.06E-06	4.60E-05
dSM	4.35E-06	7.29E-05

Table 33: Results of the enrichment analysis of the matched clozapine cohort

8.6.1.3 Haloperidol

Haloperidol, the only typical antipsychotic analyzed, did not show any significantly altered lipid species in both the t-test and the differential analysis in lipidr. The enrichment analysis of the matched haloperidol cohort revealed that PC was the most significantly enriched class with an adjusted p-value of 0.00036, followed by TAG, dSM and dCer (table 34).

Lipid class	P-value	Adjusted p-value
PC	1.08E-05	0.00036
TAG	5.50E-06	0.00036
dSM	0.00025	0.00332
dCer	0.00122	0.01363

Table 34: Results of the enrichment analysis of the matched clozapine cohort

8.6.1.4 Olanzapine

The analysis of Olanzapine, another atypical antipsychotic did not reveal any significantly altered lipid species in both the t-test and the differential analysis in lipidr. The most significantly enriched class was PC with a low adjusted p-value of 6.05E-12, followed by TAG, CAR, LPC and FA (table 35).

Lipid class	P-value	Adjusted p-value
PC	9.03E-14	6.05E-12
TAG	1.27E-07	4.27E-06
CAR	8.72E-07	1.95E-05
LPC	4.49E-06	7.53E-05
FA	0.00031	0.00350

Table 35: Results of the enrichment analysis of the matched olanzapine cohort

8.6.1.5 Paliperidone

Paliperidone did not show any significantly altered lipid species in the differential analysis in lipidr, but there was one significant but not annotated peak in the t-test. The enrichment analysis of the matched paliperidone cohort showed that the most significantly enriched classes were DAG, PC, FA, TAG, and LPC (table 36).

Lipid class	P-value	Adjusted p-value
DAG	5.44E-08	3.64E-06
PC	1.76E-06	5.88E-05
FA	2.79E-05	0.00062
TAG	0.00058	0.00775
LPC	0.00507	0.04848

Table 36: Results of the enrichment analysis of the matched paliperidone cohort

8.6.1.6 Quetiapine

Similarly to aripiprazole, quetiapine, another atypical antipsychotic, did not show any significantly altered lipid species in the differential analysis in lipidr. However, there were 4 significant but not annotated peaks found in the t-test (see supplemental material, table S3). The enrichment analysis of the matched quetiapine cohort showed that CAR was by far the most significantly enriched class with an adjusted p-value of 5.92E-08, followed by TAG, and dCer (table 37).

Lipid class	P-value	Adjusted p-value
CAR	8.84E-10	5.92E-08
TAG	0.00057	0.01272
dCer	0.00147	0.02462

Table 37: Results of the enrichment analysis of the matched quetiapine cohort

8.6.1.7 Risperidone

The t-test and differential analysis in lipidr did not show any significantly altered lipid species for risperidone, another atypical antipsychotic being studied. However, the enrichment analysis of the matched risperidone cohort demonstrated that CAR was the most significantly enriched class, with an adjusted p-value of 1.57E-06, followed by PE, FA, and TAG (table 38).

Lipid class	P-value	Adjusted p-value
CAR	2,35E-08	1,57E-06
PE	1,75E-05	0,00059
FA	5,74E-05	0,00128
TAG	0,001336	0,017898

Table 38: Results of the enrichment analysis of the matched risperidone cohort

8.6.1.8 Ziprasidone

Zisprasidone, another atypical antipsychotic, did not demonstrate any significantly altered lipid species in either the t-test or the differential analysis in lipidr. The enrichment analysis of the matched ziprasidone cohort displayed that the

Lipid class	P-value	Adjusted p-value
dSM	4.50E-08	3.02E-06
PE	0.00084	0.01411
LPC	0.00343	0.03285

most significantly enriched class was dSM, with an adjusted p-value of 3.02E-06, followed by PE and LPC (table 39).

Table 39: Results of the enrichment analysis of the matched ziprasidone cohort

8.6.1.9 Comparison of different antipsychotics effects

The overall antipsychotics subgroup displayed significant alterations in lipid species, with PC, PE, and dCer being the classes with the highest percentage of altered lipid species. The most significantly enriched class was TAG, followed by PC, CAR, FA, dCer, and DAG, similar to the results seen in the SCZ cohort. In Figure 27, the enrichment analysis results of the matched AP cohort are placed into thte context of the effects observed for specific antipsychotic drugs.

Individual drugs showed different patterns in lipid alterations. The lipid classes altered in most subgroups were FA and TAG, with TAG being upregulated in olanzapine, clozapine, risperidone, quetiapine and haloperidol, but downregulated in paliperidone and aripiprazole. Similarly FA was upregulated in some subgroups and downregulated in others. DAG was non-significantly upregulated in most drugs but significantly downregulated in paliperidone. Furthermore, opposite-effect findings for some individual drugs led to the fact that these classes did not show alterations in the overall analysis (increased PE levels in the clozapine, and risperidone cohorts and decreased PE levels in the ziprasidone cohort, figure 27).

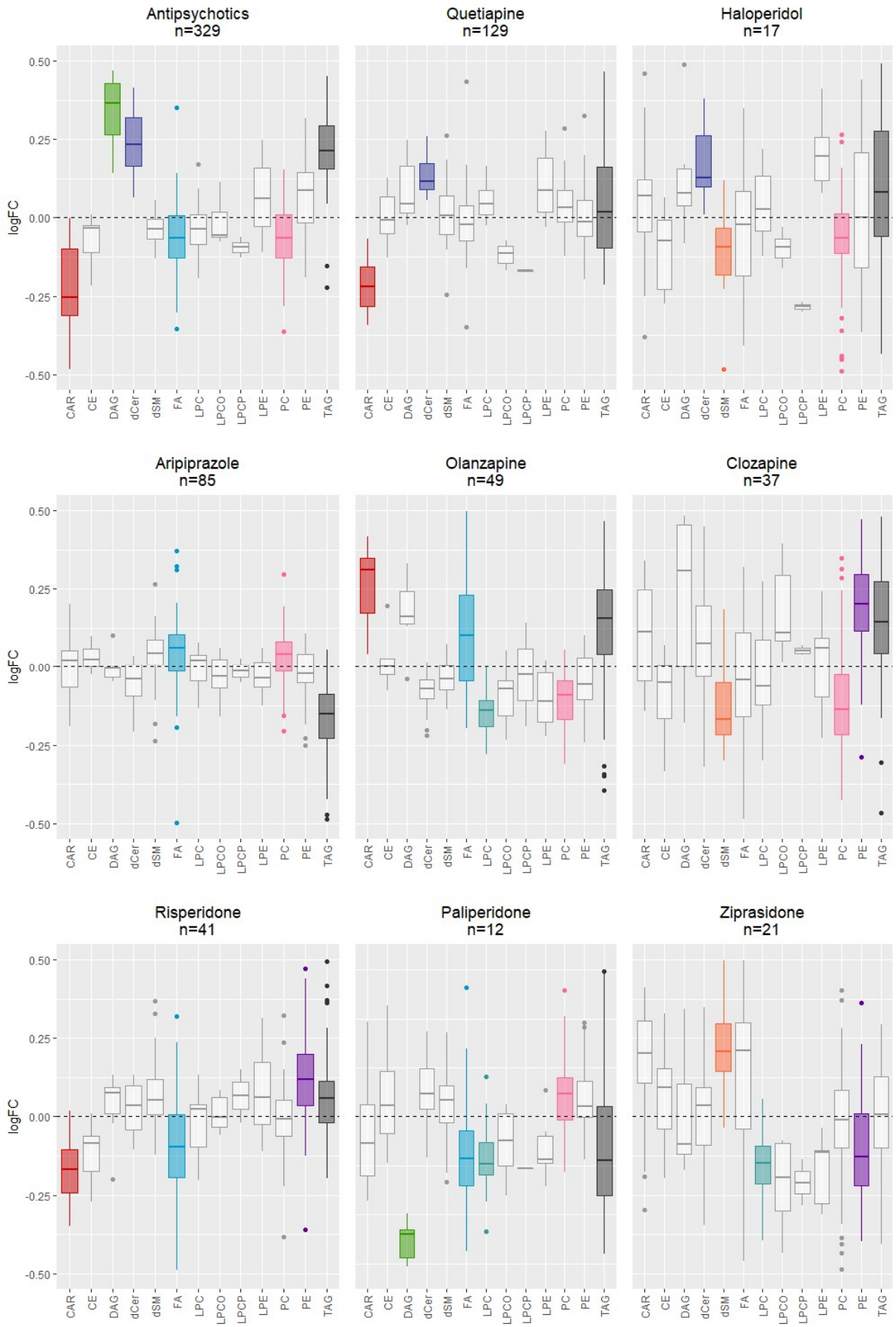

Figure 27: Boxplots comparing the results of the enrichment analysis in the matched antipsychotics cohort with the matched cohorts for aripiprazole, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

8.6.2 Antidepressants

Table 40 shows the baseline charactertistics for each of the individual drugs from the medication class antidepressants, including sertraline, escitalopram, venlafaxine, mirtazapine and bupropion.

Cohort, n	Age, mean (sd)	BMI, mean (sd)	Females, % (n)	SCZ, % (n)	BP, % (n)
Sertraline, 366	38.8 (14.6)	26.3 (5.9)	43.4 (159)	48.6 (178)	0% (0)
Samples, 178	39.3 (12.9)	28.4 (6.3)	30.3 (54)	100% (178)	0% (0)
Controls, 188	38.3 (16.0)	24.3 (4.6)	55.9 (105)	0% (0)	0% (0)
Escitalopram, 32	38.9 (15.1)	28.2 (4.9)	31.3 (10)	18.8 (6)	81.3 (26)
Samples, 16	42.3 (17.0)	29.0 (4.6)	31.3 (5)	18.8 (3)	81.3 (12)
Controls, 16	35.5 (12.6)	27.3 (5.1)	31.3 (5)	18.8 (3)	81.3 (12)
Venlafaxine, 62	44.1 (12.4)	30.1 (6.4)	51.6 (32)	41.9 (26)	58.1 (36)
Samples, 31	44.7 (13.3)	29.9 (6.4)	51.6 (16)	41.9 (13)	58.1 (18)
Controls, 31	43.4 (11.5)	30.2 (6.4)	51.6 (16)	41.9 (13)	58.1 (18)
Mirtazapine, 38	49.5 (13.3)	27.2 (5.9)	31.6 (12)	36.8 (14)	63.2 (24)
Samples, 19	47.7 (14.2)	26.9 (5.2)	36.8 (7)	36.8 (7)	63.2 (12)
Controls, 19	52.3 (12.4)	27.5 (6.7)	26.3 (5)	36.8 (7)	63.2 (12)
Bupropion, 40	45.6 (13.6)	29.4 (6.5)	32.5 (13)	10.0 (4)	90.0 (36)
Samples, 20	44.3 (15.4)	29.3 (7.3)	35.0 (7)	10.0 (2)	90.0 (18)
Controls, 20	46.9 (11.9)	29.4 (5.8)	30.0 (6)	10.0 (2)	90.0 (18)

Table 40: Baseline characteristics of the matched cohorts for the individual drugs from the antidepressants class

Enrichment analysis was performed on the matched cohorts of individuals taking different antidepressants. Figure 28 gives an overview over the signficantly enriched lipid classes in the AD cohort compared to the individual drugs sertraline, escitalopram, venlafaxine, mirtazapine and bupropion.

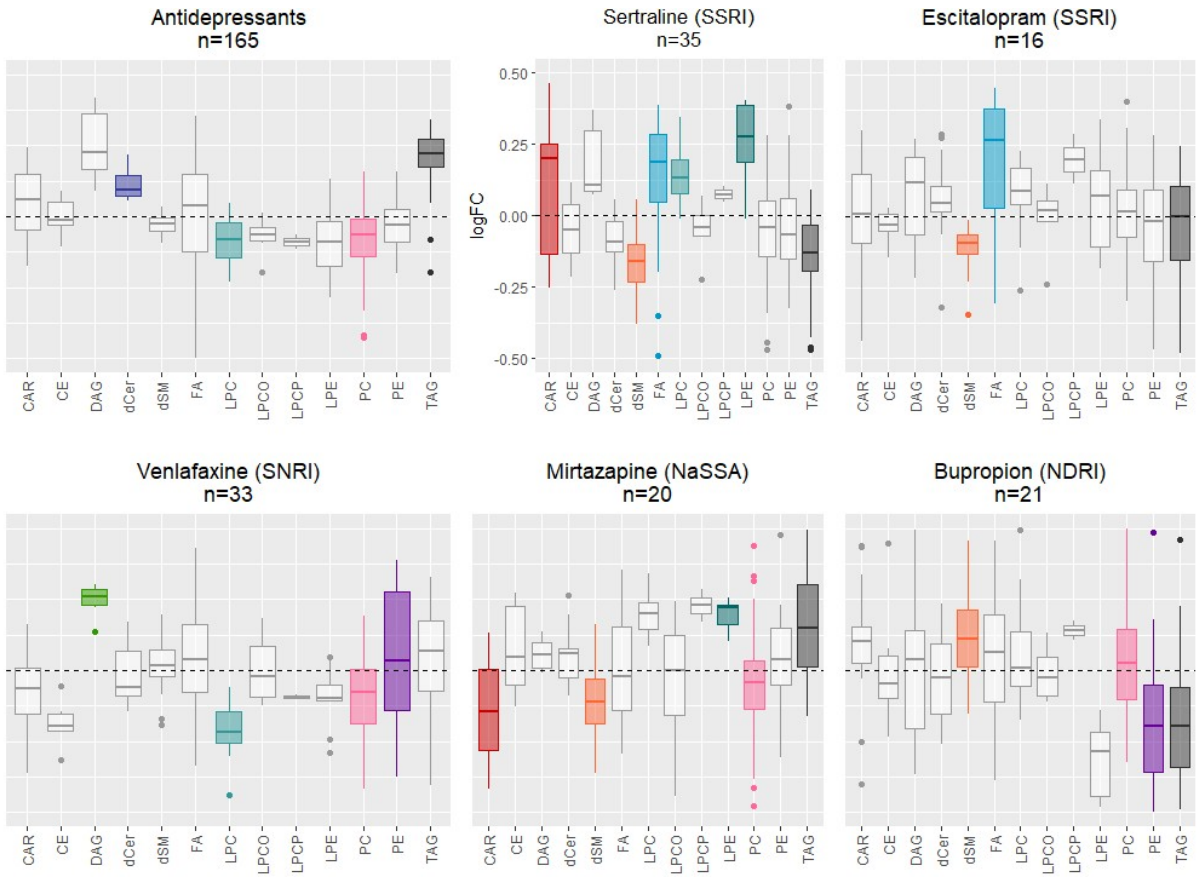

Figure 28: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antidepressants, sertraline, escitalopram, venlafaxine, mirtazapine and bupropion in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

For sertraline, the most commonly used SSRI with 35 individuals in the cohort, TAG was the most significantly enriched class with an adjusted p-value of 5.74E-09, followed by FA, dSM, CAR, LPE, and LPC (table 41).

Lipid class	P-value	Adjusted p-value
TAG	8.57E-11	5.74E-09
FA	3.99E-07	1.34E-05
dSM	2.22E-05	0.00050
CAR	5.47E-05	0.00092
LPE	0.00106	0.01011
LPC	0.00189	0.01580

Table 41: Results of the enrichment analysis of the matched sertraline cohort

For the matched escitalopram cohort (SSRI, n=16), the most significantly enriched classes were FA, with an adjusted p-value of 1.48E-07, TAG and dSM, respectively (table 42).

Lipid class	P-value	Adjusted p-value
FA	2.21E-09	1.48E-07
TAG	1.27E-06	4.26E-05
dSM	0.00051	0.00847

Table 42: Results of the enrichment analysis of the matched escitalopram cohort

In the matched venlafaxine cohort (SNRI, n=33), PC (adjusted p-value of 0.00093), LPC, DAG, and PE were the most significantly enriched classes (table 43).

Lipid class	P-value	Adjusted p-value
PC	1.38E-05	0.00093
LPC	4.97E-05	0.00167
DAG	0.00058	0.00970
PE	0.00358	0.03422

Table 43: Results of the enrichment analysis of the matched venlafaxine cohort

For the matched bupropion cohort (NDRI, n=20), TAG was the most significantly enriched class with an adjusted p-value of 2.22E-11, followed by PC, PE, and dSM, respectively (table 44).

Lipid class	P-value	Adjusted p-value
TAG	3.32E-13	2.22E-11
PC	0.00020	0.00666
PE	0.00030	0.00679
dSM	0.00112	0.01503

Table 44: Results of the enrichment analysis of the matched AD cohort

Lastly, in the matched mirtazapine cohort (NaSSA, n=20), TAG was the most significantly enriched class with an adjusted p-value of 3.07E-07, followed by CAR, PC, dSM and LPC (table 45).

Lipid class	P-value	Adjusted p-value
TAG	4.59E-09	3.07E-07
CAR	5.72E-06	0.00019
PC	0.00025	0.00419
dSM	0.00077	0.01031
LPC	0.00445	0.04259

Table 45: Results of the enrichment analysis of the matched mirtazapine cohort

8.6.3 Mood stabilizers

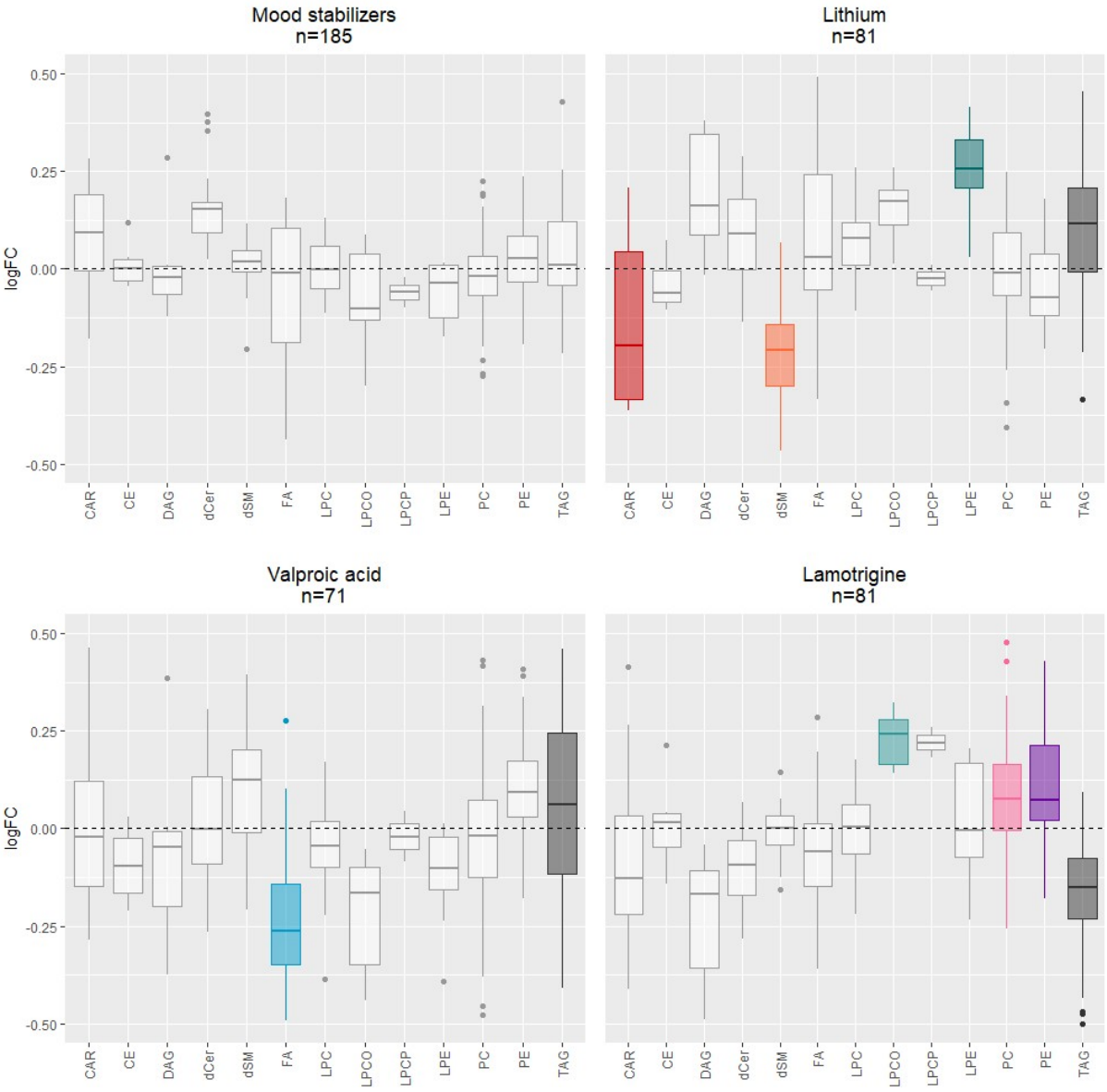

Figure 29: Boxplots comparing the results of the enrichment analysis in the matched cohorts for mood stabilizers, lithium, valproic acid and lamotrigine in lipidr (multiple hypothesis testing correction was applied and the whiskers of lipid classes with significantly altered adjusted p-values are coloured)

The next paragraph continues with the results for the lithium, lamotrigine and valproic acid cohorts. Figure 29 depicts boxplots comparing the results of the enrichment analysis in the matched cohorts for mood stabilizers, including lithium, valproic acid, and lamotrigine.

8.6.3.1 Lithium

Of the patients taking mood stabilizers, 77 with BP and 4 with SCZ were taking lithium, with a total of 81 patients. 76 of these patients were matched to 76 individuals not taking lithium. The average age of the matched patients taking lithium was 44.0 years and their average BMI was 27.7 kg/m^2. Among them, 43.4% (n=33) were female. Table 44 shows the baseline characteristics of the matched lithium cohort.

	Lithium (n=76)	**Controls (n=76)**
Age [years], mean (sd)	44.0 (12.0)	45.1 (12.9)
BMI [kg/m^2], mean (sd)	27.7 (6.1)	28.0 (5.7)
Female, % (n)	43.4 (33)	42.1 (32)
Bipolar disorder, % (n)	94.7 (72)	94.7 (72)
Schizophrenia, % (n)	5.3 (4)	5.3 (4)

Table 46: Baseline characteristics of the matched lithium cohort

8.6.3.1.1 Results t-test

The two-sided t-test for the matched lithium cohort revealed 11 peaks with significant differences after Benjamini-Hochberg correction. Two of these peaks were annotated, FA 22:1 and PEP 42:5, and each had a corrected p-value of 0.045 (table 45, for more information see supplemental material, table S3).

Table 47: Two-sided t-test for the matched lithium cohort: peaks with significant adjusted p-values after Benjamini-Hochberg correction

Peak	**Lipid species**	**P-value**	**Adjusted p-value**
gpeakneg1223	NA	0.00002	0.01764
gpeakneg3664	NA	0.00003	0.01764
gpeakneg3210	NA	0.00009	0.03656
gpeakneg1412	FA 22:1	0.00031	0.04464
gpeakneg1894	NA	0.00021	0.04464
gpeakneg3349	NA	0.00038	0.04464
gpeakneg3405	NA	0.00035	0.04464
gpeakneg4474	PE_P 42:5	0.00039	0.04464
gpeakneg4668	NA	0.00022	0.04464
gpeakpos3511	NA	0.00025	0.04464
gpeakpos6400	NA	0.00027	0.04464

8.6.3.1.2 Results lipidr

The differential analysis of the matched lithium cohort in lipidr revealed significant differences in 15 annotated peaks after Benjamini-hochberg correction (table 46). The most significant alterations were found in the classes dSM and FA, with 9 out of the 15 significant peaks belonging to dSM and 4 belonging to FA. In Figure 30, the volcano plot shows the significant alterations in lipid species mostly belonging to dSM from the differential analysis of the matched lithium cohort in lipidr. The peak with the lowest corrected p-value was FA 8:0 with a p-value of 0.00286. This result should be interpreted with care (see figure 23).

Table 48: Differential analysis for the matched lithium cohort: lipid species with significant adjusted p-values after correction for multiple testing

Lipid species	**logFC**	**P-value**	**Adjusted p-value**
FA 8:0	-2.00783	7.85E-06	0.00286
PC 42:6	-0.40680	4.15E-05	0.00755
dSM 40:3	-0.33115	8.45E-05	0.01025
FA 24:3	0.42409	0.00046	0.01901
FA 26:4	0.36965	0.00051	0.01901
dSM 32:2	-0.26979	0.00029	0.01901
dSM 33:2	-0.28421	0.00034	0.01901
dSM 38:3	-0.33843	0.00052	0.01901
dSM 39:2	-0.32151	0.00052	0.01901
dSM 42:4	-0.30326	0.00046	0.01901
FA 24:2	0.31210	0.00084	0.02654
dSM 41:3	-0.33306	0.00087	0.02654
dSM 35:2	-0.21439	0.00117	0.03269
FA 24:1	0.28855	0.00127	0.03291
dSM 41:2	-0.23978	0.00140	0.03409

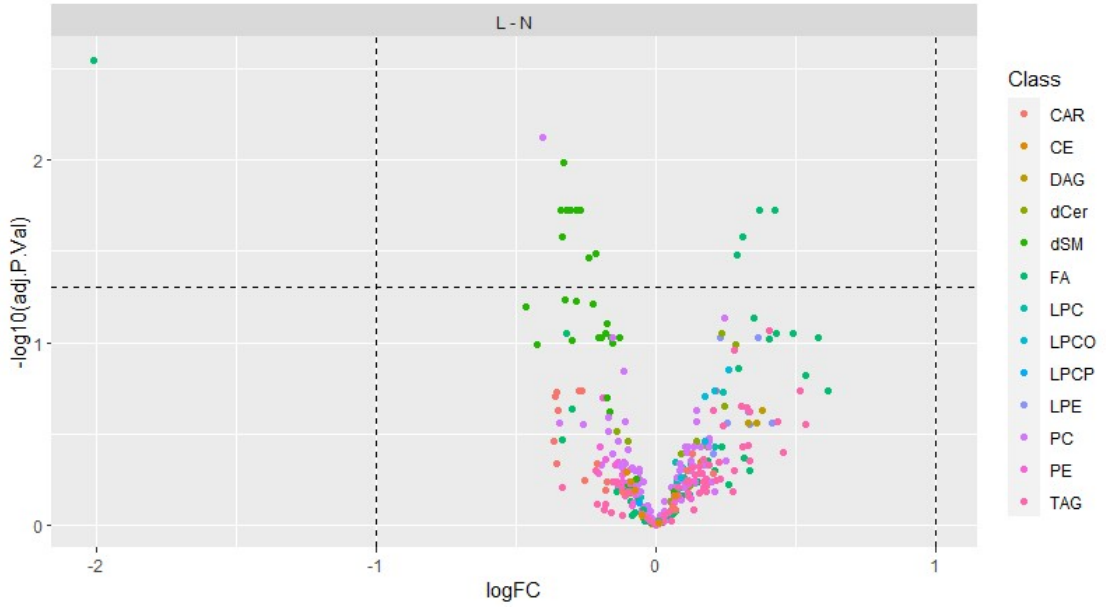

Figure 30: Volcano plot displaying the results of the differential analysis of the matched lithium cohort in lipidr (15 significantly altered lipid species mostly belonging to the class dSM; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown)

In the matched lithium cohort, the most significantly enriched classes were dSM with a remarkable adjusted p-value of 2.10E-10, followed by TAG, CAR, and LPE (table 47). Figure 31 presents a boxplot displaying the outcomes of the enrichment analysis conducted in the matched lithium.

Lipid class	P-value	Adjusted p-value
dSM	3.14E-12	2.10E-10
TAG	6.72E-05	0.00225
CAR	0.00024	0.00536
LPE	0.00182	0.03055

Table 49: Results of the enrichment analysis of the matched lithium cohort

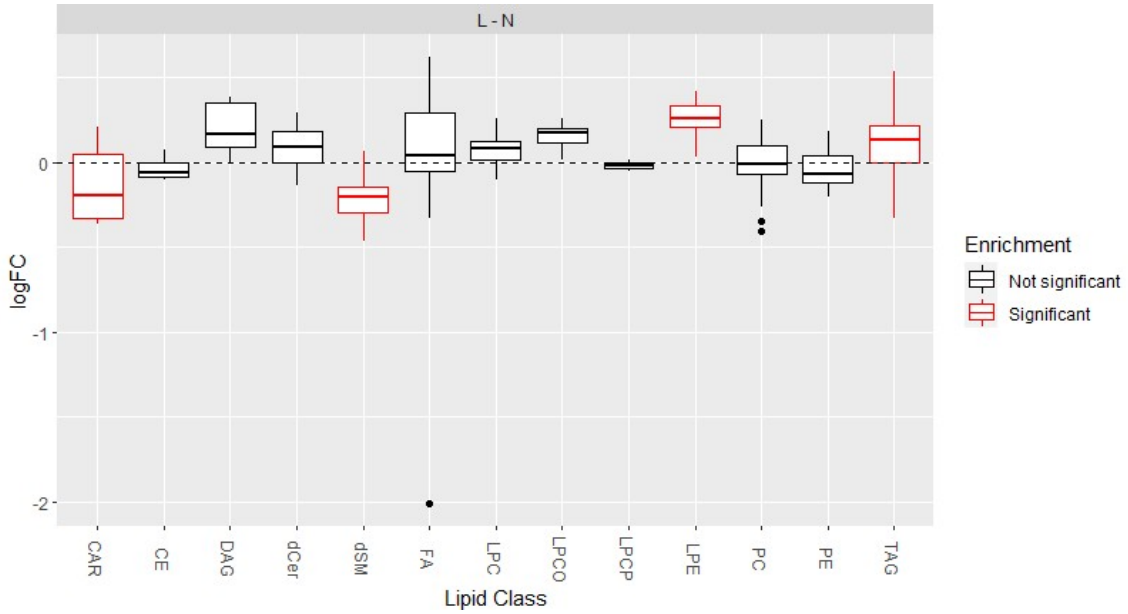

Figure 31: Boxplot showing the results of the enrichment analysis in the matched lithium cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

Based on the results of both differential and enrichment analyses, dSM seems to be by far the most significantly altered lipid class by lithium intake.

8.6.3.2 *Valproic acid*

The medication valproic acid was used by 71 individuals in the entire cohort, of which 69 were matched to 69 individuals not taking valproic acid based on gender, BMI, age, and diagnosis using nearest neighbor matching. Demographics of the cohort are shown in table 50.

	Valproic acid (n=69)	**Controls (n=69)**
Age [years], mean (sd)	45.7 (14.1)	44.7 (12.3)
BMI [kg/m^2], mean (sd)	28.5 (6.1)	28.6 (7.1)
Female, % (n)	34.8 (24)	40.6 (28)
Bipolar disorder, % (n)	91.3 (63)	91.3 (63)
Schizophrenia, % (n)	8.7 (6)	8.7 (6)

Table 50: Baseline characteristics of the matched valproic acid cohort

The differential analysis in lipidr revealed 68 significantly altered peaks. The peaks with the lowest adjusted p-values were FA 8:0, FA 26:4, and TAG 42:2. Table 51 shows the 20 lipid species with the lowest adjusted p-values after correction for multiple testing. FA 8:0 had an extremely low adjusted p-value of 5.23E-70, but this result should be interpreted with caution based on the uncommon intensity distribution of FA 8:0 as mentioned above.

The lipid classes with the highest number of significantly altered lipid species were PC, TAG, and FA, and the class with the highest percentage of altered lipid species was PC, with 37% of its species significantly altered, followed by CAR (see supplemental material, table S3).

Lipid species	**logFC**	**P-value**	**Adjusted p-value**
FA 8:0	6.50308	1.44E-72	5.23E-70
FA 26:4	-0.78311	2.54E-10	4.63E-08
TAG 42:2	2.20787	1.89E-09	2.29E-07
FA 24:3	-0.72948	1.08E-07	9.81E-06
PC 42:6	0.51343	2.61E-07	1.90E-05
FA 26:5	-0.77133	5.99E-07	3.64E-05
TAG 42:1	1.82031	8.75E-07	4.55E-05
CAR 11:1	0.63215	2.07E-06	9.42E-05
TAG 58:9	0.59473	5.86E-06	0.00021
TAG 58:8	0.51525	5.47E-06	0.00021
FA 24:4	-0.65267	8.61E-06	0.00028
PCO 38:3	-0.35776	9.46E-06	0.00029
LPCO 18:0	-0.43995	1.08E-05	0.00030
FA 11:1	-0.50387	1.73E-05	0.00045
CAR 13:1	0.71666	3.02E-05	0.00069
TAG 40:1	1.64833	2.91E-05	0.00069
PC 39:4	0.41740	4.12E-05	0.00088
PC 40:3	0.26760	4.81E-05	0.00097
dSM 39:2	0.39389	5.42E-05	0.00099
PC 42:5	-0.47746	5.36E-05	0.00099

Table 51: Differential analysis for the matched valproic acid cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing

In the enrichment analysis of the matched valproic acid cohort, TAG was the most significantly enriched class with an adjusted p-value of 0.00097, followed by FA (table 52).

Lipid class	**P-value**	**Adjusted p-value**
TAG	1.45E-05	0.00097
FA	3.27E-05	0.00109

Table 52: Results of the enrichment analysis of the matched valproic acid cohort

8.6.3.3 *Lamotrigine*

For the lamotrigine cohort, 33 individuals were taking the medication, and 32 of them were matched to 32 individuals not taking lamotrigine based on gender, BMI, age, and diagnosis using nearest neighbor matching. Demographics of the cohort are shown in table 53.

	Lamotrigine (n=32)	**Controls (n=32)**
Age [years], mean (sd)	46.4 (14.2)	48.6 (11.8)
BMI [kg/m^2], mean (sd)	27.7 (6.2)	28.7 (5.7)
Female, % (n)	50.0 (16)	43.8 (14)
Bipolar disorder, % (n)	87.5 (28)	87.5 (28)
Schizophrenia, % (n)	6.3 (2)	3.1 (1)

Table 53: Baseline characteristics of the matched lamotrigine cohort

The differential analysis in lipidr did not show any significantly altered lipid species for lamotrigine. However, the enrichment analysis of the matched lamotrigine cohort demonstrated that TAG was the most significantly enriched class, with an adjusted p-value of 6.52E-13, followed by PC, PE, and LPCO (table 54).

Lipid class	**P-value**	**Adjusted p-value**
TAG	9.73E-15	6.52E-13
PC	7.41E-10	2.48E-08
PE	9.41E-06	0.00021
LPCO	0.00340	0.03793

Table 54: Results of the enrichment analysis of the matched lamotrigine cohort

8.6.3.4 *Common effects*

The mood stabilizers are mainly used by patients with BP. In the matched mood stabilizer cohorts, each drug had very different effects on the lipidome, with no common effects observed. Interestingly, each drug showed stronger and more effects on the lipid composition than the entire mood stabilizer class taken together. This may suggest that the different effects of the drugs eliminate each other.

8.7 Medication subgroups

This phase of the analysis focuses on distinct subgroups within the medication classes. Specifically, for antipsychotics, the analysis examines two different receptor profiles, while for antidepressants, the subgroups of selective serotonin reuptake inhibitors (SSRI), serotonin-norepinephrine reuptake inhibitors (SNRI), and tricyclic antidepressants (TCA) are taken into consideration.

8.7.1 Antipsychotics: receptor profiles

Table 55 shows the baseline charactertistics for the receptor profiles ZPR (ziprasidone, paliperidone, risperidone) and CO (clozapine and olanzapine).

