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**Detection of salivary biomarkers: quali-quantitative analysis of
endogenous and exogenous compounds within oral fluid and
comparison with conventional matrices**

03/CHEM-07- Pharmaceutical Chemistry

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ABSTRACT

The rapid development of omics sciences has revolutionized biomedical research by enabling a comprehensive investigation of biological systems through high-throughput technologies. Among these disciplines, metabolomics and lipidomics provide a functional snapshot of cellular processes by analyzing small molecules and lipid species involved in metabolism, thereby bringing the gap between genotype and phenotype. This PhD research employed untargeted metabolomic and lipidomic approaches based on high-resolution liquid chromatography coupled to time of flight mass spectrometry (HPLC-QTOF-MS) to explore the molecular composition of different human biofluids (oral fluid and whole blood) and to identify potential biomarkers associated with physiological and pathological conditions.

The main objective of the study was to evaluate how the metabolic and lipidomic profiles are modulated under different physiological and pathological states. Initially, salivary metabolic and lipidomic profiles were characterized in healthy individuals and compared with blood-derived profiles under baseline physiological conditions. This comparative analysis provided insights into the molecular overlap between the two matrices and assessed the potential of saliva as a non-invasive diagnostic alternative to blood. The research was then extended to three applied context: aging, Alzheimer's disease and substance addiction. In the aging study, metabolic and lipidomic signatures were investigated to identify molecules linked to biological aging trajectories and potential longevity markers. Within the AD cohort salivary metabolic and lipidomic alterations were compared between patients and cognitively healthy controls, revealing distinct patterns in glycerophospholipids, sphingolipids, fatty acids and sterol lipids, as well as two metabolites potentially associated with neurodegenerative processes. Finally, in the addiction-focused analyses, the study explored metabolic and lipidomic perturbations related to chronic exposure to psychoactive substances, providing biochemical evidence of systemic dysregulation.

Advanced statistical and chemometric analyses, including volcano plots, partial least squares-discriminant analysis (PLS-DA), variable importance in projection (VIP= score plots and heatmaps were applied to extract biologically relevant information from high dimensional datasets. The integration of bioinformatic platforms such as MS-DIAL and MetaboAnalyst enables robust data processing compound annotation and pathway enrichment analysis.

Overall, this study underscores the potential of salivary metabolomics and lipidomics for translational applications in clinical, forensic and physiological research. The findings provide reference data on the metabolic and lipidomic composition of oral fluid, demonstrate its suitability as a diagnostic biofluid and propose molecular candidates that may serve as biomarkers for aging, Alzheimer's disease and drugs addiction. Future studies with larger cohorts and integrated multi-omics approaches will be essential to validate these findings and further advance personalized, non-invasive diagnostic strategies for human health and disease.

1. INTRODUCTION

1.1 Omics

Omics-based research represents a branch of both analytical and biological sciences whose primary purpose is to detect, characterize and quantify large pools of bioactive molecules simultaneously basing on their biochemical pathway and function in an organism or group of organisms, considering the entire system rather than individuals parts. This field provides a high-throughput screening method to efficiently and quickly discover detailed biological information on human diseases. This area of research includes: genomics, epigenomics, transcriptomics, proteomics, metabolomics, single-cell omics, spatial transcriptomics, radiomics and microbiomics; these analyses can study DNA sequences, gene transcripts, proteins and large sets of metabolites. These kinds of approaches are built on the fact that the human body or any other complex system is better understood if considered as whole¹. Data obtained from different omics techniques can be used not only to elucidate the intricate processes that normally and physiologically occur in the human body, but also to identify differentially expressed disease progression. Omics technologies have significantly advanced and paved the way for biomarker discovery, enabling a deeper understanding of pathological pathways and facilitating the identification of potentially reliable molecules for screening, diagnosis and prognosis. These insights help to clarify which biological processes or pathways differ between diseased and healthy states, contributing to the development of more targeted and effective medical interventions. Together, omics-based research offer a comprehensive view of the biological state and changes that occur in an organism, especially during a disease. Integrating data from these different sources allows researchers to build a more complete model of disease mechanisms, highlighting their indispensable role in advancing medical science and improving patient care.

Figure 1 lists some applications of omics in diseases (liver cancer, lung cancer, ovarian cancer and malignant lymphocytic cancer) and neurodegenerations (AD, PD and ALS). The figure also shows other applications, such as aging and screening of natural drugs (natural compounds obtained from flowers, seeds or plant rootstocks). The data obtained from these analyses are subsequently studied using several techniques such as: differential expression analysis, correlation analysis and network construction, and then machine learning is used to obtain diagnostic biomarkers or therapeutic targets². Biomarkers are not only useful for investigating pathogenesis at the molecular level, but also have unique advantages for assessing early and low-grade damage, playing a key role in the diagnosis and prognosis of clinical diseases and they can also be useful for determining a pharmacologic responses to a therapeutic intervention³. Usually, the determination of biomarkers requires the use of high-throughput omics methods to analyze large-scale clinical samples, comparing them with control samples, followed by statistical analysis to identify significant

differential molecules (genes, proteins or metabolites) and finally to identify target biomarkers by a series of complex bioinformatic analyses.