Cohort, n	**Age, mean (sd)**	**BMI, mean (sd)**	**Females, % (n)**	**SCZ, % (n)**	**BP, % (n)**
ZPR, 140	40.1 (13.0)	30.2 (7.1)	40.0 (56)	70.0 (98)	30.0 (42)
Samples, 70	40.1 (12.3)	30.1 (7.1)	42.9 (30)	70.0 (49)	30.0 (21)
Controls, 70	40.1 (13.8)	30.3 (7.1)	37.1 (26)	70.0 (49)	30.0 (21)
CO, 162	40.9 (13.1)	27.6 (5.2)	29.6 (48)	72.8 (118)	27.2 (44)
Samples, 81	40.6 (12.9)	27.7 (5.6)	28.4 (23)	72.8 (59)	27.2 (22)
Controls, 81	41.1 (13.3)	27.5 (4.7)	30.9 (25)	72.8 (59)	27.2 (22)

Table 55: Baseline characteristics of the matched cohorts for the receptor profiles ZPR and CO

8.7.1.1 Zisprasidone, paliperidone and risperidone (ZPR)

In the matched ZPR cohort, no significantly altered lipid species were found in both the t-test and the differential analysis in lipidr. The enrichment analysis of the matched ZPR cohort showed that TAG was the most significantly enriched class with an adjusted p-value of 3.18E-05, followed by dSM, CAR, and PC (table 56).

Lipid class	P-value	Adjusted p-value
TAG	4.75E-07	3.18E-05
dSM	1.31E-05	0.00044
CAR	0.00015	0.00255
PC	0.00286	0.03188

Table 56: Results of the enrichment analysis of the matched ZPR cohort

8.7.1.2 Clozapine and olanzapine (CO)

The differential analysis in the matched CO cohort did not reveal any significantly altered lipid species, and the t-test did not show any significant peaks either. However, the enrichment analysis demonstrated that TAG and PC were the most significantly enriched classes with adjusted p-values of 5.57E-25 and 6.40E-16, respectively, followed by dSM and CAR. The classes LPC and PE also showed significant enrichment, but to a lesser extent (table 57). Figure 32 shows boxplots comparing the results of the enrichment analysis in the matched cohorts for the receptor profile CO, clozapine and olanzapine.

Lipid class	P-value	Adjusted p-value
TAG	8.31E-27	5.57E-25
PC	1.91E-17	6.40E-16
dSM	1.24E-05	0.00028
CAR	0.00053	0.00889
PE	0.00121	0.01616
LPC	0.00394	0.04397

Table 57: Results of the enrichment analysis of the matched CO cohort

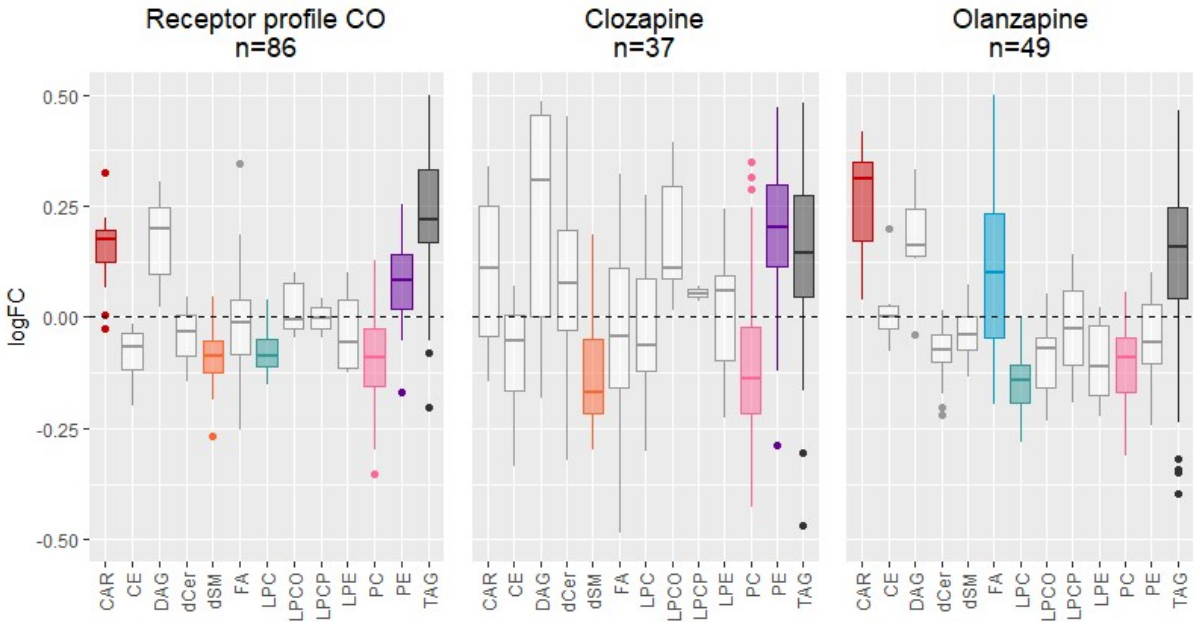

Figure 32: Boxplots comparing the results of the enrichment analysis in the matched cohorts for the receptor profile CO, clozapine and olanzapine in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

The results of the enrichment analysis of the matched CO, clozapine and olanzapine cohorts showed similarities in the lipid classes that were significantly enriched. TAG was the most significantly enriched class in both CO and olanzapine cohorts with extremely low adjusted p-values, and also showed significant enrichment in the clozapine cohort. PC was another class that was significantly downregulated in all three cohorts. Similarly dSMs were significantly downregulated in the CO and

clozapine cohorts and non significantly downregulated in the olanzapine cohorts. The enrichment in PE is only present in the clozapine and CO cohorts.

8.7.2 Antidepressants

Table 58 shows the baseline charactertistics for the following subgroups of the medication class antidepressants: selective serotonin reuptake inhibitors (SSRI, including fluoxetine, sertraline, escitalopram, paroxetine and citalopram), serotonin noradrenaline reuptake inhibitors (SNRI, including milnacipran, duloxetine, reboxetine, and venlafaxine), and tricyclic antidepressants (TCA, including amitriptyline, doxepine, clomipramine, tianeptine, and trimipramine).

Cohort, n	Age, mean (sd)	BMI, mean (sd)	Females, % (n)	SCZ, % (n)	BP, % (n)
SSRI, 132	42.1 (13.8)	29.1 (6.0)	36.4 (48)	35.6 (47)	64.4 (85)
Samples, 66	42.4 (14.4)	29.3 (5.4)	37.9 (25)	34.8 (23)	65.2 (43)
Controls, 66	41.7 (13.3)	29.0 (6.6)	34.8 (23)	36.4 (24)	63.6 (42)
SNRI, 104	45.9 (12.9)	30.6 (7.1)	45.2 (47)	29.8 (31)	70.2 (73)
Samples, 52	46.3 (13.1)	30.0 (6.8)	50.0 (26)	26.9 (14)	73.1 (38)
Controls, 52	45.4 (12.8)	31.2 (7.4)	40.4 (21)	32.7 (17)	67.3 (35)
TCA, 28	47.9 (16.5)	30.7 (6.4)	35.7 (10)	71.4 (20)	28.6 (8)
Samples, 14	48.1 (18.6)	29.7 (5.8)	35.7 (5)	64.3 (9)	35.7 (5)
Controls, 14	47.8 (14.8)	31.7 (7.7)	35.7 (5)	78.6 (11)	21.4 (3)

Table 58: Baseline characteristics of the matched cohorts for the individual drugs from the antidepressants class

8.7.2.1 SSRI

The SSRI were the most commonly used antidepressant in the matched antidepressant cohort, with 66 individuals taking an SSRI. These individuals were matched to 66 individuals not taking SSRIs based on gender, BMI, age, and diagnosis using nearest neighbor matching (table 58).

The differential analysis in lipidr did not show any significantly altered lipid species for SSRIs. However, the enrichment analysis of the matched SSRI cohort demonstrated that PC was the most significantly enriched class, with an adjusted p-value of 1.94E-06, followed by CAR, dSM, and DAG (table 59).

Lipid class	P-value	Adjusted p-value
PC	2.89E-08	1.94E-06
CAR	5.65E-05	0.00126
dSM	0.00106	0.01183
DAG	0.00149	0.01416

Table 59: Results of the enrichment analysis of the matched SSRI cohort

8.7.2.2 SNRI

The matched SNRI cohort consisted of 55 individuals taking an SNRI, of which 52 were matched to 52 individuals not taking SNRIs based on gender, BMI, age, and diagnosis using nearest neighbor matching (table 60).

The differential analysis in lipidr did not show any significantly altered lipid species for SNRIs. However, the enrichment analysis of the matched SNRI cohort demonstrated that TAG was the most significantly enriched class, with an adjusted p-value of 4.81E-09, followed by CAR and LPC (table 54).

Lipid class	P-value	Adjusted p-value
TAG	7.18E-11	4.81E-09
CAR	1.70E-07	5.68E-06
LPC	2.46E-05	0.00055

Table 60: Results of the enrichment analysis of the matched SNRI cohort

8.7.2.3 TCA

The tricyclic antidepressants (TCA) were used by 14 individuals in the entire cohort, and they were matched to 14 individuals not taking TCAs based on gender, BMI, age, and diagnosis using nearest neighbor matching (table 58).

The analysis in lipidr did not show any significantly altered lipid species for TCAs. However, the enrichment analysis of the matched TCA cohort demonstrated that TAG was the most significantly enriched class, with an adjusted p-value of 6.69E-19, followed by dSM, dCer, FA, and CAR (table 61).

Lipid class	P-value	Adjusted p-value
TAG	9.99E-21	6.69E-19
dSM	2.33E-07	7.80E-06
dCer	1.69E-05	0.00038
FA	0.00022	0.00375
CAR	0.00120	0.01339

Table 61: Results of the enrichment analysis of the matched TCA cohort

8.7.2.4 Common effects

The results of the enrichment analysis for the matched antidepressant cohort and its subgroups showed that TAG was the most significantly enriched class across several subgroups of antidepressants, including SNRIs, and TCAs. TAG was upregulated in the antidepressants, TCA, SNRI, venlafaxine, escitalopram and mirtazapine subgroups and downregulated in the bupropion, and sertraline subgroups. Figure 33 provides a comprehensive summary of the enrichment analysis outcomes for the AD cohort and its various subgroups.

In addition to TAG, PC and dSM were the second most affected lipid classes, showing alterations in many subgroups. Notably, dCer was significantly altered in the overall antidepressants cohort but not in any of the individual drugs.

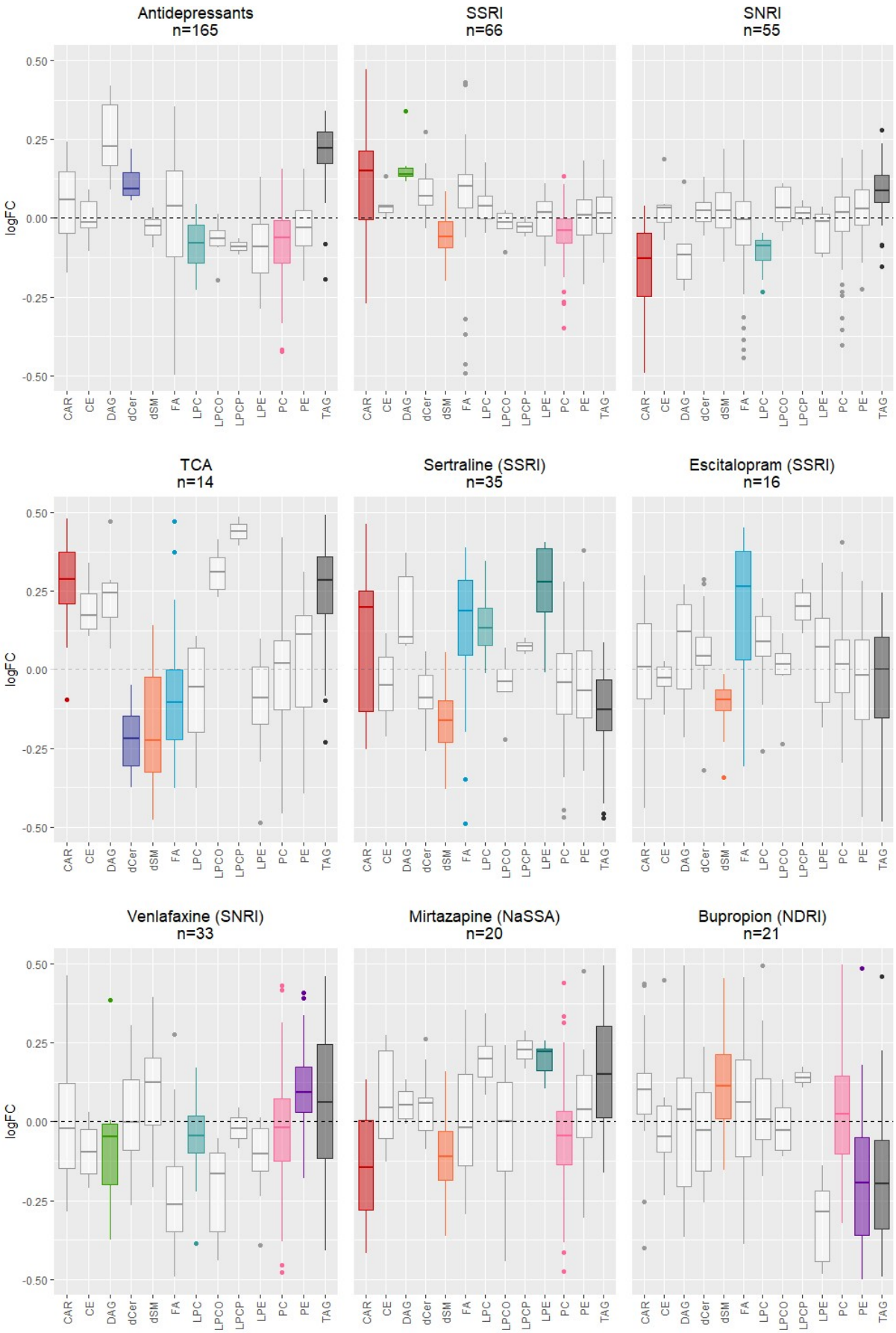

Figure 33: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antidepressants, SSRI, SNRI, TCA, sertraline, escitalopram, venlafaxine, mirtazapine and bupropion in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

8.8 Treatment response

This section of the analysis, aims to assess the relationship between the Alda-score, which reflects treatment response, and alterations observed in lipid profiles. The baseline characteristics of the Alda cohort are displayed in table 62. As mentioned above this cohort is not matched.

	Responder (n=16)	**Non-Responder (n=45)**
Age [years], mean (sd)	44.9 (14.8)	44.6 (10.5)
BMI [kg/m^2], mean (sd)	27.2 (5.0)	29.1 (5.5)
Female, % (n)	37.5 (6)	33.3 (15)

Table 62: Baseline characteristics of the matched lamotrigine cohort

The t-test for the dichotomous Alda-score did not show any significant differences between the groups after Benjamini-Hochberg correction. Furthermore, the linear model for the continuous version of the Alda-score resulted in only one peak (gpeakneg5448, adjusted p-value= 0.02177) that survived Benjamini-Hochberg correction, but it was not annotated (see supplemental material, table S3).

The differential analysis of the dichotomous Alda-score reveals 4 significantly altered peaks: dCer 42:2 (adjusted p-value = 0,00340), dCer 36:1 and FA 10:1 with an adjusted p-value of 0,04046 each, and LPE 16:1 (adjusted p-value = 0,04409 see supplemental material, table S2).

Figure 34 presents a boxplot displaying the outcomes of the enrichment analysis conducted in the Alda cohort. In the dichotomous Alda-score cohort, the most significantly enriched classes were CAR (adjusted p-value of 3.80E-07), followed by LPE, PE, dCer, and LPC (table 63).

Lipid class	**P-value**	**Adjusted p-value**
CAR	5.67E-09	3.80E-07
LPE	9.71E-06	0.00023
PE	1.02E-05	0.00023
dCer	5.68E-05	0.00095
LPC	0.00560	0.04168

Table 63: Results of the enrichment analysis of the matched Alda cohort

The classes CAR and LPE show alterations by lithium intake and an association with the Alda-score.

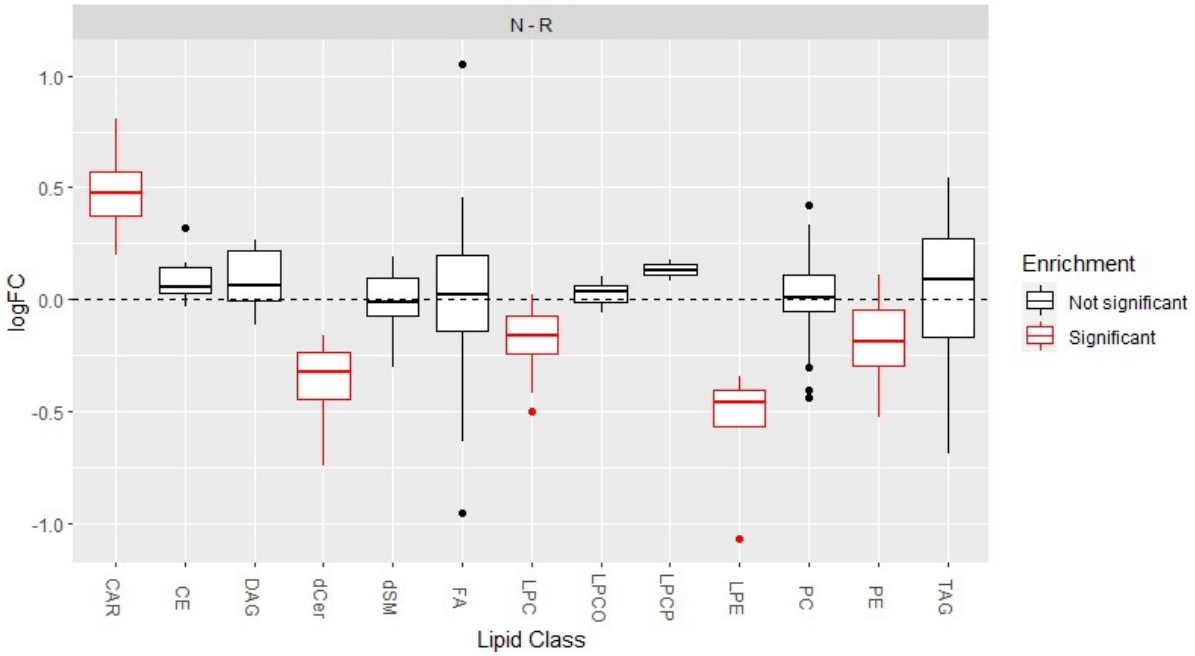

Figure 34: Boxplot showing the results of the enrichment analysis in the Alda cohort in lipidr (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

8.9 Multiple vs. single drug use

One challenge in the analysis of the effects of antipsychotics on the lipidome is that many patients take more than one antipsychotic, making it difficult to attribute specific effects to a particular drug. To account for this issue, four additional cohorts of individuals taking only one antipsychotic (aripiprazole, olanzapine, quetiapine, and risperidone) were analyzed. This analysis was only performed for these four drugs, as the sample sizes for the other antipsychotics were too small.

Table 64 shows the baseline characteristics of the single drug use cohorts: quetiapine-only, aripiprazole-only, olanzapine-only, and risperidone-only.

Cohort, n	Age, mean (sd)	BMI, mean (sd)	Females, % (n)	SCZ, % (n)	BP, % (n)
Quetiapine-only, 142	43.0 (13.2)	27.9 (6.0)	47.2 (67)	18.3 (26)	81.7 (116)
Samples, 71	43.5 (14.1)	27.4 (5.4)	50.7 (36)	19.7 (14)	80.3 (57)
Controls, 71	42.5 (12.5)	28.3 (6.6)	43.7 (31)	16.9 (12)	83.9 (59)
Aripiprazole-only, 44	41.3 (12.1)	31.3 (7.2)	22.7 (10)	20.5 (9)	79.5 (35)
Samples, 22	41.0 (12.2)	31.2 (7.1)	18.2 (4)	27.3 (6)	72.7 (16)
Controls, 22	41.5 (12.4)	31.4 (7.4)	27.3 (6)	13.6 (3)	86.4 (19)
Olanzapine-only, 54	38.6 (12.3)	28.2 (5.1)	29.6 (16)	48.1 (26)	51.2 (28)
Samples, 27	38.8 (12.0)	27.5 (5.1)	37.0 (10)	48.1 (13)	51.2 (14)
Controls, 27	38.3 (12.7)	29.0 (5.0)	22.2 (6)	48.1 (13)	51.2 (14)
Risperidone-only, 30	41.0 (13.6)	28.7 (6.5)	33.3 (10)	80.0 (24)	20.0 (6)
Samples, 15	39.3 (12.6)	28.0 (6.1)	33.3 (5)	80.0 (12)	20.0 (3)
Controls, 15	42.7 (14.7)	29.3 (7.1)	33.3 (5)	80.0 (12)	20.0 (3)

Table 64: Baseline characteristics of the matched cohorts for single drug use cohorts: quetiapine-only, aripiprazole-only, olanzapine-only, and risperidone-only

8.9.1 Quetiapine

The differential analysis of the matched quetiapine-only (single drug use) cohort did not reveal significant lipid species. The enrichment analysis demonstrated that the most significantly enriched class was TAG, with an adjusted p-value of 7.54E-08, followed by CAR, FA, and PE (table 65). These results are somewhat different from the enrichment analysis of the matched quetiapine cohort that included patients taking multiple antipsychotics, where CAR was also the most enriched class, but was followed by dCer. Notably, the single drug cohort showed stronger signals (apart from the CARs) compared to the matched quetiapine cohort that included patients taking multiple antipsychotics. There is a similarity in the tendencies of the enriched lipid classes between the single and multiple drug use cohorts.

Lipid class	P-value	Adjusted p-value
TAG	1.13E-09	7.54E-08
CAR	1.73E-08	5.80E-07
FA	2.98E-07	6.66E-06
PE	0.00049	0.00824

Table 65: Results of the enrichment analysis of the matched quetiapine-only cohort

8.9.2 Aripiprazole

In the differential analysis of the matched aripiprazole-only aripiprazole-only (single drug use) cohort, no significant lipid species were identified using lipidr. However, the enrichment analysis showed that TAG was the most significantly enriched class with an extremely low adjusted p-value of 9.21E-21, followed by FA and PC (table 66). These results are similar to the enrichment analysis of the matched aripiprazole cohort that included patients taking additional antipsychotics, where TAG was also the most enriched class, followed by PC and FA.

Lipid class	P-value	Adjusted p-value
TAG	1.37E-22	9.21E-21
FA	1.12E-10	3.76E-09
PC	3.65E-06	8.15E-05

Table 66: Results of the enrichment analysis of the matched aripiprazole-only cohort

8.9.3 Olanzapine

In the differential analysis of the matched olanzapine-only (single drug use) cohort, no significantly altered lipid species were found in lipidr. However, the enrichment analysis revealed that TAG was the most significantly enriched class with an adjusted p-value of 3.89E-09, followed by DAG, PE, PC, and FA (table 67). These results are similar to the enrichment analysis of the matched olanzapine cohort that included patients taking additional antipsychotics, where TAG was also the most enriched class followed by FA.

Lipid class	P-value	Adjusted p-value
TAG	5.81E-11	3.89E-09
DAG	6.85E-08	2.29E-06
PE	7.59E-07	1.70E-05
PC	9.21E-06	0.00015
FA	4.15E-05	0.00056

Table 67: Results of the enrichment analysis of the matched olanzapine-only cohort

8.9.4 Risperidone

The differential analysis of the matched risperidone-only (single drug use) cohort did not identify any significantly altered lipid species in lipidr. Nonetheless, the enrichment analysis demonstrated that the most significantly enriched class in the matched risperidone-only (single drug use) cohort was TAG, with an adjusted p-value of 2.12E-11, followed by CAR and dCer (table 68).

Lipid class	P-value	Adjusted p-value
TAG	3.17E-13	2.12E-11
CAR	7.44E-05	0.00249
dCer	0.00089	0.01998

Table 68: Results of the enrichment analysis of the matched risperidone-only cohort

These results differ from the enrichment analysis of the matched risperidone cohort that included patients taking multiple antipsychotics, where FA was the most enriched class, followed by dSM.

In Figure 35, the results of the enrichment analysis in lipidr are compared between single and multiple drug use in the matched cohorts for aripiprazole, olanzapine, quetiapine, and risperidone, with the upper plots including all patients taking a specific drug and the lower plots considering only patients taking just one antipsychotic.

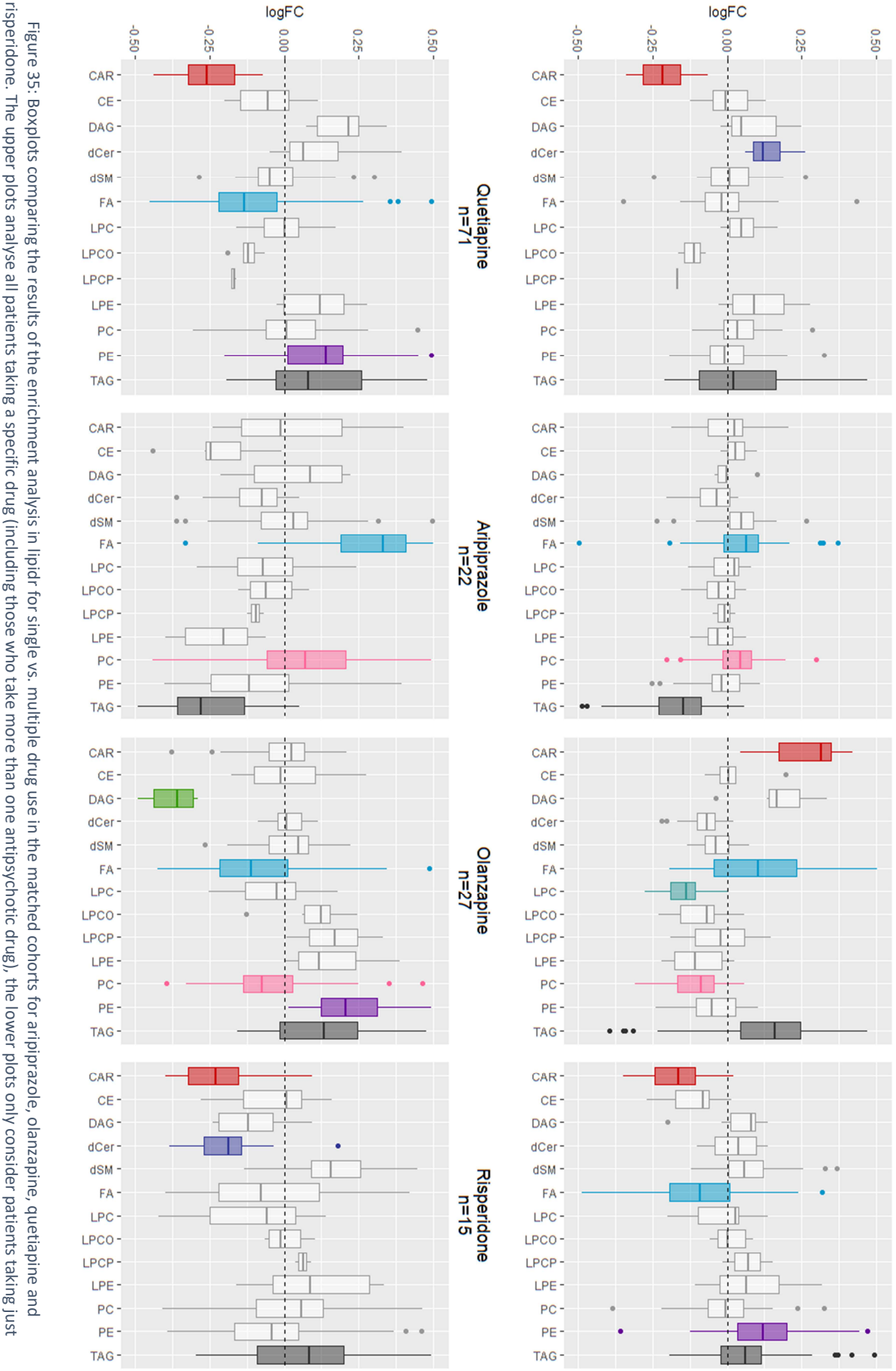

Figure 35: Boxplots comparing the results of the enrichment analysis in lipidr for single vs. multiple drug use in the matched cohorts for aripiprazole, olanzapine, quetiapine and risperidone. The upper plots analyse all patients taking a specific drug (including those who take more than one antipsychotic drug), the lower plots only consider patients taking just one antipsychotic (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

8.10 Effects by lipid class

Next, the effects of different antipsychotics on each lipid classe were compared (Figure 36).

The analysis showed that several lipid classes were consistently affected, with TAG being the most upregulated class and FA being mostly downregulated. PC, CAR and dSM were both up and downregulated depending on the drug. dCer and DAG were increased in most sub-samples, although only significantly in three and one cohorts, respectively.

Notably, aripiprazole showed a profile of alterations distinct from most other antipsychotics, being one of only two drugs with significantly downregulated TAGs, as well as one of only two drugs with downregulated dCers (although not significant), and one of only two drugs with significantly upregulated FAs.

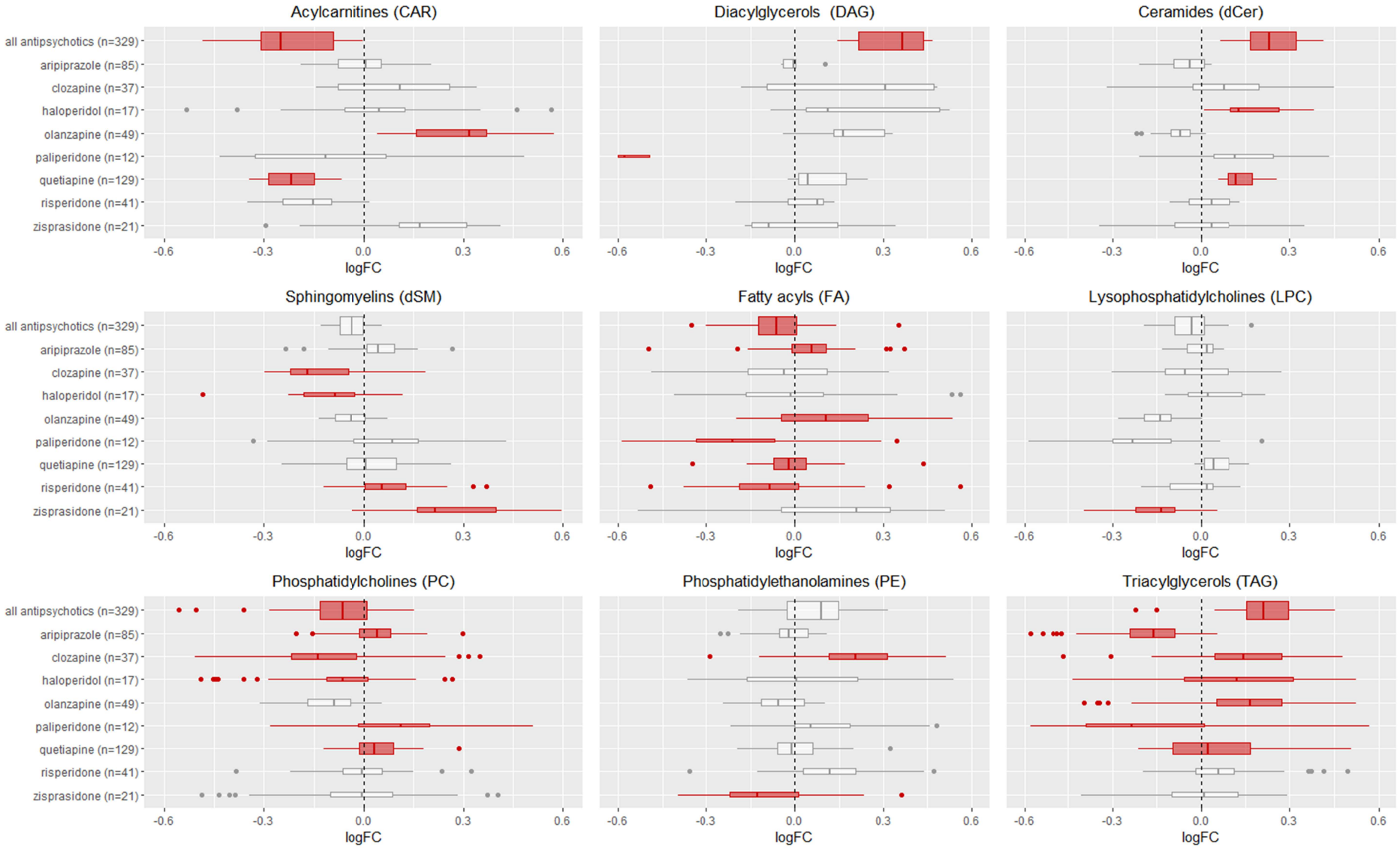

Figure 36: Horizontal boxplot comparing the effect sizes of different medications on the levels of CAR, DAG, dCer, dSM, FA, LPC, PC, PE and TAG (multiple hypothesis testing correction was applied and the whiskers of medication classes/individual drugs that significantly ($p<0.05$ after Benjamini-Hochberg correction for multiple testing) alter adjusted p-values of acylcarnitine expression are coloured red; the size of the whiskers corresponds to the size of the subgroup)

9 Discussion

9.1 Disease effects

The starting point of this thesis was to investigate potential alterations in the lipidome of patients with SCZ and BP in comparison to healthy controls. Additionally, the study aimed to identify and examine differences in lipid compositions between SCZ and BP patient groups.

Both the matched BP and SCZ cohorts exhibited a substantial number of altered lipid species and classes. The findings of this analysis align with earlier research, as the lipid classes that were found to be altered in patients with SCZ - including TAG, PC, CAR, FA, dCer, and dSM - are consistent with previous studies (Cao et al. 2019; Cao et al. 2020; Kriisa et al. 2017; Tkachev et al. 2023; Tkachev et al. 2021; Solberg et al. 2016; Liu et al. 2021). Similarly, the lipid classes that exhibited alterations in patients with BP - such as dCer, PC, TAG, and FA - correspond to earlier research in the field (Tkachev et al. 2023; Brunkhorst-Kanaan et al. 2019; Pomponi et al. 2013; Scola et al. 2018).
The lipid species that exhibited the most significant differences between individuals with SCZ and controls, and was also the second most significantly altered lipid species when comparing individuals with BP to controls (dCer 36:1), has been previously reported to be altered in patients with BP and major depressive disorder (MDD) (Brunkhorst-Kanaan et al. 2019; Demirkan et al. 2013; Gracia-Garcia et al. 2011; Tkachev et al. 2023). This analysis successfully replicated the significant differences in several dCer lipid species (dCer 34:1, dCer 38:1, dCer 42:2) observed in previous studies comparing individuals with BP and MDD to controls (Brunkhorst-Kanaan et al. 2019). In this analysis these differences were consistently observed in both the BP and SCZ cohorts. This observation highlights a common effect shared by these diseases on the lipidome, suggesting potential shared underlying mechanisms. Furthermore, the alterations in several FAs (FA 20:3, FA 20:4, FA 22:5, FA 24:1) previously identified between BP and controls (Scola et al. 2018) were replicated in the BP cohort of this analysis, but not in the SCZ cohort. These findings suggest that these FAs could serve as potential markers for differentiating between SCZ and BP, although further replication and research are needed to validate their utility.

However, it is important to acknowledge that the observed effects may partly be attributed to the widespread use of medications, particularly antipsychotics and mood stabilizers, among patients with BP and SCZ, whereas the control group did not receive such treatment. For instance, in the SCZ cohort, TAGs emerged as the most significantly enriched class; however, it is worth noting that TAG levels have been demonstrated to be influenced by the intake of antipsychotics (Vancampfort et al. 2013; Pillinger et al. 2017; Misiak et al. 2017) .

When comparing patients with BP and SCZ by matching individuals with BP to individuals with SCZ, the most significantly altered annotated lipid species were FA 8:0, FA 25:0, and PE 36:1. None of those lipids has yet been reported to be altered in SCZ or BP. The lipid classes that showed the most significant enrichment in the BP cohort compared to the SCZ cohort were TAG, CAR and dSM. The observed similarities in enriched dCers and decreased PCs again suggest shared mechanisms in how the diseases affect the lipidome. Nonetheless, differences in TAGs, CARs, and dSMs were noted,

implying that BP and SCZ belong to the schizoaffective spectrum with both shared and unique features.

9.2 Medication effects

Subsequently, the thesis proceeded to analyze the impact of various medication classes, including antipsychotics, tranquilizers, antidepressants, and mood stabilizers, as well as individual drugs and subgroups within these medication classes.

9.2.1 Antipsychotics

Antipsychotics are widely used in the treatment of various mental health disorders, including SCZ and BP. This analysis investigated the effects of antipsychotics on lipid profiles in patients with BP and SCZ using the same workflow as in the other subgroups. The sample size for the antipsychotic cohort was the largest of all medication classes, with 329 individuals taking antipsychotics in the entire cohort.

The comparative analysis of the matched antipsychotics cohort revealed a significant alteration in a total of 155 peaks. Among the top 10 most significantly altered annotated lipid species, 5 belonged to the dCer class and 4 to the PCP class. The lipid species with the lowest adjusted p-value was dCer 36:2, followed by PCP 34:2 and dCer 36:1. As mentioned in section 9.1 "Disease effects," dCer 36:1 has been previously identified as altered in patients with BP, MDD, and SCZ (Brunkhorst-Kanaan et al. 2019; Demirkan et al. 2013; Gracia-Garcia et al. 2011; Tkachev et al. 2023), while dCer 36:2 has been reported to be altered in patients with SCZ (Tkachev et al. 2023). Additionally, PCP 34:2 has demonstrated alterations in both medicated and non-medicated individuals with SCZ, as well as in patients with MDD (Wang et al. 2019; Wang et al. 2021; Leppik et al. 2020; Demirkan et al. 2013; Yan et al. 2018; Wood et al. 2015; Tkachev et al. 2023). These findings underscore the shared effects of these diseases on the lipidome and highlight the challenge of distinguishing between medication-related and disease-related alterations.

The enrichment analysis of the matched antipsychotics cohort demonstrated similar alterations to those observed in the SCZ cohort, with TAG being the most significantly enriched class (adjusted p-value: 1.59E-17). This finding is consistent with previous research indicating the impact of antipsychotic intake on TAG levels (Vancampfort et al. 2013; Pillinger et al. 2017; Misiak et al. 2017). Additionally, significant alterations were observed in the PC, CAR, dCer, FA, and DAG lipid classes. These changes align well with earlier studies (Tkachev et al. 2023; Almeida et al. 2020; Kaddurah-Daouk et al. 2007; McEvoy et al. 2013); however, none of these alterations appear to be unique to antipsychotic intake, as they have also been reported in patients with SCZ (Cao et al. 2019; Cao et al. 2020; Kriisa et al. 2017; Tkachev et al. 2023; Tkachev et al. 2021; Solberg et al. 2016; Liu et al. 2021), and partially in MDD and BP (Brunkhorst-Kanaan et al. 2019; Demirkan et al. 2013; Gracia-Garcia et al. 2011; Tkachev et al. 2023).

Individual drugs showed different patterns in lipid alterations. The lipid classes altered in most subgroups were FA and TAG, with TAG being upregulated in olanzapine, clozapine, quetiapine and haloperidol, but downregulated in paliperidone and aripiprazole. Similarly, FA was upregulated in some subgroups and downregulated in others (figure 27).

Discussion

In this analysis, risperidone exhibited effects on dSM and FA levels, which are consistent with findings from previous studies (Almeida et al. 2020; Kaddurah-Daouk et al. 2007). However, the changes observed in PE, PC, LPC, TAG, DAG, and dCer, which were reported in earlier studies (Almeida et al. 2020; Kaddurah-Daouk et al. 2007), could not be replicated. For olanzapine, the previously reported effects on TAG and FA (Kaddurah-Daouk et al. 2007) were successfully replicated, while the alterations in PE observed in this analysis were not previously documented.

Similarly, the previously reported changes in PE due to aripiprazole intake (Kaddurah-Daouk et al. 2007) could not be reproduced. Interestingly, aripiprazole exhibited unique effects on lipid classes compared to other antipsychotics, with downregulated TAGs and upregulated FAs. These distinct metabolic effects of aripiprazole may contribute to its relatively benign metabolic side effects compared to other atypical antipsychotics (Koller et al. 2021; Kaddurah-Daouk et al. 2007). In contrast, the effects on FAs and TAGs associated with olanzapine and risperidone, but not with aripiprazole, may be linked to the metabolic side effects observed with these medications (Kaddurah-Daouk et al. 2007). These findings suggest a different mechanism of action for aripiprazole, potentially associated with reduced metabolic side effects. Furthermore, future studies could explore treatment response to aripiprazole compared to other atypical antipsychotics, as its unique mechanism of action makes it an intriguing alternative for patients who do not respond to other antipsychotics or experience significant metabolic side effects.

Both this study and previous research have consistently shown that the intake of antipsychotics has a significant impact on the lipidome studies (Tkachev et al. 2023; Almeida et al. 2020; Kaddurah-Daouk et al. 2007; McEvoy et al. 2013), highlighting the importance of considering antipsychotic intake as a covariate when analyzing lipidomic data. Due to the varied effects of different antipsychotic drugs on lipid profiles, it may be necessary to account for individual drugs or subgroups with similar effects. Differentiating between disease effects and medication effects can be challenging, as evidenced by the similarities in lipid profiles between the SCZ and antipsychotics cohorts in this analysis, and the similar lipid alterations observed in both medicated as well as non-medicated and first episode patients in previous studies (Leppik et al. 2020; Liu et al. 2021; Tkachev et al. 2023; Misiak et al. 2017). Notably, the significance of lipid alterations in the SCZ cohort was generally higher (except for CARs) compared to the antipsychotics cohort, suggesting that these effects are more likely attributable to the disease itself rather than medication. For the lipid class CAR, the adjusted p-values from this analysis were similar in magnitude between the SCZ and antipsychotics cohorts. This aligns with two studies comparing pre- and post treatment lipid profiles that found CARs to be significantly altered (Cao et al. 2019; Kriisa et al. 2017), further supporting the notion that this effect is specifically related to medication intake.

In conclusion, the analysis of the antipsychotics cohort, with a large sample size of 329 individuals, revealed highly significant results, with many significantly altered peaks and affected lipid classes. The classes TAG, PC, and FA were the most commonly affected across subgroups, suggesting a shared effect between antipsychotics, but each individual drug also showed unique effects on certain lipid classes. These findings highlight the importance of considering antipsychotic intake as a covariate in

lipidomic analysis and may have implications for the mechanism of action of antipsychotic drugs. Likewise, the relationship between lipid profiles and the emergence of metabolic side effects in some patients also warrants further investigation.

9.2.2 Antidepressants

Antidepressants are commonly used not only to treat major depressive disorder in BP patients but in the treatment of various mental health and non-mental health disorders. The next part of the analysis aimed to investigate the effects of antidepressants, both as a whole class and by individual subclasses (SSRI, SNRI, and TCA), on lipid profiles in patients with BP and SCZ using the same workflow as in the previous analysis.

The differential analysis and enrichment analysis in lipidr for the matched antidepressant cohort revealed 163 significantly altered peaks, with TAG being the most significantly enriched class with a very low adjusted p-value of 6.42E-20, followed by PC, LPC and dCer. In the subgroups of antidepressants, no significantly altered peaks were found for SSRIs, SNRIs, TCA or any of the individual drugs.

In a study by Mahmoudian Dehkordi et al., alterations in lipid species, including PCO 34:2 and PCO 38:2, were observed in response to escitalopram intake (Mahmoudian Dehkordi et al. 2021). In the antidepressant cohort of our study, the significance of these lipid species was replicated; however, it could not be replicated in the escitalopram cohort, possibly due to the small sample size of the escitalopram group (n=16). Another study by Lee et al. investigating the effect of paroxetine, an SSRI, on the brain lipidome of rodents, reported increased levels of LPC, LPE, and dCer, as well as decreased levels of dSM and PC species (Lee et al. 2012). These findings align with this analysis, where non-significant increases in LPC, LPE, and dCer, and significant decreases in dSM and PC species were observed in the SSRI cohort, including the individual drugs sertraline and escitalopram (figure 33).

In another study, the lipidome of the prefrontal cortex in rodents was evaluated following the administration of fluoxetine, an SSRI, combined with repetitive transcranial magnetic stimulation. The study reported an increase in CAR and dSM levels, as well as a decrease in PE, DAG, and TAG levels. (Xue et al. 2020) These findings were partially replicated in the SSRI cohorts and their subgroups, except for the decrease in DAG. The observed increase in dSM could potentially be attributed to a decrease in ASM (acid sphingomyelinase) activity, which has been shown to be elevated in patients with major depression (Kornhuber et al. 2005), suggesting a counteracting effect of fluoxetine or SSRIs in general (Xue et al. 2020; Pinto et al. 2022). Additionally, the increase in CARs, known to stabilize membranes, improve mitochondrial function, and enhance antioxidant activity, suggests a potential antioxidant effect of this treatment (Pinto et al. 2022).

The present study aimed to investigate the effects of antidepressants, both as a class and within subclasses, on lipid profiles in patients with BP and SCZ. While specific changes varied among individual drugs and subclasses, there was a consistent impact on TAG, PC, and dSM across different

antidepressant classes. However, it is important to note that there is limited research on the effects of MDD and antidepressants on the lipidome, particularly in human plasma/serum.

9.2.3 Mood stabilizers

Mood stabilizers are a common treatment option for BP, with lithium, valproic acid, and lamotrigine being among the most frequently prescribed drugs. While the effects of lithium on the lipidome will be discussed later, the next part of the analysis aimed to investigate whether mood stabilizers other than lithium have a significant impact on the lipid profiles of patients with BP, and if so, whether the effects are similar across different mood stabilizers using the same workflow as in the previous analysis.

The results of the differential analysis and enrichment analysis in lipidr showed that each mood stabilizer (lithium, valproic acid, and lamotrigine) had distinct effects on the lipidome, with no common effects observed between them. The matched mood stabilizer cohorts revealed 40 significantly altered peaks, mostly belonging to the lipid classes PC, FA, and dCer. There was no significantly enriched lipid class in the matched mood stabilizer cohorts, even though there was an almost significant elevation of dCers (adjusted p-value = 0,07566). Caution should be exercised in interpreting the elevation of dCer, as it is observed in both the BP and SCZ cohorts, and the majority of samples in the mood stabilizer group were diagnosed with BP. Furthermore, the absence or lack of significance of dCer elevation in the individual drug cohorts suggests that this effect may be attributed more to the underlying disease rather than the medication itself. Additionally, it is worth noting that 30 out of the 40 significant lipid species in the mood stabilizer analysis are also significant in the BP cohort, highlighting the challenge of differentiating disease and medication effects due to the substantial overlap in the population.

The findings of Li et al., which analyzed blood samples of epileptic patients treated with valproic acid, showed increases in TAG, dSM, and dCer, as well as decreased PE (Li et al. 2019). In this study, a replication of the significantly increased TAG in the valproic acid cohort was observed, with a non-significant increase in dSM. However, we found non-significant decreases in dCer and increases in PE, which differed from the results of Li et al. It is important to consider that the participants in our study were primarily diagnosed with BP, while Li et al. focused on epileptic patients.

In contrast, the effects observed in the lamotrigine cohort, including increased PE and PC and decreased TAG, were distinct from the valproic acid and lithium cohorts, which exhibited few shared features. The diverse effects of individual drugs on the lipidome could suggest different mechanisms of action for these medications. Particularly for valproic acid and lithium, the effects on the lipidome were pronounced, with multiple altered lipid species. Therefore, it may be beneficial to consider the intake of valproic acid or lithium as a covariate when analyzing lipidomic data. However, caution should be exercised in grouping them into a single mood stabilizer class, as the observed effects appear to counteract each other.

9.2.4 Lithium Lipidomics

This thesis aimed to identify potential lipid biomarkers for response to lithium treatment in patients with BP. The identification of such biomarkers is important because not all patients respond to lithium treatment in the same way, and identifying patients who are likely to respond before treatment could significantly reduce the duration of untreated illness. The same workflow as in the previous analysis was applied to the Lithium as well as dichotomous Alda cohort, comparing individuals that respond to lithium to those not responding. Additionally, a linear model was used in order to reveal peaks being associated with the continuous version of the Alda-score.

The differential analysis revealed significant differences in the abundance of 15 annotated peaks between the lithium and control groups, primarily from the lipid classes dSM and FA. Among these significant lipid species, only one (FA 8:0) was also found to be significantly altered in the BP cohort, indicating that these effects are specifically associated with lithium intake and not the disease itself. The enrichment analysis demonstrated that dSM was the most significantly enriched class in the matched lithium cohort, followed by TAG, CAR, and LPE. While TAG and CAR displayed a similar trend as observed in the BP cohort, dSM and LPE exhibited an opposite trend, further emphasizing that these effects are attributed to the treatment with lithium.

Four lipids (dCer 42:2, dCer 36:1, FA 10:1, LPE 16:1) from the dCer, FA, and LPE classes showed significant differences between responders and non-responders in the Alda-score cohort. The enrichment analysis conducted on the Alda-score cohort revealed significant differences in the lipid classes CAR, LPE, LPC, dCer, and PE between responders and non-responders. Of particular interest are CAR, LPE, LPC, and dCer, as each of them exhibited an opposite trend compared to the lithium cohort. Notably, LPE and CAR demonstrated strong effect sizes in opposite directions in the Alda and lithium cohorts. These lipid classes hold potential as biomarkers for predicting lithium response; however, further validation through prospective, randomized multi-center studies is necessary to confirm these findings. It would also be interesting to compare the longitudinal lipidomic profiles and Alda-scores of patients taking lithium before treatment initiation, at the beginning of treatment, and after a longer period to assess whether the effects can be detected early in the treatment course. If this is the case, it may be possible to use these lipid biomarkers to evaluate a patient's response to lithium treatment after only a short period, which could have significant clinical implications for personalized treatment of BP.

This study demonstrated that lithium treatment has a profound impact on the lipidome, leading to significant alterations in lipid classes and peaks when compared to matched controls. These effects were predominantly observed in the lithium cohort and not evident in the BP cohort, indicating that they are specifically associated with lithium treatment. Furthermore, analysis of the Alda-score revealed notable differences between responders and non-responders, with LPE and CAR lipid classes showing significant alterations in both the lithium and Alda cohorts, but with opposite trends. Although only 4 annotated peaks differed between responders and non-responders in the Alda cohort, further investigations with larger sample sizes may identify additional peaks that could serve as potential biomarkers for predicting lithium response.

In summary, this thesis makes a valuable contribution to the field of personalized treatment in bipolar disorder by identifying potential biomarkers for lithium response. The findings highlight specific lipid classes and peaks that may hold promise as indicators of treatment outcomes. Moreover, these results help enhancing our understanding of the underlying pathophysiology and metabolic effects associated with various psychopharmacological treatments. However, further research is necessary to validate these findings and to fully explore their clinical implications.

9.3 Interaction of medication and disease

The co-incidence of lipidomic changes due to medication vs those found to be disease-specific presents an important challenge in all analyses depicted herein. To address this challenge, a comparison was made between the effects observed in the antipsychotic's cohort and the SCZ cohort. Interestingly, the alterations in the lipidome exhibited similar patterns in both cohorts, potentially attributed to a significant overlap in the population under study. However, distinguishing the effects is challenging since healthy controls do not take antipsychotics, while almost all patients with SCZ do. Interestingly, the effect sizes were slightly larger and the adjusted p-values were lower in the SCZ cohort, indicating a stronger disease effect on the lipidome.

9.4 Multiple vs. single drug use

The use of multiple antipsychotics by patients presents a challenge in attributing specific effects to a particular drug. To address this issue, single drug use cohorts were analyzed for aripiprazole, olanzapine, quetiapine, and risperidone, and compared to corresponding cohorts of patients taking multiple antipsychotics. Interestingly, the single drug use cohorts demonstrated similar results to the multiple drug use cohorts, with some effects being more prominent in the single drug use cohorts. However, caution should be exercised when interpreting the differences observed in the risperidone cohorts due to small sample sizes. In summary, this analysis suggests that the effects of some drugs may be attenuated through confounding effects in the multiple drug use cohorts.

9.5 Effects by lipid classes

The analysis of the effects of different antipsychotics on specific lipid classes showed consistent effects on several classes, including upregulation of TAG and downregulation of FA, while PC and dSM were both up and downregulated depending on the drug, and dCer and DAG were increased in most cohorts. Aripiprazole exhibited distinct effects compared to other antipsychotics, showing significant upregulation of FAs and downregulation of TAGs (figure 27). These effects were even more pronounced in the single drug use cohort (figure 35). Similarly, ziprasidone showed non-significant upregulation of FAs and was the only drug associated with a significant downregulation of PE and LPC (figure 27). It is noteworthy that aripiprazole and ziprasidone have been associated with a lower risk of weight gain, metabolic syndrome, hyperglycemia, and insulin resistance compared to other antipsychotics, particularly clozapine and olanzapine (Müller and Benkert 2021). Furthermore, aripiprazole, unlike most antipsychotics, is not associated with the development of hyperlipidemia. (Müller and Benkert 2021) These findings align with the results of this analysis, demonstrating a distinct trend in the effects of aripiprazole and ziprasidone compared to most other antipsychotics,

particularly clozapine and olanzapine, which are known to have more pronounced metabolic side effects (Müller and Benkert 2021).

An additional consideration when interpreting the results is the number of lipid species within each lipid class. TAG and FA are the most significantly altered lipid classes, and they are also the most abundant with the highest number of lipid species. As a result, these classes have greater statistical power, which increases the likelihood of detecting differences.

9.6 Sample size, significance and power

As expected, considering the statistical power that sample size affords, there appears to be a positive relationship between the sample size of a subgroup and the number of significantly enriched classes and lowest adjusted p-value in the differential analysis (figure 37) as well as the number of significant peaks (figure 38) identified in the differential analysis, with larger sample sizes generally resulting in more significant peaks and classes being detected. This trend seems to be stronger for the number of significant peaks rather than the number of significantly enriched classes and lowest adjusted p-value in the enrichment analysis. The antipsychotics and SCZ cohorts, with the largest sample sizes, had the highest number of significant peaks and significantly enriched classes, indicating a greater impact on the lipidome. Table 69 summarizes the comparison of the number of significant peaks and enriched classes with the lowest adjusted p-value for the differential and enrichment analyses in lipidr, specifically for the 15 subgroups with the highest sample size per class.

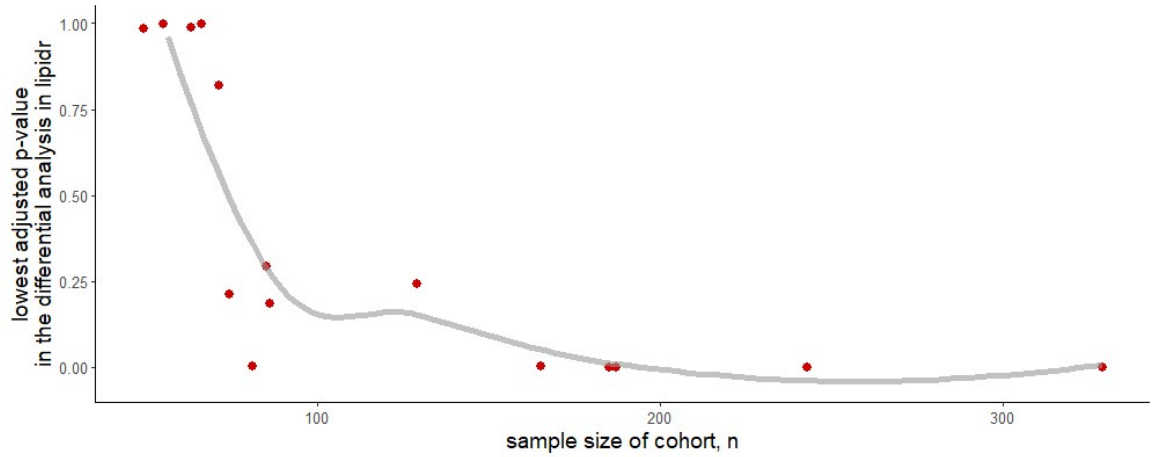

Figure 37: Scatterplot showing the lowest adjusted p-value in the differential analysis in lipidr for the 15 cohorts with the highest sample sizes (table 69) on the y-axis and the corresponding sample size of the cohort on the x-axis

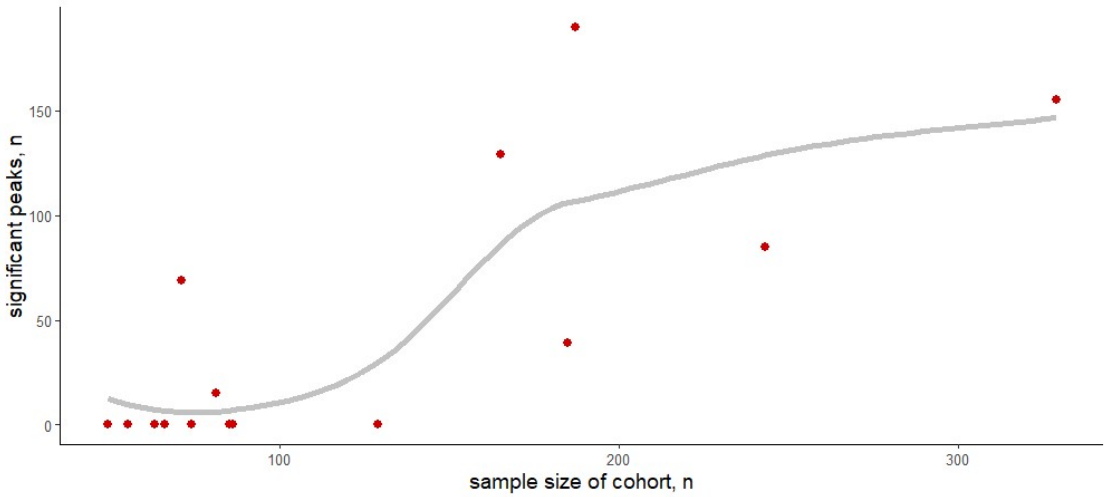

Figure 38: Scatterplot showing the number of significant peaks from the differential analysis in lipidr for the 15 cohorts with the highest sample sizes (table 69) on the y-axis and the corresponding sample size of the cohort on the x-axis

However, there are exceptions to this trend, such as BP and mood stabilizers, which despite their large sample sizes, did not show many significantly altered classes and had relatively high p-values. It is not surprising that these classes show similar results given that they have a significant overlap in population. Notably, lithium and valproic acid showed a lot of significant peaks despite their smaller sample size, with lithium showing more enriched classes and a lower lowest p-value. This suggests that lithium and valproic acid may have very different effects on the lipidome and that when they are grouped together as mood stabilizers, their effects may cancel each other out.

Taken together it seems that there is a positive relationship between sample size and the number of significant peaks identified in the differential analysis, suggesting that a certain statistical power is necessary to detect significant changes in the lipidome. It should be noted that for the enrichment analysis, smaller sample sizes appear to be sufficient for detecting significant results.

Table 69: Comparison of significant results of the differential analysis (number of significant peaks, mean effect size and lowest adjusted p-value) and enrichment analysis (number of significantly enriched classes, mean effect size and lowest adjusted p-value) in lipidr for the 15 subgroups with the highest sample size per class

Cohort	Sample size, n	Significant peaks[a], n	Significantly enriched classes[b], n	Mean effect size[a,c]	Mean effect size[b]	Lowest adjusted p-value[a]	Lowest adjusted p-value[b]
Antipsychotics	329	155	6	0.0227	0.0024	1.79E-12	2.05E-14
Bipolar disorder	243	85	2	-0.0012	0.1121	7.26E-16	0.00026
Schizophrenia	187	190	6	0.0275	0.0582	3.20E-13	1.17E-18
Mood stabilizers	185	39	1	0.0137	0.1020	1.61E-41	0.03551
Antidepressants	165	129	3	0.0213	0.0162	0.00176	1.08E-17
Quetiapine	129	0	3	0.0046	0.0143	0.24370	7.70E-11
Receptor profile CO	86	0	6	0.0261	0.1825	0.18367	8.05E-23
Aripiprazole	85	0	3	-0.0216	-0.3155	0.29385	1.77E-17
Lithium	81	15	5	0.0209	0.0075	0.00286	5.63E-09

Receptor profile ZPR	74	0	4	0.0125	-0.0544	0.21125	1.21E-07
Valproic acid	71	69	2	-0.0225	-0.0873	0.82064	0.00073
SSRI	66	0	4	0.0131	0.1374	0.99731	4.75E-06
Tranquilizers	63	0	3	0.0168	0.0330	0.98726	4.24E-07
SNRI	55	0	3	0.0024	0.0203	0.99937	1.22E-06
Olanzapine	49	0	2	0.0172	0.1654	0.98336	8.20E-21

[a]Results of the differential analysis in lipidr, [b]Results of the enrichment analysis in lipidr, [c]log FC

Additionally, it is worth noting that the size of the lipid classes may also influence their significance in the enrichment analysis, as the lipid classes with the highest number of lipid species (TAG, FA and PC) are also the classes that are significantly enriched in more subgroups than classes with fewer species. This should be taken into consideration when interpreting the results, as some lipid classes may be more likely to show significant enrichment simply due to their larger size.

Given the large size of the dataset analyzed in this study, a considerable number of tests were conducted. To address this concern, all p-values resulting from the t-tests, differential analysis, and enrichment analysis in lipidr were adjusted using the Benjamini-Hochberg procedure.

9.7 Matching

Matching is essential for obtaining reliable results. As detailed earlier, a propensity score-based matching method was employed in this analysis. A robustness test was conducted by removing one of the matching variables and rerunning the analysis. This was performed for antipsychotics, bipolar disorder, schizophrenia, and quetiapine cohorts. The match.it package in R, which offers various matching methods, was used with both full and nearest neighbor matching. For full matching, removing a variable had no effect on the results, as all 593 patients and controls were included. However, with nearest neighbor matching, used for the quetiapine cohort, removing variables led to less significant results. For example, removing diagnosis or BMI as matching variables did not change the number of significantly enriched lipid classes (dCer, CAR, and TAG). Additionally, when age was removed as a variable, only CAR remained significant (figure 39). Additionally, DAGs turned out to be significantly altered in this comparison. Therefore, when interpreting the results, the matching strategy and its influence on the findings must be considered. The only definitive way to eliminate this issue would be through a randomized controlled trial.

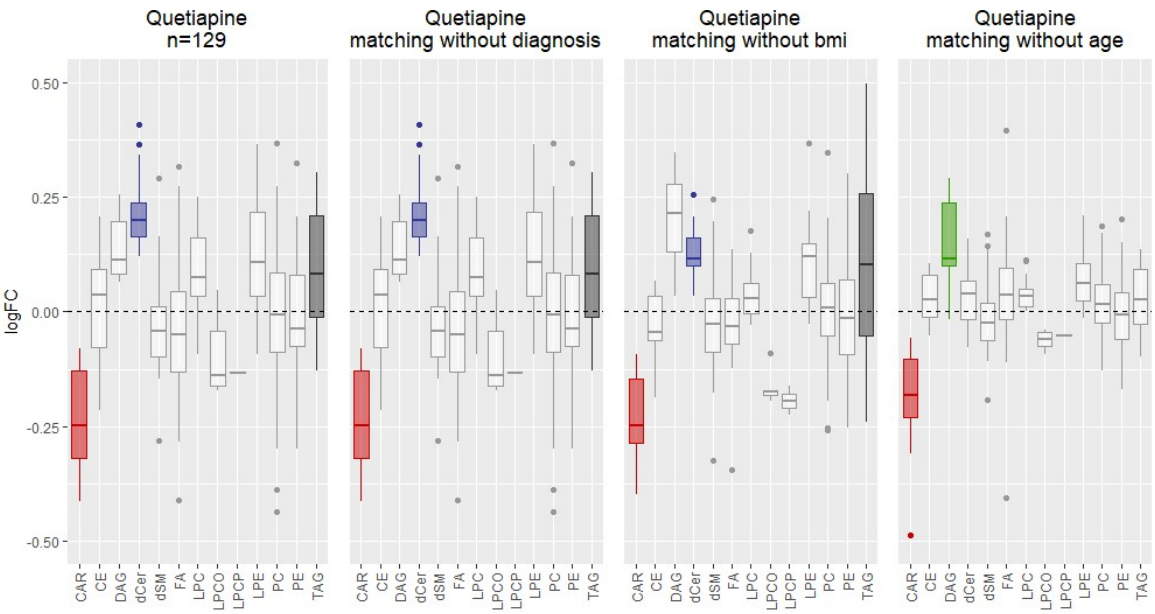

Figure 39: Boxplots comparing the results of the enrichment analysis in the quetiapine cohort removing different variables for the matching process in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured)

9.8 Limitations

Regarding the limitations, it should be noted that this study is based on a single cohort, the Germany-Austria DE-AT cohort, which may limit the generalizability of the findings to other populations.

Furthermore, the matching was only based on sex, age, BMI, and diagnosis, which may not have fully controlled for all confounding factors. Additionally, for most of the individual drugs analyzed, multiple drug use was not taken into consideration due to small sample sizes, which could have led to potential confounding effects.

Another limitation is that the study only used cross-sectional data, and longitudinal data would be more informative, especially before and after treatment. In addition, it is important to note that this analysis focused on specific medication classes, and the impact of dosing was not taken into account. The observed changes in the lipidome could potentially be influenced by the dosage of the medications administered. The dose-dependence of metabolic side effects has been demonstrated for certain antipsychotics, such as quetiapine (Dubath et al. 2021), while for other antipsychotics no dose-dependence could be established (Müller and Benkert 2021; Schoretsanitis et al. 2022; Simon et al. 2009). Other side effects, such as extrapyramidal disorders, and mortality have been shown to be dose-dependent (Müller and Benkert 2021; Molden 2021), highlighting the need for future investigations to explore the relationship between medication dosing and lipidomic changes.

10 Conclusion

This thesis aimed to investigate the impact of medication intake on the lipid profiles of patients with BP and SCZ, with a particular focus on potential lipid biomarkers for lithium response. The study found that lithium treatment has a significant impact on the lipidome, with several lipid classes and peaks significantly altered in patients taking lithium compared to matched controls. Of particular

interest were the lipid classes CAR, LPE, LPC, and dCer, which differed between responders and non-responders, suggesting their potential as biomarkers for lithium response. However, further studies with larger sample sizes are needed to validate these findings.

In addition to lithium, the analysis of the lipidome in patients taking antipsychotics and in those taking antidepressants revealed a high number of significantly altered peaks and lipid classes, particularly for SCZ and antipsychotics. Interestingly, there was a huge overlap in population between the antipsychotics cohort and the SCZ cohort, which could explain the similar patterns observed in their lipidome changes. While there were some similarities in lipidome changes across subgroups of antidepressants and antipsychotics, there were still many differences for each drug. In contrast, the mood stabilizers lithium and valproic acid showed strong effects on the lipidome, but no common trends were observed between them.

However, the study is limited by the fact that it is based on a single cohort and does not collect data on treatment response. Furthermore, matching was based on sex, age, BMI, and diagnosis, which may not have fully controlled for all confounding factors, and multiple drug use was not taken into account for most individual drugs analyzed.

Overall, this thesis demonstrates the potential of lipidomics as a tool to identify biomarkers for personalized treatment of BP and SCZ. However, the study is limited by the fact that it is based on a single cohort and does not collect data on treatment response. Furthermore, matching was based on sex, age, BMI, and diagnosis, which may not have fully controlled for all confounding factors, and multiple drug use was not taken into account for most individual drugs analyzed. Longitudinal data with treatment response and consideration of dosing could provide more informative results. Despite these limitations, the findings highlight the importance of considering medication intake as a covariate when analyzing lipidomic data in patients with BP and SCZ and may have implications for the mechanism of action of these medications.

11 List of abbreviations

AP	Antipsychotic
AD	Antidepressant
AT	Österreich
BPD/BP	Bipolar Disorder
CAR	Acylcarnitines
CE	Cholesteryl esters
CerP	Ceramide 1-phosphates
CO	Receptor profile Clozapine and Olanzapine
CTL	Healthy control
DAG	Diacylglycerols
DE	Deutschland
dCer	Ceramides
dSM	Sphingomyelins
DSM	Diagnostic and Statistical Manual of Mental Disorders
ESI	Electrospray Ionization
FA	Fatty acyls
FEP	First-episode psychosis
FGA	First Generation Antipsychotics
GC	Gas Chromatography
LC	Liquid Chromatography
LPC	Lysophosphatidylcholines
LPC_O	Ether-linked lysophosphatidylcholines
LPC_P	Lysophosphatidylcholine plasmalogens
LPE	Lysophosphatidylethanolamines
M	Mood stabilizer
MALDI	Matrix-Assisted Laser Desorption/Ionization
MS	Mass Spectrometry
NACE	Non-Aqueous Capillary Electrophoresis
PA	Glycerophosphatidic acids
PANSS	Positive and Negative Syndrome Scale
PC	Phosphatidylcholines
PC_O	Ether-linked phosphatidylcholines
PC_P	Phosphatidylcholine plasmalogens
PE	Phosphatidylethanolamines
PE_P	Phosphatidylethanolamines plasmalogens
PE_O	Ether-linked phosphatidylethanolamines
PG	Glycerophosphoglycerols
PI	Phosphatidylinositols
PI_Cer	Ceramide phosphoinositols

List of abbreviations

PS	Phosphatidylserines
PSA	Prostate-Specific Antigen
RNA	Ribonucleic Acid
SCZ	Schizophrenia
SGA	Second Generation Antipsychotics
SMI	Serious Mental Illness
SNRI	Selective Norepinephrine Reuptake Inhibitors
SSRI	Selective Serotonin Reuptake Inhibitors
TAG	Triacylglycerols
TCA	Tricyclic Antidepressants
TGA	Third Generation Antipsychotics
ZPR	Receptor profile Zisprasidone, Paliperidone and Risperidone

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13 List of figures

Figure 1: Psychosis Spectrum Disorder: while there features that are charateristic for either schizophrenia (S) or bipolar disorder (B), there is a considerable overlap in symptoms (M) (Murray et al. 2004) 6
Figure 2: Mood range and associated mood diagnosis in BP (McCormick et al. 2015) 10
Figure 3: Classification of lipidomics in the area of all Omics methods (Wu et al. 2020) 15
Figure 4: The lipidomics workflow (Züllig et al. 2020) 17
Figure 5: Upper panel: Extracted-ion chromatogram of glycerophosphoinositol, PI 37:4 (m/z 871.534 ± 5 ppm) Lower panel: Corresponding MS/MS spectrum at a retention time of 19.82 min (CID fragmented). Blue fragments of 20:4 acyl chains, red fragments of 17:0 acyl chains, green fragments of PI head groups (Züllig et al. 2020) 19
Figure 6: Profiles for receptor binding of second-generation antipsychotics and haloperidol. [a]Partial agonist activity at D_2 receptors, whereas all others are D_2 antagonists. [b]Paliperidone data are unavailable but would be expected to be similar to risperidone. (D, dopamine receptor; H_1, histamine receptor; 5-HT, serotonin receptor; Musc, muscarinic receptor; α_1 and α_2, receptors.) (Chisholm-Burns 2010) 30
Figure 8: Distribution of samples for the risperidone subgroup. The sample number is plotted on the x-axis, the log2(Area) is shown on the y-axis 33
Figure 9: Intensity distribution of lipid classes for the risperidone subgroup. The lipid class is plotted on the x-axis, the log2(Area) is shown on the y-axis. TAG triacylglycerols, FA fatty acyls, PC phosphatidylcholines, dSM sphingomyelins, dCer ceramides, LPC lysophosphatidylcholines, CAR acylcarnitines, PE phosphatidylethanolamines, LPE lysophosphatidylethanolamines, DAG diacylglycerols, LPCO ether-linked lysophosphatidylcholines, CE cholesteryl esters, LPCP lysophosphatidylcholine plasmalogens 34
Figure 10: Volcano plot displaying the results of the differential analysis comparing patients with SCZ vs. controls (Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 35
Figure 11: Vertical boxplot comparing the effect size of antipsychotics on different lipid classes (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 36
Figure 12: Horizontal boxplot comparing the effect sizes of different medications on acylcarnitines levels (multiple hypothesis testing correction was applied and the whiskers of medication classes/individual drugs that significantly ($p<0.05$ after Benjamini-Hochberg correction for multiple testing) alter adjusted p-values of acylcarnitine expression are coloured red; the size of the whiskers corresponds to the size of the subgroup) 36
Figure 13: Volcano plot displaying the results of the differential analysis of the matched BP cohort in lipidr (86 significantly altered lipid species mostly belonging to the classes PC, FA and dCer; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 40

List of figures

Figure 14: Boxplot showing the results of the enrichment analysis in the matched BP cohort in lipidr (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 41
Figure 15: Volcano plot displaying the results of the differential analysis of the matched SCZ cohort in lipidr (192 significantly altered lipid species mostly belonging to the classes TAG, PC and FA; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 43
Figure 16: Boxplot showing the results of the enrichment analysis in the matched SCZ cohort in lipidr (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 43
Figure 17: Volcano plot displaying the results of the differential analysis of the matched BP vs. SCZ cohort in lipidr (139 significantly altered lipid species mostly belonging to the classes TAG, FA and PC; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 45
Figure 18: Boxplot showing the results of the enrichment analysis in the matched BP vs. SCZ cohort in lipidr (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 46
Figure 19: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antipsychotics, antidepressants, mood stabilizers and tranquilizers in lipidr (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 47
Figure 20: Volcano plot displaying the results of the differential analysis of the matched AP cohort in lipidr (153 significantly altered lipid species mostly belonging to the classes TAG, PC and PE; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 49
Figure 21: Boxplot showing the results of the enrichment analysis in the antipsychotics cohort in lipidr (the whiskers of significantly (p<0.05, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 50
Figure 22: Volcano plot displaying the results of the differential analysis of the matched AD cohort in lipidr (98 significantly altered lipid species mostly belonging to the classes TAG, PC and FA; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 53
Figure 23: Histogram of the intensitiy distribution of FA 8:0 55
Figure 24: Volcano plot displaying the results of the differential analysis of the matched mood stabilizers cohort in lipidr 55
(40 significantly altered lipid species mostly belonging to the classes PC, FA and dCer; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 55
Figure 25: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antipsychotics, BP, SCZ and BP vs. SCZ in lipidr (the whiskers of significantly (p<0.05 after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 56

List of figures

Figure 26: Volcano plot displaying the results of the differential analysis of the matched clozapine cohort in lipidr (6 significantly altered lipid species belonging to the classes PE, PC and LPCO; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 58
Figure 27: Boxplots comparing the results of the enrichment analysis in the matched antipsychotics cohort with the matched cohorts for aripiprazole, clozapine, haloperidol, olanzapine, paliperidone, quetiapine, risperidone and ziprasidone in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 61
Figure 28: Boxplots comparing the results of the enrichment analysis in the matched cohorts for antidepressants, sertraline, escitalopram, venlafaxine, mirtazapine and bupropion in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 63
Figure 29: Boxplots comparing the results of the enrichment analysis in the matched cohorts for mood stabilizers, lithium, valproic acid and lamotrigine in lipidr (multiple hypothesis testing correction was applied and the whiskers of lipid classes with significantly altered adjusted p-values are coloured) 65
Figure 30: Volcano plot displaying the results of the differential analysis of the matched lithium cohort in lipidr (15 significantly altered lipid species mostly belonging to the class dSM; Benjamini-Hochberg correction for multiple hypothesis testing was applied and adjusted p-values are shown) 67
Figure 31: Boxplot showing the results of the enrichment analysis in the matched lithium cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 67
Figure 32: Boxplots comparing the results of the enrichment analysis in the matched cohorts for the receptor profile CO, clozapine and olanzapine in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 70
Figure 34: Boxplot showing the results of the enrichment analysis in the Alda cohort in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 75
Figure 35: Boxplots comparing the results of the enrichment analysis in lipidr for single vs. multiple drug use in the matched cohorts for aripiprazole, olanzapine, quetiapine and risperidone. The upper plots analyse all patients taking a specific drug (including those who take more than one antipsychotic drug), the lower plots only consider patients taking just one antipsychotic (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 78
Figure 36: Horizontal boxplot comparing the effect sizes of different medications on the levels of CAR, DAG, dCer, dSM, FA, LPC, PC, PE and TAG (multiple hypothesis testing correction was applied and the whiskers of medication classes/individual drugs that significantly ($p<0.05$ after Benjamini-Hochberg correction for multiple testing) alter adjusted p-values of acylcarnitine expression are coloured red; the size of the whiskers corresponds to the size of the subgroup) 80

List of figures

Figure 37: Scatterplot showing the lowest adjusted p-value in the differential analysis in lipidr for the 15 cohorts with the highest sample sizes (table 69) on the y-axis and the corresponding sample size of the cohort on the x-axis 88
Figure 38: Scatterplot showing the number of significant peaks from the differential analysis in lipidr for the 15 cohorts with the highest sample sizes (table 69) on the y-axis and the corresponding sample size of the cohort on the x-axis..... 89
Figure 39: Boxplots comparing the results of the enrichment analysis in the quetiapine cohort removing different variables for the matching process in lipidr (the whiskers of significantly ($p<0.05$, after Benjamini-Hochberg correction for multiple testing) altered lipid classes are coloured) 91

14 List of tables

Table 1: Studies assessing lipid alterations in patients with SCZ and BP (Tkachev et al. 2023) 20
Table 2: Studies assessing lipid alterations in patients with SCZ before and after treatment with antipsychotics 24
Table 3: Baseline characteristics of the individuals included in the analysis 37
Table 4: Number of different lipid species per lipid class included in this analysis 38
Table 5: Baseline characteristics of the matched BP cohort 39
Table 6: Two-sided t-test for the matched BP cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction 39
Table 7: Differential analysis for the matched BP cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 40
Table 8: Results of the enrichment analysis of the matched BP cohort 41
Table 9: Baseline characteristics of the matched SCZ cohort 41
Table 10: Two-sided t-test for the matched SCZ cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction 42
Table 11: Differential analysis for the matched SCZ cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 42
Table 12: Results of the enrichment analysis of the matched SCZ cohort 43
Table 13: Baseline characteristics of the matched BP vs. SCZ cohort 44
Table 14: Two-sided t-test for the matched BP vs. SCZ cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction 44
Table 15: Differential analysis for the matched SCZ cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 44
Table 16: Results of the enrichment analysis of the matched BP vs. SCZ cohort 45
Table 17: Baseline characteristics of the matched antipsychotics (AP) cohort 48
Table 18: Two-sided t-test for the matched AP cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction 48
Table 19: Differential analysis for the matched AP cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 49
Table 20: Results of the enrichment analysis of the matched AP cohort 50
Table 21: Baseline characteristics of the matched tranquilizers (T) cohort 51
Table 22: Results of the enrichment analysis of the matched T cohort 51
Table 23: Baseline characteristics of the matched antidepressants (AD) cohort 51
Table 24: Two-sided t-test for the matched AD cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction 52
Table 25: Differential analysis for the matched AD cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 52
Table 26: Results of the enrichment analysis of the matched AD cohort 53
Table 27: Baseline characteristics of the matched mood stabilizer (M) cohort 53

List of tables

Table 28: Two-sided t-test for the matched M cohort: 20 peaks with the lowest adjusted p-values after Benjamini-Hochberg correction 54
Table 29: Differential analysis for the matched M cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 54
Table 30: Baseline characteristics of the matched cohorts for the individual drugs from the antipsychotics class 57
Table 31: Results of the enrichment analysis of the matched aripiprazole cohort 57
Table 32: Differential analysis for the matched AP cohort: 6 lipid species with significant adjusted p-values after correction for multiple testing 58
Table 33: Results of the enrichment analysis of the matched clozapine cohort 58
Table 34: Results of the enrichment analysis of the matched clozapine cohort 58
Table 35: Results of the enrichment analysis of the matched olanzapine cohort 59
Table 36: Results of the enrichment analysis of the matched paliperidone cohort 59
Table 37: Results of the enrichment analysis of the matched quetiapine cohort 59
Table 38: Results of the enrichment analysis of the matched risperidone cohort 59
Table 39: Results of the enrichment analysis of the matched ziprasidone cohort 60
Table 40: Baseline characteristics of the matched cohorts for the individual drugs from the antidepressants class 62
Table 41: Results of the enrichment analysis of the matched sertraline cohort 63
Table 42: Results of the enrichment analysis of the matched escitalopram cohort 63
Table 43: Results of the enrichment analysis of the matched venlafaxine cohort 64
Table 44: Results of the enrichment analysis of the matched AD cohort 64
Table 45: Results of the enrichment analysis of the matched mirtazapine cohort 64
Table 45: Baseline characteristics of the matched lithium cohort 66
Table 46: Two-sided t-test for the matched lithium cohort: peaks with significant adjusted p-values after Benjamini-Hochberg correction 66
Table 47: Differential analysis for the matched lithium cohort: lipid species with significant adjusted p-values after correction for multiple testing 66
Table 48: Results of the enrichment analysis of the matched lithium cohort 67
Table 50: Baseline characteristics of the matched valproic acid cohort 68
Table 51: Differential analysis for the matched valproic acid cohort: 20 lipid species with the lowest adjusted p-values after correction for multiple testing 68
Table 52: Results of the enrichment analysis of the matched valproic acid cohort 68
Table 53: Baseline characteristics of the matched lamotrigine cohort 69
Table 54: Results of the enrichment analysis of the matched lamotrigine cohort 69
Table 55: Baseline characteristics of the matched cohorts for the receptor profiles ZPR and CO 69
Table 56: Results of the enrichment analysis of the matched ZPR cohort 70
Table 57: Results of the enrichment analysis of the matched CO cohort 70
Table 58: Baseline characteristics of the matched cohorts for the individual drugs from the antidepressants class 71

Table 59: Results of the enrichment analysis of the matched SSRI cohort 71
Table 60: Results of the enrichment analysis of the matched SNRI cohort 72
Table 61: Results of the enrichment analysis of the matched TCA cohort 72
Table 62: Baseline characteristics of the matched lamotrigine cohort 74
Table 63: Results of the enrichment analysis of the matched Alda cohort 74
Table 64: Baseline characteristics of the matched cohorts for single drug use cohorts: quetiapine-only, aripiprazole-only, olanzapine-only, and risperidone-only 75
Table 65: Results of the enrichment analysis of the matched quetiapine-only cohort 76
Table 66: Results of the enrichment analysis of the matched aripiprazole-only cohort 76
Table 67: Results of the enrichment analysis of the matched olanzapine-only cohort 76
Table 68: Results of the enrichment analysis of the matched risperidone-only cohort 76
Table 69: Comparison of significant results of the differential analysis (number of significant peaks, mean effect size and lowest adjusted p-value) and enrichment analysis (number of significantly enriched classes, mean effect size and lowest adjusted p-value) in lipidr for the 15 subgroups with the highest sample size per class 89

15 Supplementary material

Supplementary Table S1

Group	N nearest	N optimal	N cem	N full	SPD nearest	SPD optimal	SPD full	SPD cem*	SMD nearest	SMD optimal	SMD full	SMD cem*
P	24	24	15	593	0,03	0,03	0,10	0,05	0,01	0,02	-0,02	0,02
H	34	34	48	593	0,00	0,01	0,16	0,05	0,00	0,00	0,01	0,01
Z	42	42	53	593	0,00	0,03	0,60	0,04	0,00	0,01	0,08	0,00
C	68	68	72	593	0,00	0,01	0,05	0,04	0,00	0,00	0,00	0,00
R	76	76	75	593	0,02	0,02	0,14	0,04	0,00	0,00	-0,02	0,00
O	92	92	128	593	0,01	0,01	0,61	0,04	0,00	0,00	0,03	0,00
T	118	118	113	593	0,02	0,02	0,04	0,04	0,01	0,01	0,01	0,01
L	152	152	135	593	0,01	0,01	0,10	0,04	0,00	0,01	0,01	0,00
A	162	162	144	593	0,02	0,02	0,25	0,04	0,02	0,01	0,00	0,00
Q	252	252	180	593	0,03	0,02	0,76	0,04	0,02	0,00	0,01	0,00
AD	316	316	457	593	0,02	0,02	0,02	0,08	0,01	0,00	0,00	0,01
MS	352	352	165	593	1,79	1,79	0,01	0,04	1,79	1,79	0,00	0,00
SCZ	356	356	254	593	0,84	0,84	0,04	0,08	0,84	0,84	0,00	0,01
BP	376	376	341	593	1,14	0,52	0,02	0,09	1,14	0,52	0,00	0,02
AP	554	554	136	593	4,35	3,97	1,23	0,04	4,35	3,97	0,02	0,00

SPD=Standard Pair Dist. SMD=Standard Mean Dist.

Supplementary Table S2: Results differential analysis lipidr

Lipid.species	Lipid.class	logFC	AveExpr	t	P.Value	adj.P.Val	contrast
dCer 36:2	dCer	0,370	21,394	8,039	4,91E-15	1,79E-12	AP
PCP 34:2	PC	-0,289	24,883	-7,758	3,76E-14	6,84E-12	AP
dCer 36:1	dCer	0,357	23,167	7,581	1,32E-13	1,61E-11	AP
PCP 35:2	PC	-0,560	19,105	-6,890	1,42E-11	1,30E-09	AP
PCP 36:2	PC	-0,267	23,364	-6,828	2,14E-11	1,55E-09	AP
PCP 34:1	PC	-0,273	23,887	-6,641	7,03E-11	4,27E-09	AP
dCer 40:2	dCer	0,231	24,170	6,138	1,53E-09	7,96E-08	AP
dCer 34:1	dCer	0,173	24,711	5,968	4,12E-09	1,88E-07	AP
dCer 42:3	dCer	0,214	24,188	5,781	1,20E-08	4,85E-07	AP
TAG 56:5	TAG	0,311	30,617	5,472	6,56E-08	2,39E-06	AP
PE 40:4	PE	0,344	21,304	5,369	1,14E-07	3,77E-06	AP
DAG 36:2	DAG	0,320	24,487	5,216	2,53E-07	7,67E-06	AP
PCP 34:3	PC	-0,515	18,091	-5,153	3,49E-07	9,76E-06	AP
dCer 34:2	dCer	0,147	22,013	5,043	6,11E-07	1,59E-05	AP
dCer 40:3	dCer	0,412	18,933	4,987	8,07E-07	1,96E-05	AP
PCO 36:2	PC	-0,179	23,575	-4,936	1,04E-06	2,36E-05	AP
dCer 42:2	dCer	0,225	25,895	4,879	1,37E-06	2,93E-05	AP
PCO 34:1	PC	-0,171	24,774	-4,773	2,28E-06	4,62E-05	AP
CE 18:2	CE	-0,219	29,546	-4,757	2,46E-06	4,72E-05	AP
CAR 13:0	CAR	-0,478	18,585	-4,691	3,37E-06	6,13E-05	AP
PE 40:5	PE	0,279	21,735	4,656	3,98E-06	6,30E-05	AP
TAG 51:2	TAG	0,274	30,221	4,669	3,75E-06	6,30E-05	AP
TAG 55:5	TAG	0,226	26,107	4,662	3,87E-06	6,30E-05	AP
PCO 34:2	PC	-0,213	24,298	-4,615	4,81E-06	7,29E-05	AP
PC 40:4	PC	0,154	24,181	4,594	5,32E-06	7,75E-05	AP
PC 36:4	PC	-0,092	27,865	-4,519	7,51E-06	0,00010	AP
PC 37:2	PC	-0,134	23,183	-4,520	7,46E-06	0,00010	AP
CAR 12:2	CAR	-0,524	16,033	-4,510	7,83E-06	0,00010	AP
FA 11:1	FA	-0,275	20,580	-4,492	8,49E-06	0,00011	AP
dCer 38:1	dCer	0,293	22,561	4,463	9,68E-06	0,00012	AP
dCer 32:1	dCer	0,170	21,957	4,454	1,01E-05	0,00012	AP
DAG 34:3	DAG	0,430	19,809	4,409	1,24E-05	0,00014	AP
PCP 37:4	PC	-0,242	20,776	-4,399	1,29E-05	0,00014	AP
LPC 18:2	LPC	-0,205	27,753	-4,365	1,50E-05	0,00016	AP
dCer 42:4	dCer	0,305	19,368	4,332	1,73E-05	0,00018	AP
PC 34:2	PC	-0,095	29,623	-4,310	1,91E-05	0,00019	AP
CAR 10:1	CAR	-0,329	20,530	-4,270	2,27E-05	0,00022	AP
DAG 36:1	DAG	0,420	19,817	4,222	2,80E-05	0,00027	AP
PCP 40:5	PC	-0,180	22,499	-4,209	2,96E-05	0,00028	AP
DAG 34:1	DAG	0,370	22,894	4,176	3,41E-05	0,00031	AP
PE 38:3	PE	0,253	22,544	4,159	3,67E-05	0,00033	AP
dCer 43:3	dCer	0,341	19,736	4,112	4,48E-05	0,00039	AP
PE 38:4	PE	0,168	26,467	4,023	6,48E-05	0,00055	AP
CAR 13:1	CAR	-0,335	19,401	-4,011	6,81E-05	0,00056	AP
PC 40:5	PC	0,147	24,192	3,999	7,16E-05	0,00057	AP
PCO 42:7	PC	-0,372	19,037	-4,001	7,11E-05	0,00057	AP
TAG 55:6	TAG	0,204	25,997	3,943	8,99E-05	0,00070	AP
DAG 36:5	DAG	0,465	19,241	3,919	9,92E-05	0,00075	AP
CAR 11:1	CAR	-0,269	20,104	-3,900	0,00011	0,00080	AP
PEP 42:5	PE	0,238	20,720	3,851	0,00013	0,00095	AP
TAG 56:6	TAG	0,192	30,901	3,842	0,00013	0,00096	AP
PCP 32:0	PC	-0,122	22,499	-3,831	0,00014	0,00099	AP
TAG 52:6	TAG	0,280	28,116	3,784	0,00017	0,00117	AP
DAG 36:3	DAG	0,212	24,288	3,778	0,00017	0,00117	AP
TAG 50:5	TAG	0,306	27,348	3,747	0,00020	0,00130	AP
PCP 38:4	PC	-0,132	23,871	-3,730	0,00021	0,00136	AP
PCP 32:1	PC	-0,198	19,539	-3,722	0,00022	0,00137	AP
TAG 49:3	TAG	0,265	27,072	3,721	0,00022	0,00137	AP
TAG 53:3	TAG	0,187	29,328	3,689	0,00025	0,00152	AP
TAG 56:4	TAG	0,182	28,131	3,682	0,00025	0,00153	AP
dCer 44:2	dCer	0,260	19,455	3,659	0,00028	0,00165	AP
TAG 49:1	TAG	0,296	29,349	3,654	0,00028	0,00165	AP
TAG 50:4	TAG	0,247	30,050	3,642	0,00029	0,00170	AP
TAG 48:3	TAG	0,312	29,391	3,622	0,00032	0,00180	AP
TAG 50:3	TAG	0,188	31,867	3,594	0,00035	0,00197	AP
PCO 40:5	PC	-0,113	22,356	-3,587	0,00036	0,00199	AP
PC 35:2	PC	-0,113	25,639	-3,560	0,00040	0,00218	AP
TAG 51:3	TAG	0,188	29,288	3,554	0,00041	0,00220	AP
PCP 38:6	PC	-0,171	21,884	-3,549	0,00042	0,00220	AP
PCO 40:7	PC	-0,160	22,311	-3,544	0,00042	0,00221	AP
PC 38:3	PC	0,090	27,658	3,532	0,00045	0,00228	AP
TAG 48:4	TAG	0,341	26,845	3,507	0,00049	0,00246	AP
TAG 54:2	TAG	0,259	31,419	3,495	0,00051	0,00251	AP
CAR 18:2	CAR	-0,270	20,850	-3,498	0,00050	0,00251	AP

Lipid.species	logFC	AveExpr	t	P.Value	adj.P.Val	contrast
dCer 36:2	0,500	21,334	8,319	1,76E-15	3,20E-13	S
dCer 36:1	0,506	23,101	8,335	1,57E-15	3,20E-13	S
PCP 34:2	-0,380	24,896	-8,110	7,66E-15	9,29E-13	S
PCP 35:2	-0,776	19,128	-7,401	9,27E-13	8,43E-11	S
dCer 34:1	0,273	24,700	7,323	1,55E-12	9,47E-11	S
PCP 36:2	-0,356	23,378	-7,321	1,56E-12	9,47E-11	S
dCer 40:2	0,337	24,137	6,899	2,30E-11	1,19E-09	S
PCP 34:1	-0,333	23,902	-6,589	1,54E-10	6,99E-09	S
dCer 42:3	0,312	24,142	6,521	2,31E-10	9,32E-09	S
TAG 56:5	0,451	30,573	6,375	5,49E-10	2,00E-08	S
PC 37:2	-0,218	23,197	-6,057	3,43E-09	1,14E-07	S
dCer 42:2	0,347	25,862	5,941	6,59E-09	2,00E-07	S
dCer 34:2	0,206	21,987	5,745	1,93E-08	5,42E-07	S
PCP 37:4	-0,392	20,761	-5,607	4,05E-08	1,01E-06	S
PC 40:5	0,261	24,207	5,601	4,17E-08	1,01E-06	S
dCer 38:1	0,466	22,522	5,527	6,18E-08	1,40E-06	S
PC 36:4	-0,144	27,873	-5,462	8,71E-08	1,86E-06	S
PC 32:2	-0,279	25,486	-5,448	9,37E-08	1,89E-06	S
TAG 51:2	0,393	30,215	5,385	1,30E-07	2,49E-06	S
PCP 34:3	-0,664	18,177	-5,360	1,48E-07	2,68E-06	S
DAG 36:2	0,427	24,510	5,325	1,76E-07	3,05E-06	S
TAG 55:5	0,311	26,076	5,307	1,93E-07	3,20E-06	S
PE 40:4	0,409	21,311	5,153	4,19E-07	6,63E-06	S
PC 34:2	-0,140	29,626	-5,059	6,66E-07	1,01E-05	S
CAR 13:0	-0,630	18,531	-5,045	7,13E-07	1,04E-05	S
PCP 38:4	-0,215	23,844	-5,003	8,76E-07	1,23E-05	S
TAG 56:6	0,309	30,869	4,993	9,22E-07	1,24E-05	S
PCP 40:5	-0,255	22,518	-4,934	1,22E-06	1,59E-05	S
CAR 12:2	-0,723	16,007	-4,873	1,64E-06	2,05E-05	S
TAG 55:6	0,308	25,956	4,818	2,13E-06	2,58E-05	S
dCer 40:3	0,521	18,800	4,770	2,67E-06	3,13E-05	S
TAG 53:3	0,290	29,318	4,757	2,82E-06	3,21E-05	S
PCO 36:2	-0,207	23,623	-4,611	5,54E-06	6,11E-05	S
TAG 54:2	0,419	31,467	4,601	5,80E-06	6,21E-05	S
TAG 52:6	0,430	28,155	4,591	6,07E-06	6,31E-05	S
PC 35:2	-0,183	25,638	-4,553	7,20E-06	7,28E-05	S
TAG 50:4	0,377	30,073	4,503	9,02E-06	8,88E-05	S
DAG 36:1	0,562	19,894	4,458	1,10E-05	9,93E-05	S
PCP 38:6	-0,278	21,871	-4,460	1,09E-05	9,93E-05	S
TAG 50:5	0,458	27,392	4,463	1,08E-05	9,93E-05	S
TAG 52:1	0,430	31,089	4,454	1,12E-05	9,93E-05	S
TAG 51:3	0,286	29,279	4,445	1,16E-05	0,00010	S
PCP 32:0	-0,179	22,478	-4,411	1,36E-05	0,00011	S
PCO 34:2	-0,265	24,331	-4,411	1,36E-05	0,00011	S
PCP 46:8	-0,240	19,083	-4,381	1,54E-05	0,00012	S
PEP 40:6	-0,257	24,336	-4,361	1,68E-05	0,00013	S
TAG 56:4	0,267	28,115	4,353	1,74E-05	0,00013	S
dCer 32:1	0,212	21,925	4,320	2,01E-05	0,00015	S
FA 13:0	-0,330	19,671	-4,308	2,12E-05	0,00016	S
PC 33:2	-0,201	24,526	-4,289	2,29E-05	0,00017	S
TAG 52:5	0,334	30,812	4,286	2,32E-05	0,00017	S
PCP 32:1	-0,265	19,548	-4,254	2,67E-05	0,00018	S
PCP 34:0	-0,226	18,372	-4,253	2,68E-05	0,00018	S
TAG 48:3	0,457	29,438	4,249	2,72E-05	0,00018	S
CAR 10:1	-0,430	20,515	-4,232	2,93E-05	0,00019	S
TAG 50:3	0,271	31,867	4,220	3,08E-05	0,00020	S
LPCO 26:1	0,310	19,846	4,219	3,09E-05	0,00020	S
dCer 44:2	0,393	19,397	4,205	3,28E-05	0,00021	S
DAG 34:3	0,524	19,817	4,192	3,47E-05	0,00021	S
PEP 40:8	-0,348	19,480	-4,169	3,82E-05	0,00022	S
TAG 49:3	0,373	27,082	4,171	3,79E-05	0,00022	S
CAR 11:1	-0,377	20,051	-4,175	3,73E-05	0,00022	S
dSM 41:2	-0,199	26,519	-4,144	4,24E-05	0,00024	S
TAG 48:4	0,502	26,916	4,122	4,64E-05	0,00026	S
DAG 36:3	0,294	24,296	4,061	5,97E-05	0,00033	S
TAG 49:1	0,417	29,377	4,064	5,91E-05	0,00033	S
TAG 51:4	0,278	27,527	3,988	8,05E-05	0,00043	S
CAR 13:1	-0,437	19,395	-3,988	8,06E-05	0,00043	S
FA 11:1	-0,318	20,679	-3,973	8,54E-05	0,00045	S
PCO 34:1	-0,175	24,816	-3,971	8,62E-05	0,00045	S
PC 40:4	0,172	24,141	3,968	8,72E-05	0,00045	S
DAG 34:1	0,448	22,927	3,929	0,00010	0,00051	S
TAG 50:6	0,456	24,755	3,911	0,00011	0,00054	S
TAG 50:2	0,245	32,550	3,895	0,00012	0,00057	S

Supplementary material

PE 37:4	PE	0,234	20,558	3,436	0,00063	0,00306	AP		CAR 14:2	-0,517	19,345	-3,896	0,00012	0,00057	S
TAG 50:2	TAG	0,173	32,550	3,421	0,00067	0,00319	AP		PEP 42:5	0,304	20,761	3,853	0,00014	0,00066	S
PC 32:2	PC	-0,139	25,484	-3,414	0,00068	0,00323	AP		TAG 54:5	0,273	31,961	3,837	0,00015	0,00069	S
PEP 40:4	PE	0,261	23,812	3,389	0,00075	0,00349	AP		TAG 52:7	0,400	25,122	3,818	0,00016	0,00074	S
PCP 46:8	PC	-0,148	19,087	-3,359	0,00083	0,00384	AP		CE 18:2	-0,238	29,537	-3,808	0,00016	0,00076	S
TAG 52:5	TAG	0,209	30,791	3,350	0,00086	0,00391	AP		TAG 53:4	0,229	28,167	3,776	0,00019	0,00084	S
TAG 47:2	TAG	0,329	26,471	3,342	0,00088	0,00397	AP		PCP 38:5	-0,179	22,964	-3,760	0,00020	0,00089	S
PEP 36:4	PE	0,140	26,668	3,329	0,00093	0,00411	AP		FA 12:2	-0,239	19,900	-3,749	0,00021	0,00092	S
PEP 40:6	PE	-0,162	24,327	-3,321	0,00095	0,00417	AP		TAG 46:4	0,550	23,924	3,743	0,00021	0,00093	S
FA 13:0	FA	-0,200	19,688	-3,316	0,00097	0,00419	AP		CAR 18:2	-0,369	20,799	-3,738	0,00022	0,00093	S
TAG 50:0	TAG	-0,228	26,971	-3,307	0,00100	0,00428	AP		TAG 53:6	0,331	25,064	3,707	0,00024	0,00103	S
PE 34:1	PE	0,219	23,410	3,296	0,00104	0,00439	AP		LPC 22:4	0,289	19,508	3,704	0,00024	0,00103	S
TAG 47:1	TAG	0,339	27,599	3,287	0,00107	0,00449	AP		PEP 40:7	-0,211	24,901	-3,692	0,00026	0,00107	S
TAG 50:6	TAG	0,304	24,687	3,260	0,00118	0,00487	AP		TAG 48:5	0,473	24,248	3,688	0,00026	0,00107	S
PCP 36:1	PC	-0,138	22,308	-3,226	0,00132	0,00526	AP		DAG 36:5	0,567	19,175	3,678	0,00027	0,00111	S
dSM 41:2	dSM	-0,127	26,537	-3,225	0,00133	0,00526	AP		PEP 40:4	0,352	23,856	3,669	0,00028	0,00113	S
TAG 52:7	TAG	0,268	25,084	3,227	0,00132	0,00526	AP		PCO 40:7	-0,209	22,353	-3,660	0,00029	0,00116	S
TAG 52:1	TAG	0,251	31,052	3,225	0,00133	0,00526	AP		PEP 37:6	-0,419	19,234	-3,657	0,00029	0,00116	S
TAG 48:5	TAG	0,326	24,163	3,174	0,00158	0,00619	AP		dCer 42:4	0,341	19,221	3,638	0,00031	0,00123	S
CAR 10:2	CAR	-0,324	17,624	-3,126	0,00186	0,00719	AP		FA 18:2	-0,331	29,988	-3,627	0,00033	0,00126	S
PCO 42:6	PC	-0,172	20,718	-3,107	0,00198	0,00751	AP		TAG 46:3	0,522	26,345	3,626	0,00033	0,00126	S
TAG 46:2	TAG	0,353	28,621	3,109	0,00197	0,00751	AP		TAG 46:2	0,510	28,711	3,618	0,00034	0,00128	S
TAG 51:4	TAG	0,176	27,526	3,098	0,00204	0,00759	AP		TAG 52:2	0,192	33,691	3,611	0,00035	0,00130	S
CAR 14:2	CAR	-0,327	19,469	-3,097	0,00204	0,00759	AP		LPC 18:2	-0,214	27,802	-3,605	0,00036	0,00132	S
PC 36:2	PC	-0,070	28,948	-3,092	0,00208	0,00765	AP		TAG 47:2	0,445	26,523	3,592	0,00037	0,00137	S
PE 36:1	PE	0,195	23,108	3,087	0,00212	0,00770	AP		TAG 50:1	0,261	32,139	3,585	0,00038	0,00139	S
TAG 46:1	TAG	0,354	29,672	3,083	0,00215	0,00773	AP		LPE 22:5	0,292	21,860	3,580	0,00039	0,00140	S
PCP 38:5	PC	-0,115	22,955	-3,054	0,00236	0,00835	AP		CAR 16:2	-0,573	16,169	-3,567	0,00041	0,00146	S
PCO 38:5	PC	-0,103	25,060	-3,054	0,00236	0,00835	AP		PE 40:5	0,272	21,706	3,547	0,00044	0,00156	S
TAG 54:5	TAG	0,170	31,945	3,037	0,00250	0,00873	AP		FA 13:1	-0,571	19,486	-3,530	0,00047	0,00164	S
TAG 46:4	TAG	0,359	23,798	3,032	0,00253	0,00877	AP		PCO 42:7	-0,380	19,152	-3,527	0,00047	0,00164	S
PEP 40:8	PE	-0,200	19,504	-3,005	0,00277	0,00950	AP		PEP 39:6	-0,211	22,117	-3,501	0,00052	0,00177	S
FA 13:1	FA	-0,353	19,447	-2,995	0,00286	0,00972	AP		TAG 54:6	0,291	30,849	3,503	0,00052	0,00177	S
TAG 46:3	TAG	0,345	26,221	2,958	0,00322	0,01086	AP		dSM 32:0	-0,176	21,302	-3,496	0,00053	0,00179	S
LPE 22:5	LPE	0,191	21,866	2,933	0,00349	0,01134	AP		TAG 46:1	0,497	29,754	3,491	0,00054	0,00180	S
TAG 50:1	TAG	0,170	32,122	2,935	0,00346	0,01134	AP		FA 14:0	-0,254	25,364	-3,478	0,00057	0,00187	S
TAG 40:1	TAG	0,540	23,713	2,936	0,00346	0,01134	AP		dCer 43:3	0,376	19,626	3,392	0,00077	0,00252	S
TAG 47:3	TAG	0,285	24,168	2,934	0,00347	0,01134	AP		TAG 47:1	0,442	27,659	3,390	0,00077	0,00252	S
PC 33:2	PC	-0,105	24,542	-2,923	0,00360	0,01161	AP		TAG 55:7	0,281	25,145	3,383	0,00079	0,00256	S
CAR 10:0	CAR	-0,270	21,746	-2,910	0,00375	0,01198	AP		PCO 37:4	-0,262	19,488	-3,338	0,00093	0,00294	S
dSM 39:1	dSM	-0,124	25,118	-2,903	0,00383	0,01202	AP		PC 36:2	-0,094	28,955	-3,338	0,00093	0,00294	S
CAR 16:2	CAR	-0,370	16,302	-2,904	0,00382	0,01202	AP		PC 36:5	-0,130	25,424	-3,332	0,00095	0,00298	S
TAG 53:6	TAG	0,213	25,051	2,893	0,00395	0,01229	AP		TAG 47:3	0,406	24,222	3,303	0,00105	0,00327	S
TAG 48:1	TAG	0,230	31,140	2,887	0,00403	0,01242	AP		FA 22:6	-0,327	26,149	-3,296	0,00108	0,00332	S
FA 15:1	FA	-0,187	20,746	-2,844	0,00461	0,01409	AP		TAG 40:1	0,745	23,791	3,294	0,00108	0,00332	S
dCer 43:2	dCer	0,178	22,148	2,837	0,00471	0,01419	AP		dCer 40:1	0,283	24,472	3,248	0,00127	0,00385	S
TAG 53:4	TAG	0,142	28,179	2,836	0,00472	0,01419	AP		TAG 44:1	0,588	28,018	3,225	0,00137	0,00413	S
PCP 34:0	PC	-0,133	18,373	-2,816	0,00503	0,01501	AP		PCP 36:1	-0,167	22,331	-3,195	0,00152	0,00453	S
FA 10:2	FA	-0,207	18,678	-2,812	0,00508	0,01504	AP		PC 42:9	0,209	19,371	3,139	0,00183	0,00543	S
PCO 37:4	PC	-0,163	19,507	-2,792	0,00540	0,01586	AP		TAG 48:1	0,310	31,179	3,118	0,00196	0,00576	S
TAG 52:2	TAG	0,120	33,690	2,777	0,00567	0,01650	AP		PC 34:4	-0,186	24,114	-3,089	0,00216	0,00628	S
TAG 54:6	TAG	0,179	30,819	2,761	0,00594	0,01717	AP		dSM 39:1	-0,171	25,089	-3,075	0,00226	0,00653	S
TAG 44:1	TAG	0,401	27,886	2,726	0,00660	0,01892	AP		dSM 42:3	-0,123	26,728	-3,072	0,00229	0,00655	S
PCO 40:3	PC	-0,116	21,406	-2,721	0,00670	0,01906	AP		TAG 56:7	0,213	30,348	3,060	0,00238	0,00675	S
PC 38:5	PC	-0,067	26,342	-2,714	0,00684	0,01931	AP		TAG 42:2	0,627	23,993	3,035	0,00257	0,00727	S
TAG 45:2	TAG	0,305	24,151	2,700	0,00712	0,01995	AP		PE 38:4	0,162	26,478	3,011	0,00278	0,00779	S
FA 23:1	FA	-0,204	20,876	-2,693	0,00729	0,02025	AP		FA 10:2	-0,281	18,756	-3,005	0,00284	0,00789	S
PEP 40:7	PE	-0,120	24,902	-2,641	0,00849	0,02342	AP		TAG 44:2	0,535	26,213	2,990	0,00297	0,00820	S
LPCP 18:1	LPCP	-0,137	19,584	-2,629	0,00877	0,02401	AP		dCer 43:2	0,253	22,108	2,964	0,00323	0,00884	S
LPE 16:1	LPE	0,261	19,373	2,615	0,00914	0,02467	AP		TAG 42:1	0,642	25,788	2,945	0,00343	0,00933	S
FA 12:2	FA	-0,137	19,909	-2,615	0,00915	0,02467	AP		TAG 56:9	0,283	26,245	2,913	0,00380	0,01025	S
TAG 55:7	TAG	0,174	25,176	2,593	0,00975	0,02610	AP		TAG 52:4	0,174	32,677	2,902	0,00393	0,01044	S
PE 38:5	PE	0,132	25,114	2,588	0,00989	0,02627	AP		TAG 45:2	0,413	24,233	2,904	0,00391	0,01044	S
PEP 34:1	PE	0,101	22,767	2,583	0,01004	0,02648	AP		FA 15:1	-0,233	20,710	-2,896	0,00400	0,01056	S
LPE 20:3	LPE	0,164	21,699	2,580	0,01013	0,02652	AP		TAG 54:4	0,185	32,220	2,887	0,00412	0,01079	S
PC 36:5	PC	-0,079	25,393	-2,561	0,01068	0,02757	AP		dSM 39:2	-0,144	22,115	-2,873	0,00431	0,01120	S
PCO 38:4	PC	-0,079	23,106	-2,562	0,01065	0,02757	AP		PEP 36:4	0,152	26,664	2,867	0,00438	0,01130	S
LPC 22:4	LPC	0,154	19,544	2,540	0,01135	0,02890	AP		PE 40:7	-0,237	23,209	-2,856	0,00453	0,01162	S
PC 42:4	PC	0,103	20,874	2,541	0,01131	0,02890	AP		LPC 22:5	0,210	21,347	2,796	0,00545	0,01387	S
LPC 20:0	LPC	-0,138	20,236	-2,505	0,01251	0,03163	AP		TAG 43:1	0,524	23,519	2,788	0,00558	0,01410	S
FA 23:0	FA	-0,192	22,102	-2,447	0,01468	0,03685	AP		LPE 20:3	0,210	21,711	2,746	0,00633	0,01588	S
PE 40:6	PE	0,157	25,027	2,434	0,01524	0,03799	AP		PCO 42:6	-0,189	20,723	-2,722	0,00679	0,01684	S
PEP 38:5	PE	0,097	26,799	2,428	0,01547	0,03830	AP		TAG 54:3	0,167	32,450	2,722	0,00680	0,01684	S
LPC 22:6	LPC	-0,116	23,192	-2,420	0,01581	0,03837	AP		dSM 42:4	-0,148	22,444	-2,716	0,00693	0,01702	S
TAG 56:9	TAG	0,187	26,237	2,423	0,01569	0,03837	AP		TAG 41:1	0,540	21,440	2,714	0,00697	0,01702	S
TAG 44:2	TAG	0,347	26,112	2,423	0,01571	0,03837	AP		FA 17:2	-0,378	18,249	-2,684	0,00759	0,01843	S
PCO 32:0	PC	-0,083	23,173	-2,407	0,01638	0,03949	AP		PE 36:1	0,205	23,217	2,681	0,00767	0,01849	S
TAG 43:1	TAG	0,356	23,409	2,381	0,01756	0,04206	AP		LPCO 24:0	0,157	22,257	2,673	0,00786	0,01873	S
CAR 18:1	CAR	-0,125	22,802	-2,358	0,01872	0,04453	AP		TAG 40:0	0,639	24,752	2,672	0,00787	0,01873	S
LPC 18:2	LPC	-0,229	27,753	-4,325	0,00002	0,00176	AD		PE 38:3	0,209	22,549	2,670	0,00792	0,01873	S

Supplementary material

PCO 36:2	PC	-0,185	23,575	-4,512	0,00001	0,00176	AD		PCO 38:4	-0,106	23,099	-2,666	0,00802	0,01884	S
TAG 55:6	TAG	0,252	25,997	4,319	0,00002	0,00176	AD		TAG 42:0	0,580	26,499	2,659	0,00818	0,01909	S
TAG 56:5	TAG	0,279	30,617	4,308	0,00002	0,00176	AD		PC 38:5	-0,083	26,354	-2,653	0,00832	0,01928	S
LPE 18:2	LPE	-0,287	25,418	-3,908	0,00010	0,00293	AD		CAR 10:2	-0,348	17,684	-2,651	0,00838	0,01931	S
LPE 18:1	LPE	-0,280	24,122	-3,906	0,00010	0,00293	AD		CAR 12:0	-0,298	20,534	-2,644	0,00856	0,01959	S
dCer 36:1	dCer	0,218	23,167	3,976	0,00008	0,00293	AD		FA 12:1	-0,530	19,881	-2,632	0,00885	0,02013	S
PC 40:4	PC	0,153	24,181	4,023	0,00006	0,00293	AD		CAR 10:0	-0,326	21,735	-2,622	0,00909	0,02056	S
PCO 42:7	PC	-0,424	19,037	-4,039	0,00006	0,00293	AD		PCP 44:6	-0,209	19,134	-2,604	0,00958	0,02154	S
TAG 50:3	TAG	0,236	31,867	4,014	0,00007	0,00293	AD		FA 12:0	-0,188	23,632	-2,594	0,00986	0,02202	S
TAG 50:2	TAG	0,224	32,550	3,928	0,00010	0,00293	AD		TAG 44:0	0,460	27,576	2,578	0,01031	0,02289	S
TAG 51:2	TAG	0,269	30,221	4,041	0,00006	0,00293	AD		PCO 40:3	-0,130	21,455	-2,565	0,01071	0,02363	S
TAG 55:5	TAG	0,215	26,107	3,913	0,00010	0,00293	AD		PCO 38:5	-0,108	25,076	-2,560	0,01086	0,02381	S
dCer 36:2	dCer	0,206	21,394	3,825	0,00014	0,00296	AD		CAR 18:1	-0,171	22,766	-2,544	0,01138	0,02479	S
FA 11:1	FA	-0,267	20,580	-3,843	0,00013	0,00296	AD		PCO 40:5	-0,100	22,392	-2,538	0,01156	0,02504	S
PCP 34:1	PC	-0,182	23,887	-3,822	0,00015	0,00296	AD		PCP 44:7	-0,371	17,085	-2,523	0,01204	0,02593	S
PCP 36:2	PC	-0,173	23,364	-3,824	0,00015	0,00296	AD		FA 8:0	0,273	21,926	2,487	0,01333	0,02855	S
PCO 42:4	PC	-0,232	20,942	-3,875	0,00012	0,00296	AD		PCO 38:3	-0,119	22,117	-2,481	0,01356	0,02887	S
PCO 42:3	PC	-0,199	21,644	-3,803	0,00016	0,00302	AD		FA 26:4	0,157	19,832	2,456	0,01450	0,03050	S
PCP 44:7	PC	-0,514	17,001	-3,788	0,00017	0,00305	AD		PC 35:3	-0,107	22,908	-2,457	0,01448	0,03050	S
PCO 34:1	PC	-0,153	24,774	-3,774	0,00018	0,00307	AD		FA 18:3	-0,246	26,627	-2,452	0,01469	0,03073	S
PCO 40:3	PC	-0,179	21,406	-3,760	0,00019	0,00309	AD		FA 23:1	-0,204	21,039	-2,444	0,01501	0,03122	S
TAG 55:7	TAG	0,280	25,176	3,726	0,00021	0,00337	AD		LPE 16:1	0,295	19,373	2,429	0,01564	0,03220	S
PCP 34:3	PC	-0,418	18,091	-3,670	0,00026	0,00377	AD		dSM 41:3	-0,169	21,727	-2,428	0,01566	0,03220	S
PC 37:2	PC	-0,123	23,183	-3,665	0,00027	0,00377	AD		TAG 58:9	0,198	27,683	2,406	0,01664	0,03403	S
TAG 56:6	TAG	0,208	30,901	3,685	0,00025	0,00377	AD		FA 16:0	-0,155	29,520	-2,386	0,01752	0,03563	S
TAG 51:3	TAG	0,218	29,288	3,647	0,00029	0,00390	AD		TAG 41:0	0,554	22,324	2,381	0,01777	0,03593	S
PCP 46:8	PC	-0,180	19,087	-3,629	0,00031	0,00402	AD		PE 34:1	0,200	23,458	2,369	0,01835	0,03669	S
TAG 49:3	TAG	0,291	27,072	3,612	0,00033	0,00413	AD		CAR 14:0	-0,177	19,903	-2,370	0,01832	0,03669	S
TAG 50:4	TAG	0,273	30,050	3,573	0,00038	0,00464	AD		TAG 58:8	0,172	28,124	2,366	0,01851	0,03682	S
FA 8:0	FA	0,739	22,654	3,535	0,00044	0,00485	AD		PC 38:3	0,076	27,644	2,347	0,01946	0,03849	S
PCP 35:2	PC	-0,334	19,105	-3,539	0,00043	0,00485	AD		TAG 50:0	-0,208	26,974	-2,323	0,02070	0,04073	S
PCP 36:1	PC	-0,170	22,308	-3,537	0,00044	0,00485	AD		PC 30:0	-0,141	24,366	-2,303	0,02182	0,04270	S
TAG 52:6	TAG	0,295	28,116	3,524	0,00046	0,00490	AD		LPE 20:5	0,242	20,518	2,296	0,02225	0,04307	S
PCO 40:5	PC	-0,125	22,356	-3,506	0,00049	0,00509	AD		CAR 14:1	-0,236	21,208	-2,296	0,02224	0,04307	S
DAG 34:3	DAG	0,382	19,809	3,454	0,00059	0,00599	AD		PE 37:4	0,201	20,554	2,285	0,02287	0,04405	S
TAG 53:3	TAG	0,189	29,328	3,308	0,00100	0,00980	AD		FA 24:5	-0,206	20,464	-2,250	0,02501	0,04791	S
PCO 38:2	PC	-0,196	20,259	-3,290	0,00106	0,01016	AD		DAG 36:4	0,193	22,420	2,244	0,02543	0,04847	S
PCO 44:7	PC	-0,211	21,188	-3,279	0,00110	0,01030	AD		TAG 58:3	0,135	25,530	2,234	0,02611	0,04951	S
PCP 34:2	PC	-0,143	24,883	-3,261	0,00117	0,01049	AD		FA 8:0	1,742	23,065	7,063	0,00000	0,00000	BPS
TAG 52:5	TAG	0,230	30,791	3,259	0,00118	0,01049	AD		FA 25:0	-0,586	22,127	-5,451	0,00000	0,00002	BPS
TAG 51:4	TAG	0,208	27,526	3,245	0,00124	0,01074	AD		PE 36:1	-0,385	23,123	-4,829	0,00000	0,00024	BPS
PCO 44:4	PC	-0,209	20,732	-3,154	0,00169	0,01405	AD		FA 22:6	0,417	26,235	4,450	0,00001	0,00077	BPS
TAG 50:1	TAG	0,206	32,122	3,144	0,00175	0,01405	AD		FA 25:2	-0,557	19,550	-4,326	0,00002	0,00077	BPS
TAG 55:8	TAG	0,282	22,933	3,153	0,00170	0,01405	AD		FA 16:1	0,553	27,232	4,355	0,00002	0,00077	BPS
TAG 56:7	TAG	0,195	30,371	3,140	0,00178	0,01405	AD		CAR 14:2	0,568	19,414	4,347	0,00002	0,00077	BPS
DAG 36:5	DAG	0,419	19,241	3,117	0,00191	0,01467	AD		LPCO 22:1	-0,321	19,807	-4,368	0,00002	0,00077	BPS
TAG 49:1	TAG	0,286	29,349	3,114	0,00193	0,01467	AD		TAG 46:4	-0,625	23,872	-4,389	0,00001	0,00077	BPS
TAG 50:5	TAG	0,285	27,348	3,084	0,00214	0,01589	AD		TAG 46:3	-0,604	26,292	-4,282	0,00002	0,00084	BPS
FA 23:0	FA	-0,270	22,102	-3,055	0,00235	0,01632	AD		FA 18:2	0,397	30,064	4,220	0,00003	0,00099	BPS
FA 28:4	FA	-0,499	17,152	-3,052	0,00238	0,01632	AD		FA 17:2	0,568	18,388	4,178	0,00004	0,00109	BPS
FA 14:1	FA	0,322	23,448	3,066	0,00227	0,01632	AD		PCP 38:4	0,178	23,851	4,076	0,00006	0,00154	BPS
TAG 56:9	TAG	0,266	26,237	3,062	0,00230	0,01632	AD		FA 26:1	-0,565	20,657	-4,024	0,00007	0,00173	BPS
TAG 52:2	TAG	0,147	33,690	3,027	0,00258	0,01708	AD		DAG 36:1	-0,494	19,919	-4,013	0,00007	0,00173	BPS
TAG 53:4	TAG	0,171	28,179	3,030	0,00255	0,01708	AD		FA 23:0	-0,373	22,000	-3,917	0,00010	0,00203	BPS
DAG 36:1	DAG	0,340	19,817	3,010	0,00272	0,01769	AD		FA 28:4	-0,693	17,080	-3,926	0,00010	0,00203	BPS
PC 32:1	PC	0,157	26,720	2,986	0,00295	0,01881	AD		TAG 48:4	-0,458	26,936	-3,915	0,00011	0,00203	BPS
FA 27:4	FA	-0,454	18,249	-2,959	0,00321	0,02014	AD		CAR 14:0	0,292	19,991	3,947	0,00009	0,00203	BPS
TAG 52:7	TAG	0,277	25,084	2,949	0,00331	0,02043	AD		FA 26:4	-0,245	19,789	-3,886	0,00012	0,00206	BPS
FA 23:1	FA	-0,250	20,876	-2,934	0,00348	0,02110	AD		PC 40:5	-0,169	24,263	-3,886	0,00012	0,00206	BPS
LPC 20:0	LPC	-0,181	20,236	-2,914	0,00370	0,02205	AD		FA 17:1	0,334	24,284	3,813	0,00016	0,00251	BPS
TAG 57:8	TAG	0,243	23,700	2,909	0,00376	0,02205	AD		TAG 48:5	-0,478	24,240	-3,823	0,00015	0,00251	BPS
FA 12:3	FA	-0,290	18,519	-2,885	0,00406	0,02340	AD		TAG 50:6	-0,425	24,769	-3,781	0,00018	0,00253	BPS
PC 38:5	PC	-0,080	26,342	-2,880	0,00411	0,02340	AD		TAG 54:2	-0,333	31,518	-3,782	0,00018	0,00253	BPS
PCP 34:0	PC	-0,153	18,373	-2,871	0,00424	0,02374	AD		CAR 11:1	0,313	20,048	3,779	0,00018	0,00253	BPS
CAR 16:1	CAR	0,242	19,890	2,847	0,00456	0,02516	AD		CAR 16:2	0,611	16,231	3,754	0,00020	0,00259	BPS
FA 25:3	FA	-0,350	19,797	-2,823	0,00491	0,02517	AD		TAG 42:0	-0,809	26,361	-3,757	0,00020	0,00259	BPS
FA 27:3	FA	-0,427	19,789	-2,837	0,00471	0,02517	AD		PCP 32:0	0,147	22,486	3,730	0,00022	0,00265	BPS
TAG 53:6	TAG	0,235	25,051	2,833	0,00476	0,02517	AD		TAG 44:0	-0,657	27,463	-3,735	0,00021	0,00265	BPS
CAR 14:0	CAR	0,189	19,985	2,832	0,00479	0,02517	AD		dSM 42:4	0,192	22,493	3,711	0,00024	0,00276	BPS
LPCO 22:1	LPCO	-0,196	19,808	-2,825	0,00488	0,02517	AD		DAG 36:2	-0,280	24,589	-3,677	0,00027	0,00295	BPS
TAG 48:1	TAG	0,250	31,140	2,783	0,00556	0,02811	AD		TAG 46:2	-0,506	28,709	-3,683	0,00026	0,00295	BPS
PCO 46:8	PC	-0,220	19,992	-2,729	0,00654	0,03261	AD		TAG 50:5	-0,363	27,444	-3,653	0,00029	0,00296	BPS
PE 36:3	PE	-0,198	24,737	-2,716	0,00680	0,03326	AD		TAG 52:6	-0,328	28,211	-3,657	0,00029	0,00296	BPS
TAG 47:2	TAG	0,302	26,471	2,713	0,00685	0,03326	AD		TAG 44:1	-0,654	27,973	-3,653	0,00029	0,00296	BPS
DAG 36:2	DAG	0,189	24,487	2,682	0,00751	0,03597	AD		FA 18:1	0,353	31,584	3,618	0,00033	0,00328	BPS
PCO 34:2	PC	-0,140	24,298	-2,669	0,00782	0,03698	AD		TAG 48:3	-0,368	29,488	-3,548	0,00043	0,00414	BPS
TAG 58:10	TAG	0,233	26,254	2,653	0,00820	0,03827	AD		dSM 40:3	0,191	21,851	3,505	0,00051	0,00473	BPS
TAG 56:4	TAG	0,148	28,131	2,635	0,00863	0,03976	AD		FA 23:1	-0,330	20,763	-3,497	0,00052	0,00474	BPS
TAG 57:7	TAG	0,201	24,657	2,624	0,00891	0,04055	AD		PCP 37:4	0,232	20,705	3,483	0,00055	0,00488	BPS
PCO 46:7	PC	-0,280	17,247	-2,616	0,00912	0,04097	AD		CAR 13:0	0,437	18,467	3,467	0,00058	0,00504	BPS

Supplementary material

PCP 37:4	PC	-0,162	20,776	-2,590	0,00983	0,04364	AD		PC 33:2	0,142	24,521	3,431	0,00066	0,00560	BPS
TAG 58:9	TAG	0,192	27,704	2,573	0,01031	0,04521	AD		FA 22:5	0,313	25,061	3,397	0,00075	0,00579	BPS
LPC 19:0	LPC	-0,181	19,292	-2,551	0,01100	0,04574	AD		PCP 34:2	0,157	24,808	3,403	0,00073	0,00579	BPS
PCP 42:5	PC	-0,161	20,290	-2,554	0,01091	0,04574	AD		dSM 41:3	0,231	21,787	3,400	0,00074	0,00579	BPS
PCO 42:5	PC	-0,100	23,272	-2,548	0,01108	0,04574	AD		CAR 18:2	0,308	20,798	3,400	0,00074	0,00579	BPS
TAG 48:3	TAG	0,250	29,391	2,560	0,01073	0,04574	AD		TAG 46:1	-0,470	29,766	-3,389	0,00077	0,00584	BPS
TAG 52:1	TAG	0,224	31,052	2,545	0,01118	0,04574	AD		TAG 41:0	-0,766	22,193	-3,374	0,00081	0,00603	BPS
TAG 47:1	TAG	0,299	27,599	2,560	0,01070	0,04574	AD		PEP 42:5	-0,266	20,783	-3,367	0,00083	0,00605	BPS
TAG 47:3	TAG	0,279	24,168	2,538	0,01142	0,04617	AD		TAG 52:1	-0,306	31,160	-3,323	0,00097	0,00693	BPS
FA 18:4	FA	0,264	21,081	2,525	0,01182	0,04727	AD		CAR 16:1	0,314	19,917	3,313	0,00101	0,00704	BPS
TAG 52:4	TAG	0,140	32,672	2,515	0,01217	0,04816	AD		FA 16:2	0,390	21,368	3,285	0,00111	0,00761	BPS
FA 22:5	FA	0,214	24,994	2,502	0,01262	0,04836	AD		dSM 39:2	0,179	22,158	3,276	0,00114	0,00770	BPS
PC 35:2	PC	-0,090	25,639	-2,503	0,01257	0,04836	AD		FA 14:0	0,231	25,382	3,251	0,00124	0,00823	BPS
PCP 44:5	PC	-0,124	22,407	-2,507	0,01245	0,04836	AD		dSM 39:1	0,166	25,114	3,245	0,00127	0,00827	BPS
TAG 50:0	TAG	-0,195	26,971	-2,497	0,01280	0,04852	AD		PCP 35:2	0,329	18,930	3,236	0,00131	0,00837	BPS
FA 16:1	FA	0,292	27,199	2,487	0,01316	0,04938	AD		FA 20:2	0,284	24,392	3,197	0,00150	0,00939	BPS
LPC 18:1	LPC	-0,105	27,245	-2,480	0,01341	0,04981	AD		PE 36:2	-0,219	25,386	-3,192	0,00152	0,00939	BPS
FA 8:0	FA	6,503	25,320	36,099	0,00000	0,00000	V		FA 20:3	0,271	25,372	3,176	0,00161	0,00964	BPS
FA 26:4	FA	-0,783	19,547	-6,821	0,00000	0,00000	V		TAG 50:4	-0,260	30,143	-3,174	0,00162	0,00964	BPS
TAG 42:2	TAG	2,208	24,463	6,431	0,00000	0,00000	V		FA 25:3	-0,426	19,678	-3,163	0,00168	0,00968	BPS
FA 24:3	FA	-0,729	18,330	-5,605	0,00000	0,00001	V		dCer 34:1	-0,108	24,797	-3,159	0,00170	0,00968	BPS
PC 42:6	PC	0,513	20,381	5,415	0,00000	0,00002	V		TAG 44:2	-0,552	26,197	-3,167	0,00166	0,00968	BPS
FA 26:5	FA	-0,771	18,432	-5,233	0,00000	0,00004	V		PC 42:5	-0,227	19,113	-3,137	0,00183	0,00993	BPS
TAG 42:1	TAG	1,820	26,202	5,149	0,00000	0,00005	V		TAG 52:7	-0,316	25,168	-3,144	0,00179	0,00993	BPS
CAR 11:1	CAR	0,632	20,342	4,954	0,00000	0,00009	V		CAR 14:1	0,328	21,288	3,141	0,00180	0,00993	BPS
TAG 58:9	TAG	0,595	27,895	4,712	0,00001	0,00021	V		FA 12:1	0,613	19,969	3,114	0,00198	0,01058	BPS
TAG 58:8	TAG	0,515	28,346	4,729	0,00001	0,00021	V		TAG 45:2	-0,431	24,220	-3,108	0,00202	0,01063	BPS
FA 24:4	FA	-0,653	20,731	-4,621	0,00001	0,00028	V		FA 12:3	-0,328	18,417	-3,084	0,00218	0,01120	BPS
PCO 38:3	PC	-0,358	22,002	-4,599	0,00001	0,00029	V		TAG 47:2	-0,371	26,562	-3,084	0,00218	0,01120	BPS
LPCO 18:0	LPCO	-0,440	20,921	-4,567	0,00001	0,00030	V		FA 27:3	-0,508	19,616	-3,070	0,00229	0,01155	BPS
FA 11:1	FA	-0,504	20,316	-4,452	0,00002	0,00045	V		TAG 43:1	-0,562	23,489	-3,057	0,00239	0,01190	BPS
CAR 13:1	CAR	0,717	19,608	4,314	0,00003	0,00069	V		PEP 40:4	-0,300	23,885	-3,041	0,00251	0,01202	BPS
TAG 40:1	TAG	1,648	24,044	4,323	0,00003	0,00069	V		FA 14:1	0,355	23,462	3,041	0,00251	0,01202	BPS
PC 39:4	PC	0,417	18,530	4,235	0,00004	0,00088	V		TAG 47:1	-0,386	27,689	-3,049	0,00245	0,01202	BPS
PC 40:3	PC	0,268	21,484	4,196	0,00005	0,00097	V		FA 16:0	0,195	29,572	3,021	0,00268	0,01243	BPS
dSM 39:2	dSM	0,394	22,313	4,166	0,00005	0,00099	V		CAR 12:0	0,322	20,578	3,019	0,00270	0,01243	BPS
PC 42:5	PC	-0,477	18,958	-4,168	0,00005	0,00099	V		TAG 47:3	-0,360	24,246	-3,023	0,00266	0,01243	BPS
PCO 38:2	PC	-0,454	20,048	-4,128	0,00006	0,00109	V		FA 27:4	-0,499	18,114	-2,991	0,00295	0,01311	BPS
FA 24:2	FA	-0,397	20,606	-4,100	0,00007	0,00116	V		dSM 41:2	0,147	26,520	2,992	0,00294	0,01311	BPS
TAG 58:10	TAG	0,600	26,423	3,978	0,00011	0,00176	V		TAG 52:5	-0,230	30,877	-2,997	0,00290	0,01311	BPS
dSM 41:3	dSM	0,388	21,986	3,827	0,00020	0,00296	V		LPE 18:1	-0,238	24,092	-2,969	0,00317	0,01389	BPS
PC 39:3	PC	0,567	18,393	3,810	0,00021	0,00302	V		PCP 36:2	0,144	23,294	2,960	0,00325	0,01408	BPS
CAR 14:0	CAR	0,462	20,252	3,776	0,00024	0,00320	V		PEP 37:6	0,317	19,212	2,945	0,00341	0,01462	BPS
TAG 40:0	TAG	1,459	24,862	3,773	0,00024	0,00320	V		TAG 54:6	-0,230	30,892	-2,935	0,00352	0,01491	BPS
dSM 33:2	dSM	0,307	21,012	3,716	0,00029	0,00380	V		dSM 32:0	0,134	21,303	2,923	0,00366	0,01532	BPS
TAG 55:8	TAG	0,589	23,164	3,696	0,00031	0,00395	V		TAG 49:1	-0,286	29,452	-2,919	0,00371	0,01534	BPS
TAG 41:1	TAG	1,187	21,627	3,674	0,00034	0,00413	V		FA 20:4	0,251	26,916	2,899	0,00395	0,01615	BPS
TAG 57:8	TAG	0,543	23,950	3,655	0,00036	0,00426	V		PEP 40:8	0,228	19,445	2,880	0,00419	0,01694	BPS
dSM 39:1	dSM	0,302	25,219	3,638	0,00039	0,00440	V		DAG 34:1	-0,314	22,997	-2,819	0,00506	0,01976	BPS
LPC 22:5	LPC	-0,386	21,309	-3,602	0,00044	0,00484	V		PEP 39:6	0,161	22,116	2,823	0,00500	0,01976	BPS
PC 40:5	PC	-0,260	24,143	-3,583	0,00047	0,00501	V		PCP 38:6	0,165	21,837	2,822	0,00500	0,01976	BPS
TAG 56:4	TAG	0,316	28,264	3,534	0,00056	0,00579	V		CAR 12:2	0,411	15,879	2,816	0,00510	0,01976	BPS
PC 35:4	PC	0,293	23,093	3,522	0,00058	0,00587	V		dSM 44:5	0,306	17,476	2,801	0,00533	0,02044	BPS
PC 38:2	PC	0,176	23,952	3,471	0,00069	0,00679	V		TAG 40:0	-0,668	24,722	-2,780	0,00568	0,02153	BPS
PCO 32:0	PC	-0,230	23,122	-3,429	0,00080	0,00763	V		PC 32:2	0,134	25,437	2,774	0,00579	0,02172	BPS
CAR 14:1	CAR	0,609	21,628	3,379	0,00094	0,00881	V		PE 34:1	-0,221	23,454	-2,766	0,00592	0,02195	BPS
FA 24:5	FA	-0,570	20,485	-3,344	0,00106	0,00925	V		PC 39:4	0,183	18,371	2,764	0,00597	0,02195	BPS
PC 40:2	PC	0,433	19,380	3,343	0,00107	0,00925	V		PE 36:3	-0,222	24,691	-2,760	0,00603	0,02195	BPS
CAR 14:2	CAR	0,715	19,848	3,342	0,00107	0,00925	V		PE 40:4	-0,221	21,412	-2,743	0,00635	0,02289	BPS
TAG 57:7	TAG	0,431	24,916	3,301	0,00122	0,01035	V		FA 14:2	0,369	21,151	2,728	0,00664	0,02346	BPS
PC 37:2	PC	0,207	23,234	3,263	0,00139	0,01146	V		CAR 16:0	0,139	22,491	2,730	0,00660	0,02346	BPS
dCer 36:2	dCer	-0,264	21,487	-3,235	0,00152	0,01230	V		CE 18:2	0,148	29,520	2,718	0,00684	0,02396	BPS
CAR 12:0	CAR	0,505	20,876	3,181	0,00181	0,01433	V		TAG 48:1	-0,258	31,217	-2,698	0,00727	0,02520	BPS
LPC 18:0	LPC	-0,198	27,515	-3,111	0,00226	0,01630	V		FA 13:0	0,201	19,629	2,688	0,00749	0,02524	BPS
PCO 40:3	PC	-0,283	21,259	-3,108	0,00228	0,01630	V		PC 35:4	0,120	22,986	2,688	0,00748	0,02524	BPS
TAG 55:5	TAG	0,301	26,252	3,129	0,00214	0,01630	V		PCO 37:4	0,182	19,470	2,688	0,00747	0,02524	BPS
TAG 56:9	TAG	0,461	26,331	3,116	0,00223	0,01630	V		TAG 54:5	-0,184	32,022	-2,682	0,00762	0,02546	BPS
LPCO 22:1	LPCO	-0,393	19,511	-3,110	0,00227	0,01630	V		FA 18:4	0,286	21,099	2,658	0,00818	0,02706	BPS
TAG 55:7	TAG	0,413	25,379	3,096	0,00237	0,01662	V		TAG 40:1	-0,599	23,854	-2,643	0,00853	0,02797	BPS
PE 37:4	PE	0,411	20,747	3,066	0,00260	0,01788	V		PC 35:3	0,102	22,927	2,624	0,00901	0,02878	BPS
PE 40:4	PE	0,393	21,392	3,015	0,00305	0,02058	V		CAR 10:1	0,244	20,447	2,629	0,00889	0,02878	BPS
dSM 44:3	dSM	0,201	21,262	2,962	0,00360	0,02383	V		CAR 18:1	0,174	22,793	2,627	0,00895	0,02878	BPS
PC 37:5	PC	0,270	22,237	2,931	0,00394	0,02564	V		LPE 20:5	-0,253	20,515	-2,609	0,00941	0,02929	BPS
dCer 42:3	dCer	0,195	24,365	2,923	0,00404	0,02581	V		dSM 33:1	0,099	25,694	2,611	0,00935	0,02929	BPS
TAG 52:1	TAG	-0,408	30,961	-2,902	0,00431	0,02703	V		TAG 51:2	-0,185	30,335	-2,611	0,00936	0,02929	BPS
TAG 55:6	TAG	0,294	26,170	2,897	0,00438	0,02704	V		TAG 49:3	-0,226	27,167	-2,601	0,00962	0,02967	BPS
TAG 50:1	TAG	-0,297	32,057	-2,880	0,00461	0,02797	V		LPE 18:3	-0,297	19,500	-2,592	0,00988	0,03023	BPS
FA 22:3	FA	-0,411	20,994	-2,822	0,00546	0,03260	V		DAG 36:3	-0,180	24,364	-2,577	0,01032	0,03129	BPS
TAG 58:3	TAG	0,225	25,578	2,777	0,00624	0,03664	V		dCer 42:4	0,199	19,523	2,573	0,01043	0,03139	BPS
dSM 32:2	dSM	0,215	23,561	2,765	0,00647	0,03678	V		dSM 30:1	0,146	22,501	2,543	0,01135	0,03387	BPS

Supplementary material

PCO 34:0	-0,014	4,409	-2,766	6,45E-03	3,67E-02	V		PCP 32:0	0,009	4,491	3,747	2,05E-04	2,66E-03	BPS
dSM 32:0	-0,014	4,415	-2,754	6,67E-03	3,74E-02	V		dSM 42:4	0,012	4,491	3,708	2,37E-04	2,95E-03	BPS
TAG 56:6	0,012	4,956	2,719	7,38E-03	4,07E-02	V		TAG 42:0	-0,045	4,715	-3,702	2,43E-04	2,95E-03	BPS
PC 38:1	0,012	4,504	2,713	7,52E-03	4,08E-02	V		TAG 44:0	-0,035	4,776	-3,690	2,55E-04	2,99E-03	BPS
dSM 30:1	0,016	4,498	2,684	8,17E-03	4,37E-02	V		TAG 50:5	-0,019	4,777	-3,648	2,99E-04	3,20E-03	BPS
FA 23:0	-0,031	4,436	-2,633	9,43E-03	4,98E-02	V		TAG 52:6	-0,017	4,817	-3,653	2,93E-04	3,20E-03	BPS
FA 8:0	-0,116	4,543	-4,616	8,23E-06	3,00E-03	L		TAG 46:2	-0,026	4,842	-3,661	2,84E-04	3,20E-03	BPS
PC 42:6	-0,029	4,331	-4,211	4,32E-05	7,86E-03	L		DAG 36:2	-0,016	4,619	-3,634	3,15E-04	3,27E-03	BPS
dSM 40:3	-0,022	4,449	-4,027	8,86E-05	1,08E-02	L		FA 18:1	0,016	4,980	3,605	3,51E-04	3,45E-03	BPS
FA 24:3	0,033	4,206	3,554	5,05E-04	2,26E-02	L		TAG 44:1	-0,034	4,803	-3,607	3,48E-04	3,45E-03	BPS
FA 26:4	0,027	4,303	3,536	5,37E-04	2,26E-02	L		FA 23:1	-0,024	4,374	-3,548	4,33E-04	4,11E-03	BPS
dSM 32:2	-0,017	4,551	-3,694	3,07E-04	2,26E-02	L		TAG 48:3	-0,018	4,881	-3,543	4,40E-04	4,11E-03	BPS
dSM 33:2	-0,020	4,384	-3,652	3,56E-04	2,26E-02	L		dSM 40:3	0,013	4,449	3,497	5,23E-04	4,76E-03	BPS
dSM 38:3	-0,024	4,337	-3,526	5,58E-04	2,26E-02	L		PCP 37:4	0,016	4,371	3,475	5,66E-04	5,03E-03	BPS
dSM 42:4	-0,019	4,492	-3,600	4,29E-04	2,26E-02	L		PC 33:2	0,008	4,616	3,431	6,62E-04	5,74E-03	BPS
dSM 39:2	-0,021	4,469	-3,466	6,85E-04	2,50E-02	L		PCP 34:2	0,009	4,632	3,405	7,27E-04	6,16E-03	BPS
FA 24:2	0,022	4,370	3,434	7,66E-04	2,54E-02	L		FA 22:5	0,018	4,646	3,376	8,05E-04	6,54E-03	BPS
FA 24:1	0,018	4,547	3,309	1,17E-03	3,37E-02	L		dSM 41:3	0,015	4,445	3,366	8,34E-04	6,54E-03	BPS
dSM 35:2	-0,014	4,457	-3,278	1,30E-03	3,37E-02	L		CAR 16:1	0,023	4,314	3,368	8,30E-04	6,54E-03	BPS
dSM 41:3	-0,022	4,447	-3,296	1,22E-03	3,37E-02	L		TAG 46:1	-0,023	4,894	-3,363	8,44E-04	6,54E-03	BPS
dSM 41:2	-0,013	4,731	-3,231	1,51E-03	3,66E-02	L		CAR 18:2	0,021	4,377	3,344	9,02E-04	6,84E-03	BPS
FA 8:0	0,117	4,508	8,906	1,62E-17	5,91E-15	BP		TAG 52:1	-0,014	4,961	-3,336	9,28E-04	6,89E-03	BPS
dCer 36:1	0,026	4,527	7,620	1,71E-13	3,11E-11	BP		FA 14:0	0,013	4,665	3,279	1,13E-03	8,23E-03	BPS
dCer 36:2	0,027	4,412	7,296	1,50E-12	1,81E-10	BP		dSM 39:1	0,010	4,650	3,244	1,28E-03	9,11E-03	BPS
dCer 42:4	0,041	4,272	6,313	7,00E-10	6,37E-08	BP		TAG 41:0	-0,049	4,464	-3,232	1,33E-03	9,30E-03	BPS
dCer 42:3	0,016	4,592	6,050	3,22E-09	2,35E-07	BP		PCP 35:2	0,026	4,240	3,225	1,36E-03	9,36E-03	BPS
FA 23:1	-0,038	4,379	-5,842	1,04E-08	6,28E-07	BP		PEP 42:5	-0,018	4,376	-3,194	1,51E-03	9,66E-03	BPS
FA 23:0	-0,035	4,461	-5,688	2,42E-08	1,10E-06	BP		dSM 39:2	0,011	4,469	3,199	1,49E-03	9,66E-03	BPS
FA 11:1	-0,029	4,363	-5,703	2,23E-08	1,10E-06	BP		FA 16:2	0,026	4,415	3,197	1,50E-03	9,66E-03	BPS
dCer 40:3	0,047	4,234	5,512	6,20E-08	2,51E-06	BP		CAR 13:0	0,034	4,203	3,207	1,45E-03	9,66E-03	BPS
dCer 40:2	0,015	4,590	5,458	8,28E-08	3,01E-06	BP		FA 20:3	0,015	4,664	3,162	1,69E-03	9,71E-03	BPS
PCO 36:2	-0,014	4,559	-5,173	3,57E-07	1,18E-05	BP		FA 20:2	0,017	4,607	3,148	1,76E-03	9,71E-03	BPS
PCP 34:2	-0,013	4,640	-5,110	4,92E-07	1,49E-05	BP		FA 25:3	-0,032	4,295	-3,156	1,72E-03	9,71E-03	BPS
FA 27:3	-0,059	4,296	-5,046	6,73E-07	1,89E-05	BP		dCer 34:1	-0,006	4,632	-3,154	1,73E-03	9,71E-03	BPS
PC 40:4	0,011	4,593	5,023	7,54E-07	1,96E-05	BP		PE 36:2	-0,012	4,665	-3,170	1,64E-03	9,71E-03	BPS
PCP 34:3	-0,046	4,181	-4,926	1,21E-06	2,94E-05	BP		PC 42:5	-0,018	4,255	-3,153	1,74E-03	9,71E-03	BPS
TAG 56:5	0,016	4,931	4,888	1,46E-06	3,31E-05	BP		TAG 50:4	-0,013	4,913	-3,181	1,58E-03	9,71E-03	BPS
PCP 35:2	-0,034	4,265	-4,858	1,68E-06	3,59E-05	BP		TAG 52:7	-0,018	4,652	-3,148	1,77E-03	9,71E-03	BPS
dCer 34:1	0,010	4,623	4,798	2,24E-06	4,52E-05	BP		CAR 14:1	0,022	4,410	3,168	1,65E-03	9,71E-03	BPS
PC 39:4	0,023	4,192	4,782	2,41E-06	4,61E-05	BP		TAG 44:2	-0,031	4,708	-3,144	1,79E-03	9,71E-03	BPS
FA 12:3	-0,038	4,204	-4,730	3,07E-06	5,59E-05	BP		FA 14:1	0,022	4,550	3,124	1,91E-03	1,02E-02	BPS
dCer 34:2	0,011	4,457	4,663	4,19E-06	7,27E-05	BP		CAR 12:0	0,023	4,361	3,102	2,05E-03	1,08E-02	BPS
dCer 42:2	0,014	4,690	4,634	4,79E-06	7,92E-05	BP		FA 12:1	0,048	4,312	3,079	2,22E-03	1,15E-02	BPS
dCer 43:3	0,035	4,297	4,601	5,57E-06	8,45E-05	BP		TAG 45:2	-0,026	4,596	-3,068	2,30E-03	1,18E-02	BPS
PCP 36:2	-0,013	4,549	-4,606	5,46E-06	8,45E-05	BP		TAG 47:2	-0,020	4,730	-3,043	2,50E-03	1,26E-02	BPS
PCO 34:1	-0,011	4,631	-4,550	7,03E-06	1,02E-04	BP		FA 12:3	-0,025	4,200	-3,020	2,68E-03	1,32E-02	BPS
PCO 42:7	-0,039	4,249	-4,515	8,26E-06	1,16E-04	BP		FA 16:0	0,010	4,886	3,020	2,69E-03	1,32E-02	BPS
FA 25:3	-0,043	4,298	-4,425	1,23E-05	1,66E-04	BP		LPE 18:1	-0,014	4,590	-3,012	2,76E-03	1,34E-02	BPS
PCO 40:7	-0,015	4,479	-4,302	2,10E-05	2,74E-04	BP		TAG 52:5	-0,011	4,948	-3,004	2,83E-03	1,35E-02	BPS
FA 25:2	-0,043	4,284	-4,238	2,78E-05	3,38E-04	BP		TAG 47:1	-0,020	4,790	-2,999	2,87E-03	1,36E-02	BPS
PC 37:2	-0,009	4,536	-4,244	2,71E-05	3,38E-04	BP		FA 27:3	-0,038	4,288	-2,988	2,98E-03	1,39E-02	BPS
PCP 34:1	-0,012	4,581	-4,220	3,00E-05	3,52E-04	BP		TAG 43:1	-0,034	4,549	-2,983	3,02E-03	1,39E-02	BPS
LPC 18:2	-0,012	4,794	-4,210	3,13E-05	3,56E-04	BP		PEP 40:4	-0,018	4,577	-2,974	3,12E-03	1,42E-02	BPS
FA 27:4	-0,054	4,177	-4,064	5,75E-05	6,35E-04	BP		TAG 47:3	-0,021	4,598	-2,970	3,15E-03	1,42E-02	BPS
dCer 38:1	0,022	4,488	4,036	6,47E-05	6,55E-04	BP		PCP 36:2	0,009	4,542	2,959	3,27E-03	1,45E-02	BPS
PCO 34:2	-0,013	4,604	-4,048	6,15E-05	6,55E-04	BP		dSM 32:0	0,009	4,413	2,950	3,36E-03	1,46E-02	BPS
PC 36:5	-0,008	4,666	-4,042	6,32E-05	6,55E-04	BP		dSM 41:2	0,008	4,729	2,951	3,35E-03	1,46E-02	BPS
FA 26:2	-0,028	4,374	-4,010	7,18E-05	6,88E-04	BP		FA 27:4	-0,040	4,173	-2,946	3,41E-03	1,46E-02	BPS
dCer 32:1	0,012	4,453	4,014	7,08E-05	6,88E-04	BP		TAG 54:6	-0,011	4,949	-2,933	3,55E-03	1,50E-02	BPS
FA 26:1	-0,041	4,362	-3,979	8,16E-05	7,44E-04	BP		FA 20:4	0,013	4,750	2,894	4,01E-03	1,66E-02	BPS
FA 10:2	-0,027	4,222	-3,972	8,38E-05	7,44E-04	BP		TAG 49:1	-0,014	4,879	-2,894	4,01E-03	1,66E-02	BPS
TAG 55:6	0,014	4,696	3,975	8,30E-05	7,44E-04	BP		PEP 37:6	0,024	4,261	2,884	4,14E-03	1,69E-02	BPS
PCO 40:5	-0,009	4,482	-3,940	9,55E-05	8,27E-04	BP		PCP 38:6	0,011	4,448	2,843	4,69E-03	1,90E-02	BPS
PE 36:3	-0,018	4,625	-3,916	1,05E-04	8,81E-04	BP		PEP 40:8	0,017	4,280	2,836	4,79E-03	1,92E-02	BPS
TAG 56:6	0,011	4,946	3,913	1,06E-04	8,81E-04	BP		dSM 44:5	0,026	4,124	2,810	5,20E-03	2,03E-02	BPS
FA 25:0	-0,028	4,459	-3,892	1,16E-04	9,36E-04	BP		CAR 12:2	0,039	3,982	2,810	5,19E-03	2,03E-02	BPS
TAG 55:5	0,013	4,702	3,821	1,53E-04	1,21E-03	BP		PEP 39:6	0,010	4,466	2,802	5,32E-03	2,06E-02	BPS
dCer 44:2	0,026	4,274	3,761	1,93E-04	1,49E-03	BP		PC 39:4	0,015	4,198	2,794	5,45E-03	2,09E-02	BPS
PCO 40:3	-0,013	4,419	-3,706	2,39E-04	1,81E-03	BP		PE 34:1	-0,014	4,551	-2,781	5,67E-03	2,14E-02	BPS
PC 36:4	-0,005	4,801	-3,635	3,13E-04	2,33E-03	BP		TAG 40:0	-0,040	4,621	-2,779	5,70E-03	2,14E-02	BPS
LPE 18:2	-0,016	4,665	-3,628	3,20E-04	2,33E-03	BP		PE 36:3	-0,013	4,625	-2,770	5,85E-03	2,17E-02	BPS
PCP 40:5	-0,012	4,493	-3,573	3,95E-04	2,82E-03	BP		FA 14:2	0,026	4,400	2,764	5,98E-03	2,20E-02	BPS
LPE 18:1	-0,016	4,588	-3,372	8,17E-04	5,72E-03	BP		PC 32:2	0,008	4,669	2,753	6,18E-03	2,23E-02	BPS
PCO 38:2	-0,015	4,339	-3,334	9,31E-04	6,39E-03	BP		CAR 16:0	0,009	4,491	2,752	6,18E-03	2,23E-02	BPS
LPC 22:4	0,018	4,283	3,262	1,20E-03	8,06E-03	BP		CE 18:2	0,007	4,883	2,725	6,70E-03	2,39E-02	BPS
FA 28:4	-0,051	4,080	-3,244	1,27E-03	8,44E-03	BP		PE 40:4	-0,015	4,419	-2,721	6,78E-03	2,40E-02	BPS
FA 22:3	0,018	4,382	3,189	1,54E-03	9,98E-03	BP		FA 13:0	0,015	4,294	2,715	6,90E-03	2,42E-02	BPS
PCP 44:7	-0,039	4,083	-3,136	1,83E-03	1,17E-02	BP		DAG 34:1	-0,019	4,522	-2,708	7,06E-03	2,45E-02	BPS
FA 20:3	0,015	4,662	3,092	2,12E-03	1,30E-02	BP		PCO 37:4	0,014	4,282	2,703	7,15E-03	2,46E-02	BPS
FA 22:5	0,017	4,644	3,089	2,14E-03	1,30E-02	BP		TAG 48:1	-0,012	4,964	-2,695	7,32E-03	2,49E-02	BPS

Supplementary material

DAG 36:5	0,034	4,253	3,091	2,13E-03	1,30E-02	BP		PC 35:4	0,007	4,522	2,683	7,60E-03	2,52E-02	BPS
LPCO 26:1	0,014	4,306	3,068	2,29E-03	1,37E-02	BP		TAG 54:5	-0,008	5,001	-2,679	7,69E-03	2,52E-02	BPS
PE 36:2	-0,011	4,662	-2,995	2,91E-03	1,71E-02	BP		CAR 10:1	0,018	4,352	2,683	7,59E-03	2,52E-02	BPS
dCer 43:2	0,015	4,464	2,976	3,09E-03	1,77E-02	BP		TAG 40:1	-0,037	4,569	-2,679	7,68E-03	2,52E-02	BPS
PC 32:2	-0,008	4,673	-2,975	3,10E-03	1,77E-02	BP		CAR 18:1	0,011	4,510	2,648	8,41E-03	2,73E-02	BPS
PE 40:5	0,014	4,437	2,933	3,55E-03	1,99E-02	BP		LPE 20:5	-0,018	4,357	-2,619	9,14E-03	2,86E-02	BPS
TAG 51:2	0,010	4,912	2,908	3,83E-03	2,11E-02	BP		dSM 33:1	0,006	4,683	2,618	9,18E-03	2,86E-02	BPS
PC 34:2	-0,004	4,889	-2,858	4,48E-03	2,43E-02	BP		PC 35:3	0,006	4,519	2,628	8,92E-03	2,86E-02	BPS
TAG 56:4	0,009	4,810	2,830	4,88E-03	2,61E-02	BP		FA 18:4	0,019	4,397	2,624	9,02E-03	2,86E-02	BPS
PEP 40:6	-0,010	4,606	-2,822	5,01E-03	2,61E-02	BP		TAG 51:2	-0,009	4,923	-2,622	9,07E-03	2,86E-02	BPS
LPCO 24:0	0,010	4,475	2,820	5,03E-03	2,61E-02	BP		TAG 49:3	-0,012	4,763	-2,587	1,00E-02	3,10E-02	BPS
CAR 10:2	-0,028	4,138	-2,770	5,85E-03	3,00E-02	BP		FA 26:2	-0,018	4,372	-2,573	1,04E-02	3,16E-02	BPS
PCO 44:7	-0,013	4,401	-2,763	5,98E-03	3,02E-02	BP		LPE 18:3	-0,022	4,283	-2,570	1,05E-02	3,16E-02	BPS
FA 20:4	0,012	4,748	2,710	7,00E-03	3,44E-02	BP		dCer 42:4	0,015	4,286	2,575	1,04E-02	3,16E-02	BPS
PCP 38:5	-0,008	4,521	-2,712	6,95E-03	3,44E-02	BP		DAG 36:3	-0,011	4,606	-2,548	1,12E-02	3,34E-02	BPS
PCP 36:1	-0,009	4,480	-2,692	7,39E-03	3,54E-02	BP		dSM 30:1	0,009	4,491	2,532	1,17E-02	3,47E-02	BPS
PCP 44:3	0,010	4,358	2,696	7,29E-03	3,54E-02	BP		FA 15:1	0,014	4,372	2,504	1,27E-02	3,72E-02	BPS
PCO 42:4	-0,011	4,387	-2,664	8,02E-03	3,79E-02	BP		PCP 34:1	0,008	4,574	2,501	1,28E-02	3,72E-02	BPS
PC 38:5	-0,004	4,719	-2,644	8,51E-03	3,97E-02	BP		TAG 50:1	-0,008	5,009	-2,491	1,31E-02	3,79E-02	BPS
PC 42:5	-0,015	4,252	-2,600	9,65E-03	4,45E-02	BP		TAG 54:3	-0,006	5,021	-2,483	1,34E-02	3,85E-02	BPS
LPC 18:3	-0,012	4,457	-2,591	9,90E-03	4,47E-02	BP		PC 35:2	0,005	4,679	2,471	1,39E-02	3,95E-02	BPS
FA 13:1	-0,028	4,283	-2,587	1,00E-02	4,47E-02	BP		FA 22:3	0,013	4,387	2,460	1,43E-02	4,01E-02	BPS
TAG 53:3	0,008	4,870	2,576	1,03E-02	4,47E-02	BP		LPE 20:4	-0,008	4,644	-2,461	1,42E-02	4,01E-02	BPS
TAG 57:7	0,013	4,621	2,581	1,02E-02	4,47E-02	BP		PC 34:2	0,003	4,888	2,447	1,48E-02	4,12E-02	BPS
LPCO 22:1	-0,014	4,301	-2,579	1,02E-02	4,47E-02	BP		dSM 38:3	0,011	4,335	2,436	1,53E-02	4,22E-02	BPS
PC 40:2	-0,016	4,275	-2,566	1,06E-02	4,56E-02	BP		PCP 46:8	0,010	4,251	2,409	1,64E-02	4,50E-02	BPS
FA 8:0	0,101	4,519	7,084	6,17E-12	2,25E-09	BP		dSM 42:3	0,005	4,741	2,386	1,75E-02	4,75E-02	BPS
FA 25:0	-0,039	4,466	-5,398	1,15E-07	2,09E-05	BP		FA 20:1	0,012	4,653	2,380	1,78E-02	4,76E-02	BPS
PE 36:1	-0,024	4,530	-4,811	2,12E-06	2,57E-04	BP		FA 24:1	-0,008	4,548	-2,380	1,77E-02	4,76E-02	BPS
FA 22:6	0,023	4,712	4,463	1,05E-05	8,80E-04	BP		dSM 33:2	0,008	4,386	2,369	1,83E-02	4,85E-02	BPS
dCer 42:2	-0,5282	26,14	-4,826	9,34E-06	0,00340	Alda		TAG 46:0	-0,015	4,812	-2,367	1,84E-02	4,85E-02	BPS
dCer 36:1	-0,4439	23,37	-3,797	0,00033	0,04046	Alda		DAG 34:3	-0,021	4,314	-2,361	1,87E-02	0,0489408	BPS
FA 10:1	0,34559	20,22	3,905	0,00023	0,04046	Alda								
LPE 16:1	-1,0703	19,37	-3,682	0,00048	0,04409	Alda								

Supplementary Table S3: Results t-test

Lipid.species	lithium	alda	AP	AD	T	MS	BP	S	Q	A	O	C	R	H	P	Z	CO	ZPR	BPS
CAR 10:3	0,339	0,986	0,909	0,895	0,940	0,293	0,087	0,847	0,917	0,693	0,998	0,984	0,999	0,999	0,996	0,921	0,935	0,894	0,834
CAR 10:2	0,885	0,977	0,004	0,555	0,897	0,636	0,022	0,029	0,196	0,484	0,998	0,670	0,999	0,999	0,966	0,949	0,883	0,752	0,233
CAR 10:1	0,809	0,757	0,000	0,945	0,897	0,750	0,067	0,000	0,917	0,829	0,998	0,496	0,999	0,999	0,857	0,931	0,871	0,963	0,009
CAR 10:0	0,733	0,757	0,007	0,388	0,897	0,991	0,313	0,007	0,917	0,672	0,998	0,280	0,999	0,999	0,976	0,921	0,603	0,730	0,001
CAR 11:1	0,278	0,932	0,001	0,573	0,897	0,164	0,490	0,001	0,917	0,458	0,998	0,868	0,999	0,999	0,996	0,932	0,970	0,959	0,003
CAR 12:2	0,321	0,757	0,000	0,653	0,897	0,914	0,060	0,000	0,917	0,929	0,998	0,965	0,999	0,999	0,976	0,969	0,815	0,820	0,010
CAR 12:0	0,324	0,757	0,031	0,370	0,897	0,058	0,760	0,013	0,917	0,507	0,998	0,352	0,999	0,999	0,996	0,921	0,806	0,746	0,214
CAR 13:1	0,178	0,827	0,001	0,285	0,897	0,486	0,085	0,001	0,917	0,457	0,998	0,959	0,999	0,999	0,984	0,921	0,976	0,876	0,475
CAR 13:0	0,350	0,788	0,001	0,774	0,897	0,170	0,375	0,000	0,917	0,761	0,998	0,965	0,999	0,999	0,976	0,921	0,958	0,943	0,857
CAR 14:2	0,376	0,757	0,007	0,718	0,897	0,073	0,843	0,001	0,917	0,989	0,998	0,667	0,999	0,999	0,966	0,921	0,970	0,855	0,038
CAR 14:1	0,358	0,909	0,211	0,409	0,897	0,057	0,500	0,060	0,917	0,758	0,998	0,319	0,999	0,999	0,976	0,921	0,925	0,567	0,032
CAR 14:0	0,354	0,882	0,269	0,096	0,897	0,008	0,192	0,033	0,917	0,502	0,998	0,123	0,999	0,999	0,967	0,921	0,981	0,995	0,001
CAR 16:2	0,485	0,757	0,012	0,564	0,897	0,166	0,887	0,004	0,917	0,814	0,998	0,992	0,999	0,999	0,966	0,921	0,937	0,946	0,008
CAR 16:0	0,240	0,961	0,800	0,050	0,988	0,177	0,202	0,984	0,917	0,872	0,998	0,084	0,999	0,999	0,984	0,931	0,886	0,943	0,020
CAR 18:2	0,763	0,864	0,003	0,601	0,897	0,411	0,698	0,001	0,372	0,891	0,998	0,565	0,999	0,999	0,810	0,921	0,815	0,933	0,005
CAR 18:1	0,381	0,852	0,259	0,502	0,897	0,360	0,770	0,223	0,917	0,854	0,998	0,138	0,999	0,999	0,976	0,921	0,978	0,902	0,000
CAR 18:0	0,290	0,826	0,797	0,281	0,937	0,063	0,073	0,428	0,917	0,583	0,998	0,150	0,999	0,999	0,984	0,921	0,799	0,792	0,602
CE 18:3	0,369	0,986	0,159	0,485	0,909	0,372	0,313	0,386	0,932	0,451	0,998	0,143	0,999	0,999	0,966	0,969	0,976	0,903	0,031
CE 18:2	0,654	0,977	0,720	0,738	0,897	0,096	0,232	0,418	0,974	0,448	0,998	0,134	0,999	0,999	0,966	0,951	0,699	0,928	0,981
CE 20:4	0,956	0,961	0,332	0,778	0,897	0,423	0,075	0,440	0,917	0,755	0,998	0,619	0,999	0,999	0,967	0,921	0,967	0,765	0,857
CE 20:3	0,371	0,816	0,339	0,960	0,897	0,669	0,500	0,007	0,932	0,661	0,998	0,273	0,999	0,999	0,996	0,991	0,894	0,904	0,052
CE 22:6	0,209	0,872	0,372	0,970	0,919	0,722	0,324	0,760	0,990	0,742	0,998	0,228	0,999	0,999	0,966	0,921	0,779	0,792	0,010
DAG 34:3	0,412	0,986	0,001	0,234	0,897	0,551	0,199	0,000	0,952	0,884	0,998	0,526	0,999	0,999	0,244	0,921	0,945	0,869	0,102
DAG 34:1	0,389	0,986	0,006	0,245	0,897	0,806	0,354	0,004	0,997	0,913	0,998	0,784	0,999	0,999	0,235	0,935	0,660	0,902	0,682
DAG 36:5	0,578	0,979	0,005	0,423	0,897	0,477	0,775	0,007	0,990	0,979	0,998	0,560	0,999	0,999	0,966	0,932	0,871	0,960	0,786
DAG 36:4	0,073	0,757	0,383	0,864	0,968	0,166	0,433	0,038	0,917	0,784	0,998	0,836	0,999	0,999	0,966	0,932	0,952	0,902	0,745
DAG 36:3	0,073	0,760	0,137	0,698	0,897	0,927	0,929	0,254	0,965	0,850	0,998	0,848	0,999	0,999	0,984	0,975	0,856	0,946	0,027
DAG 36:2	0,178	0,757	0,256	0,816	0,991	0,090	0,214	0,046	0,917	0,502	0,998	0,784	0,999	0,999	0,857	0,931	0,603	0,946	0,208
DAG 36:1	0,238	0,932	0,542	0,166	0,981	0,837	0,194	0,405	0,944	0,631	0,998	0,229	0,999	0,999	0,984	0,932	0,997	0,917	0,031
dCer 34:2	0,264	0,961	0,000	0,006	0,897	0,130	0,000	0,000	0,924	0,662	0,998	0,124	0,999	0,999	0,463	0,954	0,939	0,784	0,002
dCer 34:1	0,216	0,757	0,046	0,862	0,988	0,634	0,023	0,002	0,990	0,741	0,998	0,185	0,999	0,999	0,966	0,921	0,970	0,869	0,045
dCer 36:2	0,106	0,927	0,037	0,718	0,983	0,206	0,298	0,001	0,944	0,755	0,998	0,971	0,999	0,999	0,966	0,921	0,840	0,792	0,527
dCer 36:1	0,457	0,986	0,000	0,179	0,932	0,889	0,272	0,000	0,990	0,836	0,998	0,310	0,999	0,999	0,587	0,921	0,935	0,836	0,000
dCer 38:1	0,330	0,954	0,000	0,108	0,981	0,748	0,123	0,000	0,944	0,884	0,998	0,220	0,999	0,999	0,637	0,921	0,935	0,894	0,763
dCer 40:3	0,325	0,977	0,457	0,946	0,947	0,225	0,324	0,726	0,955	0,677	0,998	0,999	0,999	0,999	0,983	0,921	0,835	0,985	0,017
dCer 40:2	0,329	0,961	0,002	0,026	0,929	0,346	0,130	0,004	0,965	0,970	0,998	0,161	0,999	0,999	0,966	0,969	0,952	0,948	0,009
dCer 40:1	0,905	0,852	0,009	0,162	0,927	0,254	0,273	0,007	0,979	0,661	0,998	0,906	0,999	0,999	0,225	0,932	0,964	0,946	0,045
dCer 41:1	0,713	0,851	0,054	0,756	0,897	0,082	0,027	0,003	0,917	0,558	0,998	0,667	0,999	0,999	0,976	0,921	0,776	0,960	0,871
dCer 42:4	0,745	0,987	0,152	0,421	0,897	0,735	0,424	0,039	0,944	0,908	0,998	0,921	0,999	0,999	0,066	0,929	0,957	0,770	0,002
dCer 42:3	0,521	0,977	0,025	0,432	0,897	0,440	0,189	0,005	0,965	0,788	0,998	0,376	0,999	0,999	0,234	0,931	0,957	0,960	0,019
dCer 42:2	0,598	0,978	0,022	0,242	0,897	0,384	0,123	0,004	0,980	0,697	0,998	0,493	0,999	0,999	0,225	0,921	0,970	0,784	0,016
dCer 42:1	0,788	0,895	0,042	0,309	0,919	0,110	0,277	0,070	0,963	0,854	0,998	0,694	0,999	0,999	0,589	0,999	0,952	0,885	0,000
dCer 43:3	0,768	0,986	0,082	0,828	0,897	0,394	0,493	0,214	0,984	0,723	0,998	0,213	0,999	0,999	0,996	0,921	0,935	0,792	0,001
dCer 43:2	0,804	0,827	0,116	0,366	0,897	0,856	0,505	0,386	0,944	0,599	0,998	0,168	0,999	0,999	0,966	0,921	0,925	0,769	0,003
dCer 43:2	0,182	0,954	0,239	0,586	0,919	0,181	0,243	0,882	0,917	0,448	0,998	0,349	0,999	0,999	0,966	0,931	0,603	0,790	0,903
dCer 43:1	0,185	0,757	0,006	0,167	0,988	0,017	0,011	0,002	0,984	0,484	0,998	0,560	0,999	0,999	0,966	0,921	0,699	0,792	0,201
dCer 44:2	0,797	0,950	0,002	0,037	0,897	0,595	0,009	0,000	0,917	0,631	0,998	0,250	0,999	0,999	0,996	0,991	0,805	0,792	0,029
dCer 44:2	0,239	0,977	0,487	0,665	0,972	0,446	0,881	0,224	0,932	0,325	0,998	0,581	0,999	0,999	0,984	0,931	0,815	0,963	0,003
dSM 30:1	0,276	0,977	0,082	0,961	0,986	0,465	0,516	0,061	0,944	0,448	0,998	0,554	0,999	0,999	0,976	0,921	0,831	0,902	0,001
dSM 32:2	0,816	0,757	0,026	0,640	0,897	0,870	0,809	0,011	0,917	0,884	0,998	0,344	0,999	0,999	0,976	0,921	0,799	0,954	0,010
dSM 32:0	0,761	0,986	0,444	0,756	0,929	0,470	0,568	0,032	0,932	0,689	0,998	0,899	0,999	0,999	0,976	0,935	0,734	0,608	0,108
dSM 33:1	0,248	0,986	0,646	0,465	0,897	0,241	0,797	0,385	0,965	0,794	0,998	0,553	0,999	0,999	0,976	0,921	0,935	0,902	0,020
dSM 34:3	0,790	0,757	0,007	0,284	0,937	0,941	0,207	0,005	0,945	0,989	0,998	0,953	0,999	0,999	0,966	0,969	0,984	0,813	0,000
dSM 34:2	0,265	0,977	0,858	0,375	0,959	0,518	0,620	0,726	0,944	0,585	0,998	0,965	0,999	0,999	0,967	0,921	0,871	0,960	0,000
dSM 34:1	0,290	0,986	0,032	0,323	0,897	0,095	0,797	0,010	0,968	0,915	0,998	0,482	0,999	0,999	0,998	0,921	0,976	0,820	0,002
dSM 35:2	0,665	0,757	0,000	0,866	0,919	0,981	0,367	0,000	0,965	0,764	0,998	0,120	0,999	0,999	0,996	0,921	0,761	0,717	0,921
dSM 35:1	0,781	0,954	0,000	0,013	0,986	0,108	0,021	0,001	0,952	0,882	0,998	0,107	0,999	0,999	0,948	0,951	0,776	0,962	0,000
dSM 36:4	0,457	0,864	0,004	0,057	0,897	0,236	0,025	0,009	0,969	0,890	0,998	0,107	0,999	0,999	0,966	0,969	0,603	0,700	0,482
dSM 36:3	0,604	0,950	0,042	0,862	0,897	0,015	0,080	0,118	0,932	0,502	0,998	0,137	0,999	0,999	0,861	0,986	0,994	0,733	0,005
dSM 36:2	0,690	0,816	0,001	0,097	0,919	0,460	0,760	0,000	0,990	0,856	0,998	0,539	0,999	0,999	0,998	0,921	0,619	0,837	0,000
dSM 36:1	0,713	0,976	0,085	0,765	0,897	0,123	0,079	0,012	0,917	0,724	0,998	0,669	0,999	0,999	0,996	0,921	0,858	0,769	0,001
dSM 37:2	0,885	0,977	0,575	0,677	0,919	0,991	0,790	0,346	0,917	0,973	0,998	0,702	0,999	0,999	0,932	0,921	0,700	0,985	0,617
dSM 38:3	0,816	0,975	0,730	0,325	0,897	0,043	0,992	0,705	0,965	0,448	0,998	0,353	0,999	0,999	0,857	0,935	0,969	0,957	0,000
dSM 38:2	0,791	0,838	0,425	0,832	0,897	0,500	0,259	0,061	0,932	0,457	0,998	0,520	0,999	0,999	0,976	0,946	0,856	0,960	0,030
dSM 39:2	0,757	0,772	0,003	0,668	0,897	0,700	0,315	0,001	0,944	0,502	0,998	0,316	0,999	0,999	0,865	0,921	0,978	0,871	0,040
dSM 39:1	0,396	0,950	0,742	0,862	0,897	0,705	0,793	0,936	0,933	0,554	0,998	0,809	0,999	0,999	0,638	0,935	0,867	0,811	0,002
dSM 40:3	0,234	0,950	0,248	0,013	0,897	0,049	0,061	0,429	0,944	0,660	0,998	0,846	0,999	0,999	0,914	0,921	0,970	0,820	0,027
dSM 40:2	0,761	0,932	0,227	0,798	0,897	0,732	0,530	0,028	0,940	0,693	0,998	0,853	0,999	0,999	0,966	0,959	0,794	0,769	0,125
dSM 41:3	0,816	0,816	0,037	0,110	0,919	0,224	0,005	0,036	0,960	0,891	0,998	0,422	0,999	0,999	0,966	0,921	0,870	0,796	0,167
dSM 41:2	0,073	0,986	0,961	0,064	0,897	0,329	0,365	0,237	0,965	0,649	0,998	0,676	0,999	0,999	0,996	0,921	0,984	0,967	0,019
dSM 42:4	0,883	0,757	0,081	0,516	0,919	0,728	0,737	0,012	0,968	0,884	0,998	0,904	0,999	0,999	0,967	0,921	0,831	0,995	0,876
dSM 42:2	0,353	0,977	0,402	0,364	0,919	0,314	0,820	0,318	0,940	0,484	0,998	0,868	0,999	0,999	0,971	0,921	0,815	0,904	0,000
dSM 43:2	0,531	0,986	0,071	0,306	0,919	0,981	0,637	0,187	0,955	0,731	0,998	0,944	0,999	0,999	0,966	0,985	0,856	0,780	0,000
dSM 44:5	0,956	0,977	0,077	0,544	0,988	0,355	0,531	0,114	0,950	0,479	0,998	0,541	0,999	0,999	0,984	0,982	0,970	0,842	0,261

Supplementary material

dSM 44:4	0,819	0,757	0,134	0,267	0,919	0,965	0,474	0,004	0,944	0,448	0,998	0,894	0,999	0,999	0,967	0,921	0,699	0,910	0,564
dSM 44:3	0,073	0,757	0,902	0,865	0,897	0,097	0,499	0,691	0,986	0,502	0,998	0,158	0,999	0,999	0,895	0,931	0,925	0,831	0,038
dSM 44:2	0,957	0,852	0,075	0,510	0,919	0,275	0,101	0,139	0,944	0,484	0,998	0,401	0,999	0,999	0,983	0,921	0,870	0,879	0,399
FA 19:1	0,942	0,954	0,734	0,028	0,897	0,177	0,087	0,356	0,974	0,839	0,998	0,805	0,999	0,999	0,976	0,921	0,987	0,700	0,004
FA 20:5	0,854	0,766	0,487	0,857	0,919	0,971	0,791	0,088	0,917	0,627	0,998	0,948	0,999	0,999	0,966	0,921	0,925	0,769	0,779
FA 20:4	0,111	0,979	0,476	0,530	0,897	0,748	0,369	0,866	0,965	0,973	0,998	0,124	0,999	0,999	0,976	0,951	0,983	0,700	0,000
FA 20:3	0,061	0,954	0,969	0,895	0,937	0,889	0,731	0,858	0,933	0,585	0,998	0,525	0,999	0,999	0,976	0,921	0,859	0,825	0,010
FA 20:2	0,926	0,986	0,545	0,096	0,919	0,240	0,371	0,221	0,965	0,531	0,998	0,482	0,999	0,999	0,996	0,932	0,870	0,879	0,145
FA 20:1	0,348	0,757	0,542	0,084	0,934	0,176	0,002	0,747	0,983	0,888	0,998	0,615	0,999	0,999	0,967	0,921	0,603	0,902	0,852
FA 21:1	0,595	0,827	0,116	0,096	0,937	0,329	0,115	0,328	0,944	0,760	1,000	0,394	0,999	0,999	0,966	0,921	0,776	0,710	0,789
FA 22:6	0,741	0,757	0,381	0,080	0,999	0,180	0,030	0,998	0,965	0,912	0,998	0,712	0,999	0,999	0,976	0,921	0,935	0,826	0,834
FA 22:5	0,183	0,954	0,004	0,976	0,991	0,005	0,001	0,000	0,984	0,574	0,998	0,918	0,999	0,999	0,976	0,921	0,871	0,792	0,040
FA 22:3	0,735	0,862	0,065	0,060	0,897	0,081	0,005	0,449	0,991	0,828	0,998	0,426	0,999	0,999	0,971	0,921	0,815	0,988	0,054
FA 22:2	0,687	0,757	0,907	0,570	0,940	0,390	0,348	0,512	0,924	0,723	0,998	0,908	0,999	0,999	0,984	0,921	0,976	0,801	0,010
FA 22:1	0,045	0,926	0,001	0,637	0,919	0,037	0,001	0,000	0,976	0,887	0,998	0,349	0,999	0,999	0,971	0,932	0,603	0,784	0,000
FA 23:1	0,710	0,757	0,682	0,179	0,940	0,511	0,662	0,107	0,932	0,724	0,998	0,999	0,999	0,999	0,966	0,921	0,681	0,910	0,668
FA 23:0	0,263	0,977	0,873	0,205	0,897	0,026	0,021	0,402	0,944	0,885	0,998	0,992	0,999	0,999	0,748	0,935	0,603	0,780	0,830
FA 24:4	0,182	0,988	0,562	0,153	0,988	0,013	0,000	0,846	0,917	0,975	0,998	0,974	0,999	0,999	0,932	0,921	0,730	0,784	0,922
FA 24:2	0,675	0,950	0,102	0,133	0,897	0,200	0,030	0,055	0,932	0,606	0,998	0,676	0,999	0,999	0,966	0,988	0,870	0,960	0,840
FA 24:1	0,694	0,757	0,521	0,090	0,972	0,187	0,006	0,780	0,990	0,970	0,998	0,676	0,999	0,999	0,971	0,921	0,901	0,784	0,003
FA 8:0	0,617	0,986	0,229	0,271	0,919	0,094	0,154	0,184	0,917	0,554	0,998	0,646	0,999	0,999	0,895	0,921	0,925	0,894	0,991
FA 25:3	0,883	0,757	0,229	0,382	0,988	0,233	0,758	0,005	0,968	0,992	0,998	0,861	0,999	0,999	0,966	0,921	0,894	0,817	0,040
FA 25:2	0,728	0,757	0,958	0,069	0,988	0,157	0,071	0,500	0,965	0,750	0,998	0,518	0,999	0,999	0,976	0,921	0,925	0,885	0,000
FA 25:0	0,682	0,950	0,048	0,062	0,897	0,000	0,000	0,308	0,968	0,674	0,998	0,907	0,999	0,999	0,971	0,921	0,976	0,869	0,534
FA 26:5	0,764	0,990	0,016	0,028	0,995	0,630	0,099	0,001	0,917	0,457	0,998	0,994	0,999	0,999	0,966	0,921	0,943	0,917	0,096
FA 26:4	0,264	0,859	0,510	0,057	0,919	0,013	0,019	0,539	0,944	0,574	0,998	0,751	0,999	0,999	0,976	0,590	0,942	0,801	0,256
FA 26:2	0,400	0,757	0,438	0,081	0,959	0,001	0,000	0,722	0,965	0,885	0,998	0,785	0,999	0,999	0,966	0,921	0,933	0,946	0,779
FA 26:2	0,641	0,975	0,686	0,156	0,919	0,006	0,008	0,123	0,944	0,652	0,998	0,703	0,999	0,999	0,895	0,921	0,883	0,765	0,535
FA 26:1	0,078	0,757	0,012	0,976	0,897	0,426	0,025	0,011	0,945	0,565	0,998	0,791	0,999	0,999	0,982	0,921	0,935	0,700	0,766
FA 27:4	0,324	0,757	0,142	0,025	0,919	0,000	0,000	0,691	0,933	0,884	0,998	0,351	0,999	0,999	0,684	0,932	0,730	0,872	0,458
FA 27:3	0,329	0,986	0,425	0,062	0,897	0,002	0,000	0,839	0,975	0,979	0,998	0,667	0,999	0,999	0,637	0,921	0,754	0,708	0,004
FA 28:4	0,238	0,950	0,686	0,011	0,897	0,012	0,000	0,095	0,917	0,484	0,998	0,669	0,999	0,999	0,984	0,921	0,989	0,920	0,273
FA 10:3	0,957	0,788	0,754	0,051	0,988	0,314	0,076	0,677	0,965	0,923	0,998	0,539	0,999	0,999	0,966	0,921	0,935	0,567	0,285
FA 10:2	0,601	0,950	0,873	0,617	0,991	0,274	0,541	0,292	0,932	0,884	0,998	0,478	0,999	0,999	0,971	0,921	0,964	0,705	0,601
FA 10:1	0,957	0,757	0,996	0,731	0,897	0,036	0,220	0,365	0,917	0,985	0,998	0,229	0,999	0,999	0,966	0,932	0,865	0,749	0,944
FA 11:1	0,939	0,827	0,478	0,262	0,897	0,233	0,297	0,048	0,933	0,812	0,998	0,676	0,999	0,999	0,976	0,921	0,871	0,959	0,000
FA 12:3	0,865	0,828	0,855	0,141	0,933	0,208	0,143	0,418	0,965	0,691	0,998	0,444	0,999	0,999	0,976	0,921	0,871	0,792	0,000
FA 12:2	0,942	0,983	0,961	0,915	0,988	0,487	0,867	0,772	0,968	0,484	0,998	0,660	0,999	0,999	0,996	0,946	0,935	0,567	0,511
FA 12:1	0,110	0,977	0,890	0,907	0,919	0,052	0,253	0,998	0,984	0,755	0,998	0,597	0,999	0,999	0,966	0,975	0,894	0,844	0,015
FA 12:0	0,608	0,757	0,826	0,127	0,988	0,719	0,699	0,357	0,952	0,675	0,998	0,922	0,999	0,999	0,984	0,921	0,603	0,792	0,914
FA 13:1	0,745	0,757	0,943	0,243	0,968	0,188	0,155	0,410	0,932	0,854	0,998	0,587	0,999	0,999	0,984	0,921	0,937	0,842	0,953
FA 13:0	0,932	0,757	0,409	0,138	0,897	0,202	0,218	0,837	0,968	0,758	0,998	0,349	0,999	0,999	0,996	0,921	0,603	0,856	0,171
FA 14:2	0,309	0,961	0,136	0,915	0,919	0,453	0,214	0,103	0,965	0,734	0,998	0,965	0,999	0,999	0,984	0,935	0,761	0,626	0,715
FA 14:1	0,671	0,986	0,901	0,356	0,919	0,973	0,771	0,926	0,991	0,794	0,998	0,754	0,999	0,999	0,966	0,921	0,705	0,784	0,876
FA 14:0	0,734	0,757	0,364	0,101	0,991	0,230	0,031	0,871	0,965	0,887	0,998	0,589	0,999	0,999	0,971	0,921	0,957	0,796	0,791
FA 15:1	0,815	0,757	0,837	0,025	0,932	0,401	0,190	0,441	0,917	0,932	0,998	0,351	0,999	0,999	0,966	0,921	0,699	0,946	0,830
FA 16:2	0,605	0,757	0,848	0,637	0,919	0,530	0,477	0,636	0,932	0,660	0,998	0,871	0,999	0,999	0,976	0,946	0,970	0,913	0,008
FA 16:1	0,274	0,954	0,238	0,622	0,897	0,539	0,884	0,452	0,965	0,507	0,998	0,458	0,999	0,999	0,966	0,982	0,886	0,756	0,007
FA 16:0	0,932	0,926	0,955	0,070	0,925	0,242	0,066	0,372	0,945	0,973	0,998	0,422	0,999	0,999	0,976	0,921	0,643	0,928	0,416
FA 17:2	0,861	0,977	0,776	0,821	0,897	0,806	0,839	0,603	0,954	0,452	0,998	0,903	0,999	0,999	0,996	0,921	0,815	0,906	0,206
FA 17:1	0,956	0,757	0,319	0,509	0,988	0,317	0,553	0,036	0,965	0,921	0,998	0,848	0,999	0,999	0,966	0,921	0,606	0,960	0,076
FA 17:0	0,732	0,760	0,445	0,088	0,988	0,177	0,024	0,843	0,968	0,794	0,998	0,413	0,999	0,999	0,967	0,921	0,669	0,567	0,775
FA 18:4	0,380	0,954	0,099	0,364	0,897	0,290	0,023	0,376	0,965	0,914	0,998	0,138	0,999	0,999	0,971	0,969	0,863	0,960	0,999
FA 18:2	0,989	0,895	0,900	0,063	0,979	0,155	0,075	0,156	0,944	0,959	0,998	0,445	0,999	0,999	0,996	0,921	0,761	0,894	0,141
FA 18:1	0,445	0,957	0,278	0,756	0,988	0,462	0,651	0,076	0,917	0,882	0,998	0,974	0,999	0,999	0,984	0,988	0,728	0,869	0,269
LPC 14:0	0,310	0,757	0,627	0,211	0,921	0,837	0,996	0,449	0,965	0,534	0,998	0,465	0,999	0,999	0,976	0,921	0,705	0,792	0,520
LPC 15:0	0,742	0,864	0,000	0,136	0,897	0,189	0,000	0,000	0,917	0,521	0,998	0,217	0,999	0,999	0,976	0,932	0,734	0,749	0,224
LPC 16:1	0,208	0,816	0,265	0,708	0,981	0,026	0,113	0,030	0,933	0,631	0,998	0,554	0,999	0,999	0,996	0,921	0,734	0,885	0,539
LPC 16:0	0,521	0,882	0,620	0,299	0,897	0,697	0,903	0,985	0,932	0,973	0,998	0,275	0,999	0,999	0,976	0,921	0,886	0,767	0,503
LPC 17:0	0,939	0,757	0,180	0,109	0,897	0,794	0,346	0,983	0,932	0,756	0,998	0,954	0,999	0,999	0,966	0,921	0,821	0,946	0,034
LPC 18:3	0,263	0,977	0,503	0,080	0,933	0,032	0,101	0,012	0,932	0,846	0,998	0,647	0,999	0,999	0,895	0,334	0,746	0,820	0,487
LPC 18:2	0,521	0,800	0,000	0,176	0,919	0,012	0,000	0,000	0,917	0,457	0,998	0,426	0,999	0,999	0,996	0,931	0,603	0,770	0,991
LPC 18:1	0,875	0,986	0,334	0,718	0,919	0,849	0,677	0,998	0,965	0,929	0,998	0,426	0,999	0,999	0,966	0,988	0,831	0,784	0,005
LPC 18:0	0,233	0,757	0,952	0,018	0,988	0,042	0,123	0,101	0,944	0,963	0,998	0,826	0,999	0,999	0,976	0,921	0,977	0,928	0,001
LPC 19:1	0,073	0,757	0,237	0,626	0,988	0,976	0,308	0,012	0,974	0,706	0,998	0,218	0,999	0,999	0,966	0,931	0,706	0,948	0,914
LPC 19:0	0,110	0,986	0,000	0,042	0,919	0,890	0,101	0,000	0,944	0,892	0,998	0,210	0,999	0,999	0,966	0,963	0,901	0,577	0,471
LPC 20:5	0,885	0,757	0,814	0,248	0,959	0,810	0,887	0,750	0,917	0,451	0,998	0,961	0,999	0,999	0,966	0,921	0,754	0,567	0,619
LPC 20:4	0,357	0,986	0,000	0,016	0,991	0,347	0,026	0,000	0,973	0,972	0,998	0,107	0,999	0,999	0,976	0,921	0,819	0,987	0,779
LPC 20:2	0,369	0,983	0,003	0,011	0,919	0,127	0,019	0,037	0,965	0,858	0,998	0,235	0,999	0,999	0,996	0,977	0,810	0,790	0,020
LPC 20:1	0,353	0,852	0,000	0,029	0,960	0,876	0,113	0,000	0,947	0,853	0,998	0,262	0,999	0,999	0,401	0,980	0,970	0,823	0,737
LPC 20:0	0,695	0,977	0,261	0,701	0,897	0,784	0,996	0,071	0,933	0,973	0,998	0,991	0,999	0,999	0,091	0,932	0,660	0,836	0,876
LPC 22:6	0,786	0,757	0,679	0,323	0,948	0,694	0,795	0,931	0,960	0,577	0,998	0,768	0,999	0,999	0,989	0,969	0,958	0,723	0,289
LPC 22:5	0,643	0,889	0,402	0,779	0,983	0,720	0,690	0,101	0,944	0,512	0,998	0,660	0,999	0,999	0,966	0,946	0,871	0,749	0,929
LPC 22:4	0,255	0,954	0,006	0,062	0,968	0,412	0,130	0,006	0,979	0,981	0,998	0,165	0,999	0,999	0,966	0,921	0,606	0,704	0,501
LPC_O 16:0	0,443	0,827	0,757	0,329	0,988	0,811	0,858	0,540	0,932	0,693	0,998	0,422	0,999	0,999	0,971	0,935	0,761	0,792	0,929
LPC_O 18:1	0,240	0,977	0,826	0,193	0,919	0,161	0,793	0,055	0,917	0,683	0,998	0,608	0,999	0,999	0,966	0,921	0,942	0,675	0,124
LPC_O 18:0	0,135	0,986	0,857	0,510	0,983	0,403	0,995	0,076	0,924	0,510	0,998	0,394	0,999	0,999	0,976	0,921	0,886	0,913	0,846
LPC_O 22:1	0,106	0,977	0,692	0,024	0,983	0,002	0,083	0,033	0,933	0,833	0,998	0,218	0,999	0,999	0,976	0,921	0,700	0,938	0,343

Supplementary material

LPC_O 24:1	0,115	0,957	0,248	0,367	0,897	0,750	0,433	0,000	0,932	0,641	0,998	0,126	0,999	0,999	0,996	0,921	0,649	0,843	0,216
LPC_O 24:0	0,154	0,986	0,019	0,370	0,897	0,047	0,001	0,000	0,933	0,666	0,998	0,060	0,999	0,999	0,996	0,931	0,901	0,567	0,138
LPC_O 26:1	0,240	0,954	0,005	0,961	0,897	0,204	0,001	0,000	0,940	0,530	0,998	0,060	0,999	0,999	0,996	0,946	0,766	0,913	0,667
LPC_P 16:0	0,993	0,961	0,664	0,718	0,897	0,856	0,790	0,483	0,917	0,512	0,998	0,805	0,999	0,999	0,976	0,921	0,805	0,776	0,000
LPC_P 18:1	0,761	0,954	0,219	0,276	0,919	0,400	0,585	0,385	0,917	0,750	0,998	0,765	0,999	0,999	0,984	0,921	0,859	0,744	0,258
LPE 16:1	0,138	0,986	0,004	0,061	0,940	0,201	0,008	0,000	0,965	0,558	0,998	0,188	0,999	0,999	0,959	0,921	0,754	0,746	0,696
LPE 16:0	0,311	0,757	0,545	0,171	0,929	0,890	0,917	0,554	0,968	0,512	0,998	0,490	0,999	0,999	0,976	0,921	0,766	0,780	0,065
LPE 18:3	0,683	0,977	0,005	0,083	0,981	0,074	0,878	0,000	0,924	0,693	0,998	0,826	0,999	0,999	0,879	0,921	0,734	0,957	0,002
LPE 18:2	0,757	0,986	0,420	0,929	0,897	0,852	0,677	0,153	0,968	0,457	0,998	0,903	0,999	0,999	0,976	0,921	0,699	0,941	0,055
LPE 18:1	0,210	0,757	0,000	0,086	0,897	0,166	0,000	0,000	0,917	0,858	0,998	0,359	0,999	0,999	0,984	0,921	0,766	0,902	0,210
LPE 20:5	0,373	0,757	0,826	0,007	0,988	0,195	0,003	0,933	0,983	0,969	0,998	0,669	0,999	0,999	0,976	0,931	0,957	0,628	0,790
LPE 20:4	0,178	0,757	0,000	0,014	0,897	0,013	0,000	0,000	0,924	0,890	0,998	0,245	0,999	0,999	0,966	0,991	0,936	0,796	0,221
LPE 20:3	0,310	0,816	0,947	0,322	0,940	0,313	0,997	0,070	0,984	0,822	0,998	0,802	0,999	0,999	0,966	0,921	0,699	0,769	0,258
LPE 22:5	0,513	0,757	0,021	0,007	0,994	0,405	0,027	0,110	0,965	0,624	0,998	0,748	0,999	0,999	0,966	0,921	0,815	0,803	0,784
PC 30:1	0,334	0,826	0,000	0,636	0,897	0,870	0,354	0,000	0,965	0,872	0,998	0,673	0,999	0,999	0,996	0,921	0,959	0,752	0,876
PC 30:0	0,733	0,757	0,011	0,099	0,933	0,463	0,112	0,043	0,990	0,659	0,998	0,373	0,999	0,999	0,996	0,991	0,603	0,675	0,882
PC 32:2	0,521	0,977	0,002	0,069	0,919	0,067	0,618	0,003	0,990	0,674	0,998	0,426	0,999	0,999	0,998	0,975	0,603	0,577	0,758
PC 32:1	0,073	0,978	0,912	0,879	0,940	0,258	0,156	0,850	0,933	0,929	0,998	0,944	0,999	0,999	0,984	0,921	0,643	0,789	0,286
PC 32:0	0,394	0,864	0,371	0,649	0,983	0,852	0,344	0,182	0,990	0,541	0,998	0,660	0,999	0,999	0,996	0,921	0,643	0,790	0,431
PC 33:1	0,446	0,988	0,000	0,009	0,919	0,848	0,011	0,000	0,968	0,788	0,998	0,349	0,999	0,999	0,967	0,991	0,761	0,648	0,674
PC 33:0	0,837	0,977	0,014	0,034	0,897	0,669	0,282	0,089	0,979	0,457	0,998	0,761	0,999	0,999	0,967	0,921	0,603	0,577	0,245
PC 34:4	0,353	0,902	0,375	0,582	0,897	0,067	0,089	0,820	0,990	0,886	0,998	0,646	0,999	0,999	0,976	0,921	0,936	0,608	0,846
PC 34:3	0,909	0,961	0,000	0,432	0,927	0,710	0,194	0,000	0,968	0,872	0,998	0,260	0,999	0,999	0,967	0,921	0,603	0,675	0,116
PC 34:3	0,324	0,977	0,640	0,205	0,897	0,356	0,411	0,736	0,950	0,451	0,998	0,933	0,999	0,999	0,966	0,921	0,614	0,648	0,612
PC 34:2	0,602	0,757	0,145	0,095	0,897	0,171	0,552	0,309	0,917	0,457	0,998	0,489	0,999	0,999	0,996	0,932	0,867	0,885	0,408
PC 34:1	0,979	0,882	0,036	0,100	0,897	0,417	0,000	0,022	0,996	0,484	0,998	0,785	0,999	0,999	0,976	0,940	0,603	0,608	0,733
PC 34:0	0,823	0,940	0,167	0,331	0,897	0,149	0,425	0,871	0,917	0,643	0,998	0,386	0,999	0,999	0,976	0,991	0,815	0,608	0,091
PC 35:4	0,993	0,926	0,095	0,814	0,897	0,304	0,499	0,437	0,917	0,484	0,998	0,876	0,999	0,999	0,966	0,932	0,761	0,792	0,226
PC 35:3	0,749	0,864	0,785	0,554	0,937	0,889	0,533	0,928	0,965	0,484	0,998	0,597	0,999	0,999	0,976	0,921	0,633	0,608	0,862
PC 35:2	0,346	0,977	0,240	0,638	0,897	0,117	0,069	0,282	0,990	0,858	0,998	0,801	0,999	0,999	0,916	0,921	0,865	0,643	0,941
PC 35:1	0,759	0,939	0,703	0,975	0,897	0,629	0,273	0,273	0,965	0,884	0,998	0,662	0,999	0,999	0,976	0,921	0,721	0,681	0,455
PC 36:5	0,216	0,924	0,731	0,732	0,897	0,801	0,966	0,850	0,965	0,565	0,998	0,945	0,999	0,999	0,996	0,921	0,858	0,784	0,879
PC 36:5	0,687	0,950	0,491	0,718	0,919	0,972	0,841	0,524	0,990	0,647	0,998	0,784	0,999	0,999	0,966	0,921	0,641	0,577	0,965
PC 36:4	0,061	0,986	0,728	0,897	0,972	0,117	0,291	0,342	0,945	0,755	0,998	0,565	0,999	0,999	0,996	0,334	0,976	0,844	0,055
PC 36:4	0,998	0,986	0,000	0,007	0,959	0,000	0,000	0,000	0,917	0,973	0,998	0,442	0,999	0,999	0,996	0,921	0,603	0,608	0,812
PC 36:3	0,246	0,886	0,008	0,214	0,988	0,350	0,471	0,026	0,965	0,789	0,998	0,517	0,999	0,999	0,984	0,921	0,700	0,917	0,056
PC 36:2	0,913	0,757	0,279	0,962	0,919	0,460	0,937	0,027	0,924	0,448	0,998	0,894	0,999	0,999	0,984	0,921	0,606	0,577	0,046
PC 36:1	0,763	0,986	0,001	0,011	0,937	0,079	0,022	0,026	0,939	0,769	0,998	0,401	0,999	0,999	0,915	0,988	0,776	0,689	0,613
PC 36:0	0,857	0,827	0,679	0,961	0,988	0,043	0,247	0,961	0,954	0,970	0,998	0,417	0,999	0,999	0,996	0,921	0,669	0,608	0,584
PC 37:5	0,602	0,757	0,633	0,392	0,988	0,867	0,452	0,510	0,917	0,484	0,998	0,945	0,999	0,999	0,966	0,921	0,699	0,675	0,582
PC 37:2	0,913	0,980	0,010	0,014	0,988	0,236	0,020	0,112	0,944	0,844	0,998	0,761	0,999	0,999	0,966	0,921	0,603	0,823	0,585
PC 38:5	0,186	0,827	0,833	0,299	0,897	0,751	0,522	0,718	0,952	0,507	0,998	0,349	0,999	0,999	0,967	0,921	0,603	0,577	0,732
PC 38:4	0,761	0,961	0,000	0,006	0,925	0,890	0,000	0,000	0,917	0,913	0,998	0,566	0,999	0,999	0,976	0,921	0,902	0,648	0,926
PC 38:4	0,277	0,986	0,526	0,996	0,919	0,015	0,221	0,602	0,917	0,448	0,998	0,854	0,999	0,999	0,966	0,978	0,641	0,987	0,330
PC 38:3	0,110	0,980	0,008	0,346	0,972	0,068	0,080	0,360	0,932	0,628	0,998	0,475	0,999	0,999	0,966	0,921	0,675	0,567	0,728
PC 38:2	0,418	0,814	0,280	0,612	0,897	0,078	0,492	0,743	0,965	0,810	0,998	0,766	0,999	0,999	0,589	0,921	0,812	0,946	0,023
PC 38:2	0,402	0,977	0,380	0,406	0,897	0,643	0,332	0,183	0,965	0,646	0,998	0,867	0,999	0,999	0,966	0,921	0,734	0,957	0,557
PC 38:1	0,580	0,950	0,123	0,253	0,940	0,705	0,903	0,455	0,984	0,731	0,998	0,948	0,999	0,999	0,660	0,921	0,894	0,792	0,017
PC 39:4	0,956	0,757	0,288	0,566	0,919	0,418	0,863	0,570	0,917	0,565	0,998	0,217	0,999	0,999	0,971	0,932	0,666	0,801	0,430
PC 39:3	0,328	0,986	0,549	0,483	0,897	0,147	0,574	0,445	0,944	0,448	0,998	0,945	0,999	0,999	0,966	0,997	0,603	0,596	0,904
PC 40:5	0,649	0,977	0,068	0,480	0,919	0,038	0,875	0,011	0,917	0,956	0,998	0,665	0,999	0,999	0,971	0,921	0,705	0,796	0,000
PC 40:4	0,701	0,977	0,026	0,208	0,897	0,256	0,239	0,095	0,944	0,755	0,998	0,538	0,999	0,999	0,984	0,921	0,776	0,917	0,068
PC 40:3	0,809	0,986	0,262	0,576	0,919	0,025	0,122	0,548	0,991	0,737	0,998	0,164	0,999	0,999	0,966	0,921	0,706	0,963	0,192
PC 40:3	0,624	0,757	0,535	0,756	0,959	0,297	0,859	0,492	0,965	0,458	0,998	0,868	0,999	0,999	0,996	0,969	0,903	0,608	0,359
PC 40:2	0,323	0,950	0,039	0,691	0,897	0,073	0,751	0,005	0,917	0,989	0,998	0,565	0,999	0,999	0,989	0,921	0,687	0,827	0,921
PC 42:9	0,884	0,871	0,255	0,692	0,897	0,971	0,112	0,141	0,965	0,704	0,998	0,945	0,999	0,999	0,744	0,998	0,871	0,790	0,022
PC 42:6	0,554	0,977	0,692	0,240	0,988	0,543	0,272	0,428	0,944	0,758	0,998	0,703	0,999	0,999	0,966	0,921	0,761	0,608	0,356
PC 42:5	0,883	0,757	0,341	0,718	0,919	0,683	0,876	0,191	0,944	0,973	0,998	0,761	0,999	0,999	0,996	0,982	0,846	0,885	0,921
PC 42:4	0,800	0,800	0,001	0,153	0,897	0,235	0,003	0,134	0,917	0,660	0,998	0,401	0,999	0,999	0,966	0,935	0,699	0,777	0,883
PC_O 32:0	0,608	0,980	0,000	0,017	0,940	0,908	0,001	0,000	0,945	0,659	0,998	0,188	0,999	0,999	0,989	0,995	0,606	0,567	0,921
PC_O 34:2	0,768	0,986	0,273	0,130	0,897	0,908	0,886	0,107	0,990	0,824	0,998	0,493	0,999	0,999	0,966	0,921	0,867	0,700	0,933
PC_O 34:1	0,797	0,963	0,256	0,101	0,921	0,448	0,190	0,041	0,984	0,484	0,998	0,401	0,999	0,999	0,996	0,921	0,878	0,582	0,326
PC_O 36:4	0,956	0,757	0,191	0,097	0,958	0,106	0,275	0,185	0,955	0,530	0,998	0,587	0,999	0,999	0,998	0,969	0,603	0,608	0,038
PC_O 36:2	0,939	0,990	0,001	0,637	0,919	0,901	0,151	0,000	0,968	0,684	0,998	0,385	0,999	0,999	0,966	0,931	0,734	0,947	0,060
PC_O 36:1	0,443	0,757	0,422	0,718	0,784	0,022	0,221	0,529	0,932	0,448	0,998	0,343	0,999	0,999	0,976	0,932	0,669	0,792	0,127
PC_O 37:4	0,216	0,954	0,548	0,213	0,897	0,266	0,594	0,520	0,924	0,502	0,998	0,975	0,999	0,999	0,987	0,921	0,730	0,744	0,963
PC_O 38:5	0,290	0,977	0,381	0,575	0,927	0,818	0,917	0,788	0,917	0,484	0,998	0,815	0,999	0,999	0,998	0,921	0,935	0,837	0,005
PC_O 38:4	0,324	0,939	0,664	0,775	0,988	0,668	0,762	0,778	0,990	0,457	0,998	0,803	0,999	0,999	0,966	0,969	0,815	0,792	0,904
PC_O 38:3	0,659	0,961	0,003	0,128	0,897	0,976	0,202	0,002	0,955	0,898	0,998	0,718	0,999	0,999	0,984	0,932	0,603	0,784	0,815
PC_O 38:2	0,867	0,816	0,000	0,036	0,897	0,224	0,000	0,000	0,917	0,724	0,998	0,130	0,999	0,999	0,967	0,991	0,728	0,917	0,839
PC_O 40:7	0,419	0,986	0,481	0,440	0,897	0,236	0,998	0,379	0,917	0,761	0,998	0,262	0,999	0,999	0,996	0,921	0,603	0,608	0,882
PC_O 40:5	0,117	0,757	0,813	0,519	0,988	0,215	0,076	0,981	0,961	0,719	0,998	0,739	0,999	0,999	0,966	0,921	0,603	0,596	0,864
PC_O 40:5	0,489	0,768	0,013	0,067	0,905	0,248	0,009	0,000	0,984	0,828	0,998	0,995	0,999	0,999	0,996	0,975	0,637	0,664	0,280
PC_O 40:4	0,952	0,757	0,001	0,255	0,897	0,216	0,049	0,001	0,917	0,457	0,998	0,506	0,999	0,999	0,979	0,921	0,603	0,577	0,682
PC_O 40:4	0,354	0,988	0,542	0,432	0,897	0,057	0,108	0,850	0,932	0,915	0,998	0,960	0,999	0,999	0,984	0,969	0,643	0,577	0,398
PC_O 40:3	0,425	0,986	0,006	0,009	0,932	0,078	0,002	0,028	0,968	0,983	0,998	0,876	0,999	0,999	0,984	0,931	0,603	0,567	0,299
PC_O 42:7	0,739	0,757	0,006	0,027	0,983	0,810	0,027	0,012	0,965	0,883	0,998	0,868	0,999	0,999	0,968	0,921	0,801	0,963	0,103
PC_O 42:6	0,761	0,954	0,011	0,007	0,988	0,170	0,087	0,128	0,990	0,978	0,998	0,916	0,999	0,999	0,932	0,932	0,761	0,817	0,326

PC_O 42:5	0,928	0,757	0,000	0,283	0,916	0,177	0,018	0,002	0,917	0,484	0,998	0,254	0,999	0,999	0,966	0,932	0,843	0,928	0,086
PC_O 42:4	0,231	0,963	0,306	0,072	0,897	0,446	0,413	0,083	0,965	0,593	0,998	0,349	0,999	0,999	0,968	0,921	0,643	0,939	0,243
PC_O 44:8	0,346	0,988	0,459	0,082	0,940	0,838	0,896	0,441	0,939	0,755	0,998	0,646	0,999	0,999	0,966	0,935	0,776	0,608	0,341
PC_O 44:7	0,417	0,864	0,717	0,011	0,897	0,955	0,875	0,141	0,984	0,565	0,998	0,560	0,999	0,999	0,966	0,921	0,935	0,664	0,197
PC_O 44:4	0,989	0,864	0,043	0,168	0,897	0,200	0,196	0,014	0,917	0,558	0,998	0,349	0,999	0,999	0,983	0,972	0,771	0,836	0,857
PC_O 46:8	0,885	0,852	0,256	0,959	0,929	0,981	0,932	0,189	0,932	0,890	0,998	0,107	0,999	0,999	0,976	0,921	0,865	0,837	0,002
PC_O 46:7	0,854	0,983	0,230	0,456	0,897	0,585	0,937	0,588	0,932	0,557	0,998	0,784	0,999	0,999	0,976	0,334	0,776	0,963	0,094
PC_O 46:6	0,599	0,961	0,304	0,874	0,897	0,271	0,749	0,300	0,991	0,463	0,998	0,561	0,999	0,999	0,966	0,969	0,830	0,963	0,003
PC_O 46:5	0,738	0,909	0,240	0,483	0,897	0,801	0,476	0,620	0,932	0,898	0,998	0,942	0,999	0,999	0,987	0,969	0,942	0,784	0,249
PC_P 32:1	0,956	0,757	0,041	0,183	0,897	0,008	0,151	0,042	0,944	0,451	0,998	0,217	0,999	0,999	0,998	0,921	0,676	0,792	0,549
PC_P 32:0	0,729	0,864	0,000	0,081	0,919	0,437	0,016	0,000	0,917	0,484	0,998	0,868	0,999	0,999	0,967	0,921	0,833	0,902	0,140
PC_P 34:3	0,858	0,977	0,139	0,383	0,897	0,019	0,334	0,809	0,917	0,554	0,998	0,084	0,999	0,999	0,984	0,921	0,603	0,567	0,763
PC_P 34:2	0,795	0,961	0,980	0,505	0,897	0,629	0,896	0,976	0,979	0,829	0,998	0,560	0,999	0,999	0,996	0,929	0,776	0,820	0,002
PC_P 34:0	0,885	0,986	0,001	0,005	0,897	0,040	0,002	0,015	0,984	0,741	0,998	0,349	0,999	0,999	0,966	0,921	0,935	0,784	0,749
PC_P 35:2	0,593	0,983	0,246	0,864	0,897	0,067	0,135	0,256	0,984	0,975	0,998	0,980	0,999	0,999	0,966	0,921	0,728	0,577	0,857
PC_P 36:5	0,810	0,827	0,029	0,172	0,897	0,631	0,005	0,008	0,965	0,538	0,998	0,992	0,999	0,999	0,996	0,935	0,888	0,880	0,004
PC_P 36:2	0,449	0,828	0,049	0,620	0,897	0,087	0,961	0,053	0,917	0,797	0,998	0,605	0,999	0,999	0,976	0,921	0,603	0,567	0,633
PC_P 36:1	0,450	0,862	0,069	0,609	0,940	0,548	0,298	0,006	0,917	0,741	0,998	0,543	0,999	0,999	0,967	0,921	0,603	0,700	0,000
PC_P 37:1	0,054	0,975	0,703	0,696	0,988	0,433	0,233	0,176	0,972	0,928	0,998	0,876	0,999	0,999	0,966	0,921	0,643	0,608	0,876
PC_P 38:6	0,946	0,827	0,000	0,064	0,988	0,801	0,013	0,000	0,917	0,583	0,998	0,812	0,999	0,999	0,971	0,921	0,603	0,643	0,210
PC_P 38:5	0,464	0,757	0,085	0,923	0,988	0,225	0,505	0,195	0,932	0,554	0,998	0,903	0,999	0,999	0,966	0,932	0,614	0,675	0,650
PC_P 38:5	0,749	0,978	0,155	0,103	0,919	0,979	0,194	0,414	0,947	0,562	0,998	0,561	0,999	0,999	0,966	0,969	0,699	0,577	0,075
PC_P 38:4	0,353	0,954	0,001	0,070	0,959	0,889	0,009	0,000	0,984	0,972	0,998	0,594	0,999	0,999	0,996	0,921	0,840	0,567	0,871
PC_P 40:7	0,276	0,977	0,033	0,048	0,972	0,799	0,056	0,039	0,965	0,452	0,998	0,742	0,999	0,999	0,967	0,969	0,643	0,567	0,882
PC_P 40:5	0,396	0,828	0,000	0,214	0,960	0,629	0,056	0,000	0,917	0,993	0,998	0,413	0,999	0,999	0,967	0,921	0,603	0,608	0,084
PC_P 40:3	0,335	0,932	0,521	0,149	0,925	0,900	0,189	0,311	0,965	0,554	0,998	0,894	0,999	0,999	0,966	0,935	0,821	0,902	0,014
PC_P 42:5	0,532	0,977	0,283	0,010	0,897	0,681	0,127	0,238	0,979	0,938	0,998	0,608	0,999	0,999	0,987	0,935	0,603	0,567	0,839
PC_P 42:3	0,170	0,757	0,797	0,877	0,897	0,462	0,703	0,651	0,944	0,830	0,998	0,922	0,999	0,999	0,996	0,928	0,676	0,577	0,721
PC_P 44:7	0,939	0,939	0,828	0,076	0,929	0,081	0,117	0,793	0,965	0,752	0,998	0,256	0,999	0,999	0,996	0,932	0,603	0,577	0,282
PC_P 44:6	0,234	0,757	0,819	0,576	0,897	0,715	0,932	0,731	0,965	0,832	0,998	0,581	0,999	0,999	0,976	0,946	0,603	0,567	0,447
PC_P 44:5	0,741	0,932	0,007	0,119	0,919	0,045	0,027	0,011	0,939	0,709	0,998	0,453	0,999	0,999	0,976	0,921	0,606	0,577	0,258
PC_P 44:3	0,854	0,838	0,083	0,034	0,919	0,059	0,001	0,506	0,944	0,786	0,998	0,173	0,999	0,999	0,971	0,921	0,606	0,608	0,713
PC_P 46:8	0,315	0,757	0,332	0,687	0,897	0,229	0,408	0,123	0,965	0,554	0,998	0,593	0,999	0,999	0,984	0,931	0,870	0,906	0,185
PE 34:2	0,687	0,983	0,027	0,072	0,940	0,067	0,139	0,023	0,984	0,972	0,998	0,600	0,999	0,999	0,725	0,932	0,827	0,957	0,160
PE 34:1	0,986	0,986	0,013	0,079	0,972	0,057	0,046	0,119	0,932	0,966	0,998	0,868	0,999	0,999	0,966	0,921	0,603	0,567	0,857
PE 35:2	0,885	0,800	0,017	0,627	0,897	0,595	0,370	0,011	0,968	0,721	0,998	0,363	0,999	0,999	0,996	0,921	0,687	0,837	0,391
PE 36:5	0,353	0,977	0,324	0,791	0,929	0,163	0,198	0,523	0,965	0,618	0,998	0,921	0,999	0,999	0,984	0,921	0,606	0,567	0,168
PE 36:4	0,688	0,864	0,485	0,775	0,897	0,221	0,997	0,511	0,944	0,871	0,998	0,107	0,999	0,999	0,998	0,932	0,603	0,655	0,021
PE 36:3	0,507	0,757	0,274	0,414	0,897	0,642	0,852	0,722	0,917	0,879	0,998	0,213	0,999	0,999	0,731	0,991	0,603	0,894	0,577
PE 36:2	0,907	0,757	0,039	0,952	0,897	0,602	0,978	0,108	0,944	0,597	0,998	0,098	0,999	0,999	0,966	0,931	0,997	0,842	0,088
PE 38:6	0,948	0,961	0,646	0,235	0,919	0,045	0,297	0,270	0,973	0,882	0,998	0,680	0,999	0,999	0,971	0,921	0,957	0,577	0,816
PE 38:5	0,111	0,978	0,606	0,209	0,897	0,883	0,859	0,978	0,944	0,936	0,998	0,981	0,999	0,999	0,984	0,991	0,699	0,902	0,009
PE 38:4	0,248	0,988	0,485	0,952	0,925	0,900	0,876	0,647	0,954	0,871	0,998	0,531	0,999	0,999	0,976	0,921	0,603	0,577	0,737
PE 38:3	0,956	0,757	0,599	0,629	0,968	0,530	0,277	0,141	0,965	0,660	0,998	0,251	0,999	0,999	0,996	0,969	0,705	0,855	0,003
PE 40:7	0,559	0,977	0,002	0,006	0,919	0,117	0,001	0,034	0,984	0,756	0,998	0,669	0,999	0,999	0,984	0,921	0,669	0,567	0,745
PE 40:6	0,607	0,926	0,968	0,427	0,897	0,498	0,499	0,170	0,917	0,554	0,998	0,251	0,999	0,999	0,979	0,936	0,754	0,856	0,007
PE 40:5	0,345	0,757	0,002	0,086	0,897	0,086	0,018	0,005	0,917	0,660	0,998	0,373	0,999	0,999	0,996	0,932	0,805	0,628	0,779
PE 40:5	0,604	0,977	0,000	0,009	0,897	0,832	0,000	0,000	0,984	0,554	0,998	0,520	0,999	0,999	0,982	0,921	0,706	0,902	0,003
PE 40:4	0,849	0,983	0,518	0,874	0,897	0,101	0,839	0,392	0,965	0,579	0,998	0,396	0,999	0,999	0,966	0,921	0,728	0,604	0,284
PE_P 34:1	0,305	0,757	0,319	0,687	0,919	0,329	0,639	0,198	0,944	0,919	0,998	0,451	0,999	0,999	0,984	0,921	0,619	0,597	0,830
PE_P 35:2	0,273	0,757	0,423	0,976	0,940	0,530	0,875	0,060	0,933	0,457	0,998	0,904	0,999	0,999	0,984	0,931	0,742	0,820	0,022
PE_P 36:5	0,741	0,977	0,001	0,007	0,897	0,008	0,001	0,004	0,944	0,798	0,998	0,143	0,999	0,999	0,966	0,969	0,835	0,567	0,999
PE_P 36:4	0,855	0,961	0,617	0,282	0,897	0,123	0,561	0,793	0,965	0,574	0,998	0,682	0,999	0,999	0,996	0,988	0,776	0,923	0,006
PE_P 36:3	0,110	0,757	0,016	0,282	0,988	0,016	0,019	0,012	0,968	0,522	0,998	0,525	0,999	0,999	0,976	0,921	0,606	0,723	0,283
PE_P 36:2	0,749	0,788	0,372	0,680	0,897	0,890	0,614	0,137	0,917	0,628	0,998	0,647	0,999	0,999	0,976	0,998	0,989	0,769	0,525
PE_P 37:6	0,885	0,980	0,063	0,818	0,897	0,797	0,530	0,370	0,984	0,755	0,998	0,258	0,999	0,999	0,996	0,921	0,917	0,948	0,391
PE_P 37:5	0,599	0,892	0,150	0,805	0,897	0,360	0,622	0,265	0,933	0,565	0,998	0,316	0,999	0,999	0,996	0,921	0,603	0,820	0,208
PE_P 37:4	0,671	0,988	0,255	0,702	0,897	0,067	0,837	0,043	0,932	0,484	0,998	0,444	0,999	0,999	0,976	0,921	0,776	0,946	0,015
PE_P 38:6	0,788	0,864	0,000	0,503	0,897	0,629	0,288	0,010	0,944	0,750	0,998	0,138	0,999	0,999	0,996	0,921	0,669	0,567	0,744
PE_P 38:6	0,843	0,757	0,162	0,913	0,897	0,161	0,608	0,909	0,917	0,457	0,998	0,714	0,999	0,999	0,966	0,935	0,603	0,577	0,845
PE_P 38:5	0,473	0,957	0,060	0,744	0,919	0,166	0,696	0,012	0,924	0,921	0,998	0,827	0,999	0,999	0,744	0,921	0,643	0,739	0,305
PE_P 38:4	0,815	0,926	0,863	0,567	0,910	0,719	0,471	0,948	0,974	0,582	0,998	0,667	0,999	0,999	0,987	0,932	0,603	0,567	0,308
PE_P 38:4	0,106	0,986	0,773	0,884	0,919	0,912	0,876	0,302	0,933	0,632	0,998	0,349	0,999	0,999	0,996	0,921	0,761	0,855	0,770
PE_P 38:3	0,397	0,986	0,305	0,584	0,983	0,194	0,649	0,126	0,932	0,725	0,998	0,785	0,999	0,999	0,976	0,969	0,603	0,596	0,772
PE_P 39:6	0,380	0,961	0,273	0,998	0,897	0,995	0,966	0,035	0,965	0,898	0,998	0,989	0,999	0,999	0,966	0,921	0,603	0,567	0,744
PE_P 40:8	0,647	0,977	0,040	0,485	0,988	0,621	0,050	0,001	0,952	0,931	0,998	0,605	0,999	0,999	0,966	0,921	0,643	0,577	0,319
PE_P 40:7	0,239	0,757	0,014	0,086	0,897	0,367	0,153	0,057	0,933	0,879	0,998	0,167	0,999	0,999	0,966	0,975	0,603	0,567	0,981
PE_P 40:6	0,538	0,950	0,001	0,167	0,897	0,028	0,014	0,040	0,984	0,750	0,998	0,060	0,999	0,999	0,967	0,969	0,603	0,577	0,618
PE_P 40:4	0,673	0,977	0,609	0,218	0,988	0,405	0,622	0,731	0,932	0,558	0,998	0,372	0,999	0,999	0,996	0,991	0,669	0,792	0,012
PE_P 42:7	0,348	0,988	0,475	0,179	0,937	0,448	0,726	0,354	0,965	0,810	0,998	0,506	0,999	0,999	0,996	0,991	0,603	0,608	0,788
PE_P 42:5	0,045	0,987	0,468	0,874	0,897	0,015	0,243	0,154	0,944	0,568	0,998	0,948	0,999	0,999	0,966	0,334	0,603	0,792	0,936
PE_P 44:8	0,609	0,838	0,006	0,061	0,897	0,000	0,000	0,076	0,917	0,451	0,998	0,508	0,999	0,999	0,967	0,921	0,637	0,567	0,509
PE_P 44:7	0,775	0,977	0,504	0,961	0,897	0,181	0,806	0,095	0,922	0,724	0,998	0,854	0,999	0,999	0,971	0,951	0,870	0,655	0,264
TAG 48:5	0,956	0,977	0,002	0,150	0,988	0,801	0,023	0,000	0,965	0,973	0,998	0,217	0,999	0,999	0,966	0,991	0,603	0,577	0,245
TAG 48:4	0,788	0,954	0,319	0,460	0,897	0,405	0,354	0,185	0,965	0,451	0,998	0,130	0,999	0,999	0,968	0,921	0,603	0,596	0,726
TAG 48:3	0,696	0,961	0,282	0,488	0,919	0,901	0,101	0,019	0,968	0,652	0,998	0,167	0,999	0,999	0,966	0,921	0,767	0,608	0,667
TAG 48:1	0,788	0,950	0,001	0,191	0,919	0,629	0,005	0,002	0,917	0,451	0,998	0,695	0,999	0,999	0,996	0,935	0,809	0,902	0,045
TAG 48:0	0,255	0,977	0,007	0,299	0,897	0,925	0,857	0,001	0,974	0,557	0,998	0,277	0,999	0,999	0,966	0,935	0,603	0,608	0,038

Supplementary material

TAG 49:3	0,660	0,986	0,139	0,772	0,897	0,900	0,937	0,056	0,933	0,575	0,998	0,876	0,999	0,999	0,568	0,921	0,603	0,567	0,565
TAG 49:1	0,513	0,961	0,005	0,169	0,897	0,535	0,726	0,000	0,990	0,457	0,998	0,472	0,999	0,999	0,966	0,991	0,670	0,987	0,013
TAG 49:0	0,667	0,983	0,966	0,645	0,988	0,986	0,909	0,388	0,955	0,631	0,998	0,217	0,999	0,999	0,996	0,921	0,603	0,898	0,563
TAG 50:6	0,612	0,990	0,746	0,777	0,897	0,069	0,230	0,812	0,965	0,448	0,998	0,427	0,999	0,999	0,966	0,935	0,801	0,985	0,013
TAG 50:5	0,238	0,977	0,945	0,772	0,919	0,188	0,887	0,417	0,984	0,606	0,998	0,566	0,999	0,999	0,996	0,921	0,620	0,567	0,160
TAG 50:4	0,110	0,988	0,839	0,174	0,897	0,512	0,859	0,024	0,944	0,554	0,998	0,107	0,999	0,999	0,967	0,921	0,643	0,567	0,009
TAG 50:3	0,535	0,986	0,076	0,051	0,960	0,636	0,672	0,270	0,973	0,724	0,998	0,645	0,999	0,999	0,966	0,935	0,603	0,803	0,001
TAG 50:2	0,255	0,986	0,015	0,486	0,897	0,815	0,862	0,001	0,990	0,457	0,998	0,518	0,999	0,999	0,967	0,921	0,886	0,567	0,999
TAG 50:0	0,600	0,988	0,002	0,062	0,897	0,068	0,002	0,003	0,991	0,457	0,998	0,169	0,999	0,999	0,968	0,921	0,761	0,604	0,318
TAG 51:4	0,720	0,852	0,586	0,777	0,897	0,520	0,671	0,225	0,944	0,451	0,998	0,669	0,999	0,999	0,401	0,955	0,606	0,792	0,001
TAG 51:3	0,831	0,864	0,640	0,582	0,921	0,921	0,809	0,710	0,991	0,725	0,998	0,560	0,999	0,999	0,660	0,935	0,603	0,567	0,763
TAG 51:2	0,627	0,977	0,000	0,009	0,897	0,924	0,064	0,000	0,965	0,507	0,998	0,168	0,999	0,999	0,996	0,969	0,643	0,757	0,763
TAG 52:7	0,369	0,932	0,162	0,025	0,919	0,313	0,095	0,429	0,933	0,902	0,998	0,386	0,999	0,999	0,976	0,969	0,925	0,762	0,097
TAG 51:0	0,219	0,988	0,001	0,031	0,897	0,683	0,055	0,000	0,939	0,590	0,998	0,260	0,999	0,999	0,306	0,921	0,699	0,567	0,896
TAG 52:6	0,238	0,864	0,354	0,077	0,897	0,115	0,062	0,836	0,984	0,756	0,998	0,256	0,999	0,999	0,996	0,997	0,978	0,577	0,775
TAG 52:5	0,093	0,977	0,000	0,009	0,959	0,521	0,019	0,000	0,955	0,563	0,998	0,138	0,999	0,999	0,966	0,921	0,721	0,567	0,883
TAG 52:4	0,928	0,986	0,465	0,259	0,897	0,991	0,470	0,129	0,968	0,502	0,998	0,941	0,999	0,999	0,996	0,921	0,884	0,567	0,102
TAG 52:2	0,739	0,979	0,085	0,584	0,897	0,013	0,859	0,069	0,953	0,505	0,998	0,500	0,999	0,999	0,989	0,969	0,933	0,567	0,125
TAG 52:1	0,276	0,977	0,048	0,019	0,925	0,315	0,272	0,014	0,917	0,448	0,998	0,107	0,999	0,999	0,458	0,937	0,643	0,844	0,007
TAG 53:6	0,274	0,838	0,089	0,778	0,919	0,889	0,506	0,008	0,940	0,484	0,998	0,525	0,999	0,999	0,744	0,921	0,603	0,567	0,890
TAG 53:4	0,135	0,924	0,315	0,637	0,897	0,409	0,490	0,129	0,965	0,921	0,998	0,097	0,999	0,999	0,966	0,921	0,736	0,628	0,688
TAG 53:3	0,612	0,986	0,000	0,041	0,897	0,275	0,027	0,000	0,964	0,448	0,998	0,120	0,999	0,999	0,976	0,932	0,606	0,867	0,001
TAG 54:5	0,783	0,986	0,007	0,022	0,897	0,015	0,023	0,000	0,965	0,457	0,998	0,277	0,999	0,999	0,966	0,965	0,660	0,608	0,717
TAG 54:4	0,868	0,977	0,000	0,010	0,897	0,011	0,001	0,000	0,944	0,448	0,998	0,183	0,999	0,999	0,966	0,932	0,761	0,577	0,607
TAG 54:2	0,766	0,979	0,640	0,183	0,897	0,236	0,709	0,128	0,372	0,484	0,998	0,135	0,999	0,999	0,514	0,993	0,700	0,837	0,059
TAG 55:8	0,957	0,977	0,140	0,284	0,937	0,282	0,709	0,031	0,944	0,457	0,998	0,745	0,999	0,999	0,589	0,921	0,856	0,567	0,770
TAG 55:7	0,380	0,986	0,002	0,025	0,919	0,209	0,022	0,000	0,917	0,457	0,998	0,241	0,999	0,999	0,649	0,991	0,603	0,820	0,092
TAG 55:6	0,255	0,986	0,000	0,029	0,919	0,235	0,008	0,000	0,917	0,507	0,998	0,138	0,999	0,999	0,424	0,921	0,603	0,946	0,025
TAG 55:5	0,802	0,988	0,995	0,811	0,897	0,779	0,866	0,856	0,917	0,794	0,998	0,451	0,999	0,999	0,225	0,921	0,603	0,608	0,449
TAG 56:9	0,649	0,986	0,001	0,091	0,897	0,203	0,004	0,001	0,965	0,448	0,998	0,385	0,999	0,999	0,966	0,932	0,782	0,577	0,561
TAG 56:7	0,956	0,988	0,020	0,225	0,897	0,028	0,002	0,003	0,917	0,707	0,998	0,995	0,999	0,999	0,589	0,931	0,603	0,608	0,885
TAG 56:6	0,867	0,980	0,773	0,178	0,897	0,384	0,954	0,896	0,944	0,502	0,998	0,130	0,999	0,999	0,996	0,981	0,606	0,987	0,876
TAG 56:5	0,913	0,986	0,095	0,378	0,940	0,049	0,462	0,032	0,965	0,484	0,998	0,669	0,999	0,999	0,630	0,921	0,776	0,956	0,204
TAG 56:4	0,955	0,977	0,391	0,414	0,897	0,248	0,882	0,129	0,917	0,448	0,998	0,526	0,999	0,999	0,244	0,921	0,603	0,567	0,815
TAG 57:8	0,594	0,988	0,002	0,590	0,897	0,236	0,158	0,000	0,924	0,451	0,998	0,304	0,999	0,999	0,424	0,921	0,606	0,615	0,876
TAG 57:7	0,330	0,986	0,004	0,037	0,897	0,816	0,103	0,000	0,917	0,574	0,998	0,332	0,999	0,999	0,161	0,921	0,928	0,746	0,744
TAG 58:10	0,998	0,826	0,010	0,618	0,897	0,195	0,102	0,211	0,968	0,606	0,998	0,188	0,999	0,999	0,966	0,921	0,865	0,648	0,745
TAG 58:9	0,457	0,938	0,709	0,856	0,897	0,078	0,236	0,464	0,984	0,451	0,998	0,343	0,999	0,999	0,966	0,921	0,645	0,698	0,159
TAG 58:3	0,759	0,977	0,238	0,142	0,897	0,078	0,465	0,244	0,933	0,820	0,998	0,538	0,999	0,999	0,966	0,932	0,603	0,664	0,997
TAG 40:1	0,831	0,816	0,480	0,846	0,940	0,964	0,867	0,276	0,944	0,937	0,998	0,671	0,999	0,999	0,966	0,921	0,997	0,567	0,154
TAG 40:0	0,733	0,957	0,063	0,302	0,897	0,215	0,742	0,012	0,968	0,488	0,998	0,647	0,999	0,999	0,966	0,969	0,603	0,762	0,022
TAG 41:1	0,788	0,986	0,691	0,706	0,897	0,761	0,829	0,892	0,917	0,565	0,998	0,968	0,999	0,999	0,984	0,921	0,940	0,978	0,356
TAG 41:0	0,245	0,950	0,720	0,666	0,897	0,440	0,875	0,984	0,939	0,451	0,998	0,107	0,999	0,999	0,563	0,946	0,603	0,955	0,015
TAG 42:2	0,633	0,986	0,092	0,668	0,897	0,360	0,776	0,071	0,917	0,755	0,998	0,894	0,999	0,999	0,966	0,921	0,603	0,577	0,834
TAG 42:1	0,492	0,977	0,066	0,666	0,897	0,913	0,490	0,011	0,933	0,632	0,998	0,605	0,999	0,999	0,588	0,969	0,637	0,869	0,022
TAG 42:0	0,797	0,977	0,044	0,301	0,897	0,057	0,441	0,009	0,952	0,458	0,998	0,645	0,999	0,999	0,856	0,969	0,705	0,577	0,013
TAG 43:1	0,239	0,757	0,026	0,134	0,897	0,193	0,240	0,009	0,968	0,448	0,998	0,161	0,999	0,999	0,996	0,921	0,643	0,567	0,445
TAG 44:2	0,854	0,986	0,101	0,392	0,897	0,405	0,508	0,225	0,955	0,448	0,998	0,479	0,999	0,999	0,966	0,921	0,779	0,567	0,558
TAG 44:1	0,946	0,909	0,041	0,711	0,959	0,683	0,153	0,005	0,476	0,583	0,998	0,526	0,999	0,999	0,976	0,932	0,766	0,957	0,447
TAG 44:0	0,599	0,986	0,091	0,625	0,897	0,889	0,795	0,026	0,952	0,755	0,998	0,507	0,999	0,999	0,562	0,969	0,825	0,762	0,429
TAG 45:2	0,742	0,977	0,082	0,415	0,897	0,149	0,421	0,025	0,932	0,448	0,998	0,385	0,999	0,999	0,996	0,921	0,603	0,567	0,145
TAG 46:4	0,513	0,864	0,075	0,877	0,897	0,991	0,069	0,080	0,950	0,457	0,998	0,730	0,999	0,999	0,996	0,993	0,606	0,985	0,041
TAG 46:3	0,660	0,986	0,931	0,812	0,902	0,924	0,670	0,216	0,955	0,457	0,998	0,200	0,999	0,999	0,984	0,921	0,894	0,985	0,173
TAG 46:1	0,093	0,977	0,182	0,179	0,958	0,170	0,012	0,589	0,974	0,457	0,998	0,322	0,999	0,999	0,996	0,921	0,641	0,648	0,876
TAG 46:0	0,385	0,986	0,175	0,283	0,968	0,971	0,298	0,405	0,944	0,502	0,998	0,754	0,999	0,999	0,857	0,969	0,964	0,608	0,921
TAG 47:3	0,411	0,954	0,228	0,975	0,897	0,411	0,273	0,026	0,944	0,457	0,998	0,148	0,999	0,999	0,976	0,935	0,650	0,675	0,001
TAG 47:2	0,534	0,986	0,505	0,756	0,897	0,530	0,917	0,760	0,968	0,882	0,998	0,744	0,999	0,999	0,998	0,921	0,970	0,628	0,135

AP=Antipsychotics

AD=Antidepressants

T=Tranquilizers

MS=Mood stabilizers

BP=Bipolar disorder (vs. control)

S=Schizophrenia

Q=Quetiapine

A=Aripiprazole

O=Olanzapine

C=Clozapine

R=Risperidone

H=Haloperidol

P=Paliperidone

Z=Zisprasidone

CO=Receptor profile (C&O)

ZPR=Receptor profile (Z&P&R)

BPS=Bipolar disorder (vs. S)

Supplementary Table S4: Results enrichment analysis lipidr

contrast	set	pval	padj	log2err	ES	NES	size
Alda	Class_CAR	5,67E-09	3,80E-07	0,76146	0,85283	2,48573	18
Alda	Class_LPE	9,71E-06	0,00023	0,59333	-0,90423	-2,09403	9
Alda	Class_PE	1,02E-05	0,00023	0,59333	-0,62957	-2,04002	39
Alda	Class_dCer	5,68E-05	0,00095	0,55733	-0,75743	-2,04175	17
Alda	Class_LPC	0,005598	0,04168	0,40702	-0,62607	-1,70021	18
Lithium	Class_dSM	3,14E-12	2,10E-10	0,89867	-0,83177	-2,77990	31
Lithium	Class_TAG	6,72E-05	0,00225	0,53843	0,51449	1,89394	69
Lithium	Class_CAR	0,00024	0,00536	0,51885	-0,71626	-2,06605	18
Lithium	Class_LPE	0,00182	0,03055	0,45506	0,78506	1,79907	9
Antipsychotics	Class_TAG	2,38E-19	1,59E-17	1,13309	0,77977	2,88371	69
Antipsychotics	Class_PC	1,65E-10	5,52E-09	0,82666	-0,53597	-2,50063	90
Antipsychotics	Class_CAR	1,96E-08	4,38E-07	0,73376	-0,83310	-2,62895	18
Antipsychotics	Class_dCer	0,00012	0,00197	0,53843	0,71799	1,98812	17
Antipsychotics	Class_FA	0,00027	0,00359	0,49849	-0,45380	-1,91480	52
Antipsychotics	Class_DAG	0,00270	0,02259	0,43171	0,80384	1,73633	7
Antidepressants	Class_TAG	9,59E-22	6,42E-20	1,20398	0,80685	2,94503	69
Antidepressants	Class_PC	1,02E-11	3,43E-10	0,87533	-0,57743	-2,57354	90
Antidepressants	Class_LPC	0,00102	0,01706	0,45506	-0,64582	-1,98335	18
Antidepressants	Class_dCer	0,00302	0,03370	0,43171	0,65130	1,81817	17
Tranquilizers	Class_TAG	1,52E-09	1,02E-07	0,78819	0,71492	2,16397	69
Tranquilizers	Class_CAR	8,68E-08	2,91E-06	0,70498	-0,85798	-2,44810	18
Tranquilizers	Class_dSM	0,00076	0,01276	0,47727	-0,59439	-1,89722	31
Bipolar disorder	Class_dCer	5,79E-07	3,88E-05	0,65944	0,85304	2,31986	17
Bipolar disorder	Class_PC	2,13E-05	0,00060	0,57561	-0,52222	-1,88438	90
Bipolar disorder	Class_TAG	0,00019	0,00313	0,51885	0,51300	1,81361	69
Bipolar disorder	Class_FA	0,00351	0,03918	0,43171	-0,51225	-1,68856	52
Schizophrenia	Class_TAG	5,09E-22	3,41E-20	1,21254	0,81523	2,97572	69
Schizophrenia	Class_PC	8,13E-09	2,72E-07	0,74774	-0,53120	-2,45042	90
Schizophrenia	Class_FA	1,28E-07	2,86E-06	0,69013	-0,58618	-2,47027	52
Schizophrenia	Class_CAR	1,73E-07	2,90E-06	0,69013	-0,81235	-2,52548	18
Schizophrenia	Class_dCer	1,23E-05	0,00016	0,59333	0,76657	2,12146	17
Bipolar disorder vs. SCZ	Class_TAG	9,78E-16	6,55E-14	1,01754	-0,77118	-2,59048	69
Bipolar disorder vs. SCZ	Class_CAR	2,04E-05	0,00068	0,57561	0,78666	2,24847	18
Bipolar disorder vs. SCZ	Class_dSM	0,00035	0,00581	0,49849	0,62412	2,01587	31
Bipolar disorder vs. SCZ	Class_FA	0,00068	0,00910	0,47727	0,50689	1,82583	52
Bipolar disorder vs. SCZ	Class_PC	0,00583	0,04950	0,40702	0,36963	1,48562	90
Quetiapine	Class_TAG	1,13E-09	7,54E-08	0,78819	0,65562	2,29723	69
Quetiapine	Class_CAR	1,73E-08	5,80E-07	0,73376	-0,84118	-2,62477	18
Quetiapine	Class_FA	2,98E-07	6,66E-06	0,67496	-0,57559	-2,33632	52
Quetiapine	Class_PE	0,00049	0,00824	0,47727	0,57966	1,85309	39
Olanzapine	Class_TAG	5,81E-11	3,89E-09	0,85134	0,69137	2,32350	69
Olanzapine	Class_DAG	6,85E-08	2,29E-06	0,70498	-0,96359	-2,24200	7
Olanzapine	Class_PE	7,59E-07	1,70E-05	0,65944	0,69508	2,15708	39
Olanzapine	Class_PC	9,21E-06	0,00015	0,59333	-0,41689	-1,92169	90
Olanzapine	Class_FA	4,15E-05	0,00056	0,55733	-0,49540	-2,06143	52
Aripiprazole	Class_TAG	1,37E-22	9,21E-21	1,22950	-0,82646	-2,97682	69
Aripiprazole	Class_FA	1,12E-10	3,76E-09	0,83909	0,69975	2,70645	52
Aripiprazole	Class_PC	3,65E-06	8,15E-05	0,62726	0,46886	2,00661	90
Clozapine	Class_PC	4,64E-11	3,11E-09	0,85134	-0,56056	-2,67692	90
Clozapine	Class_PE	1,08E-06	3,61E-05	0,64355	0,63514	2,26090	39
Clozapine	Class_TAG	2,06E-06	4,60E-05	0,62726	0,53782	2,16948	69
Clozapine	Class_dSM	4,35E-06	7,29E-05	0,61053	-0,62852	-2,38363	31

Risperidone	Class_TAG	3,17E-13	2,12E-11	0,93260	0,76355	2,38811	69
Risperidone	Class_CAR	7,44E-05	0,00249	0,53843	-0,73041	-2,09843	18
Risperidone	Class_dCer	0,00089	0,01998	0,47727	-0,70300	-1,98431	17
Haloperidol	Class_PC	1,08E-05	0,00036	0,59333	-0,46321	-1,88158	90
Haloperidol	Class_TAG	5,50E-06	0,00036	0,61053	0,55977	1,97229	69
Haloperidol	Class_dSM	0,00025	0,00332	0,49849	-0,59064	-1,92784	31
Haloperidol	Class_dCer	0,00122	0,01363	0,45506	0,68575	1,85179	17
Paliperidone	Class_DAG	5,44E-08	3,64E-06	0,71951	-0,96359	-2,10639	7
Paliperidone	Class_PC	1,76E-06	5,88E-05	0,64355	0,53392	2,05036	90
Paliperidone	Class_FA	2,79E-05	0,00062	0,57561	-0,55494	-2,05357	52
Paliperidone	Class_TAG	0,00058	0,00775	0,47727	0,47643	1,74173	69
Paliperidone	Class_LPC	0,00507	0,04848	0,40702	-0,62365	-1,77462	18
Zisprasidone	Class_dSM	4,50E-08	3,02E-06	0,71951	0,71136	2,44228	31
Zisprasidone	Class_PE	0,00084	0,01411	0,47727	-0,53534	-1,89927	39
Zisprasidone	Class_LPC	0,00343	0,03285	0,43171	-0,61832	-1,83194	18
Valproic acid	Class_TAG	1,45E-05	0,00097	0,59333	0,66069	1,98750	69
Valproic acid	Class_FA	3,27E-05	0,00109	0,55733	-0,54606	-1,96044	52
Venlafaxine	Class_PC	1,38E-05	0,00093	0,59333	-0,48748	-1,96269	90
Venlafaxine	Class_LPC	4,97E-05	0,00167	0,55733	-0,73070	-2,15156	18
Venlafaxine	Class_DAG	0,00058	0,00970	0,47727	0,84598	1,97424	7
Venlafaxine	Class_PE	0,00358	0,03422	0,43171	0,44188	1,71183	39
Sertraline	Class_TAG	8,57E-11	5,74E-09	0,83909	-0,62862	-2,62002	69
Sertraline	Class_FA	3,99E-07	1,34E-05	0,67496	0,64926	2,19643	52
Sertraline	Class_dSM	2,22E-05	0,00050	0,57561	-0,63365	-2,22238	31
Sertraline	Class_CAR	5,47E-05	0,00092	0,55733	0,76863	2,10262	18
Sertraline	Class_LPE	0,00106	0,01011	0,45506	0,80704	1,83378	9
Sertraline	Class_LPC	0,00189	0,01580	0,45506	0,68576	1,87593	18
ZPR	Class_TAG	4,75E-07	3,18E-05	0,67496	-0,55215	-2,24062	69
ZPR	Class_dSM	1,31E-05	0,00044	0,59333	0,64741	2,19192	31
ZPR	Class_CAR	0,00015	0,00255	0,51885	-0,70255	-2,08035	18
ZPR	Class_PC	0,00286	0,03188	0,43171	0,39621	1,61331	90
CO	Class_TAG	8,31E-27	5,57E-25	1,34223	0,85455	2,85410	69
CO	Class_PC	1,91E-17	6,40E-16	1,07687	-0,65940	-3,16535	90
CO	Class_dSM	1,24E-05	0,00028	0,59333	-0,61355	-2,42576	31
CO	Class_CAR	0,00053	0,00889	0,47727	0,70316	1,86732	18
CO	Class_PE	0,00121	0,01616	0,45506	0,56458	1,74410	39
CO	Class_LPC	0,00394	0,04397	0,40702	-0,57349	-1,86430	18
Mirtazapine	Class_TAG	4,59E-09	3,07E-07	0,76146	0,64222	2,25422	69
Mirtazapine	Class_CAR	5,72E-06	0,00019	0,61053	-0,80225	-2,33067	18
Mirtazapine	Class_PC	0,00025	0,00419	0,49849	-0,41658	-1,73848	90
Mirtazapine	Class_dSM	0,00077	0,01031	0,47727	-0,58578	-1,91813	31
Mirtazapine	Class_LPC	0,00445	0,04259	0,40702	0,65284	1,76245	18
Bupropion	Class_TAG	3,32E-13	2,22E-11	0,93260	-0,69710	-2,66713	69
Bupropion	Class_PC	0,00020	0,00666	0,51885	0,41823	1,74359	90
Bupropion	Class_PE	0,00030	0,00679	0,49849	-0,55646	-1,90050	39
Bupropion	Class_dSM	0,00112	0,01503	0,45506	0,55606	1,85955	31
Escitalopram	Class_FA	2,21E-09	1,48E-07	0,77494	0,69292	2,44638	52
Escitalopram	Class_TAG	1,27E-06	4,26E-05	0,64355	-0,60500	-2,09856	69
Escitalopram	Class_dSM	0,00051	0,00847	0,47727	-0,64150	-1,93649	31
SSRI	Class_PC	2,89E-08	1,94E-06	0,73376	-0,55080	-2,26789	90
SSRI	Class_CAR	5,65E-05	0,00126	0,55733	0,76715	1,99070	18
SSRI	Class_dSM	0,00106	0,01183	0,45506	-0,58560	-1,94703	31
SSRI	Class_DAG	0,00149	0,01416	0,45506	0,85714	1,74604	7

SNRI	Class_TAG	7,18E-11	4,81E-09	0,83909	0,63314	2,57333	69
SNRI	Class_CAR	1,70E-07	5,68E-06	0,69013	-0,83823	-2,33550	18
SNRI	Class_LPC	2,46E-05	0,00055	0,57561	-0,76591	-2,13400	18
TCA	Class_TAG	9,99E-21	6,69E-19	1,17789	0,80574	2,88181	69
TCA	Class_dSM	2,33E-07	7,80E-06	0,69013	-0,69488	-2,49713	31
TCA	Class_dCer	1,69E-05	0,00038	0,57561	-0,75722	-2,32840	17
TCA	Class_FA	0,00022	0,00375	0,51885	-0,48376	-1,94405	52
TCA	Class_CAR	0,00120	0,01339	0,45506	0,67275	1,83509	18
Lamotrigine	Class_TAG	9,73E-15	6,52E-13	0,98655	-0,74441	-2,57006	69
Lamotrigine	Class_PC	7,41E-10	2,48E-08	0,80122	0,56220	2,39784	90
Lamotrigine	Class_PE	9,41E-06	0,00021	0,59333	0,60006	2,21769	39
Lamotrigine	Class_LPCO	0,00340	0,03793	0,43171	0,82402	1,78442	6

16 Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Affidavit

Weber, Annika Lucie

Surname, first name

I hereby declare, that the submitted thesis entitled:

Lipidomic analysis of medication classes in individuals with psychosis spectrum disorders

is my own work. I have only used the sources indicated and have not made unauthorised use of services of a third party. Where the work of others has been quoted or reproduced, the source is always given.

I further declare that the dissertation presented here has not been submitted in the same or similar form to any other institution for the purpose of obtaining an academic degree.

München, 16.12.2024

Place, Date

Annika Weber

Signature doctoral candidate

17 Confirmation of congruency

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Dekanat Medizinische Fakultät
Promotionsbüro

Confirmation of congruency between printed and electronic version of the doctoral thesis

Weber, Annika Lucie

Surname, first name

I hereby declare that the electronic version of the submitted thesis, entitled:

Lipidomic analysis of medication classes in individuals with psychosis spectrum disorders

is congruent with the printed version both in content and format.

Munich, 16.12.2024

Place, Date

Annika Weber

Signature doctoral candidate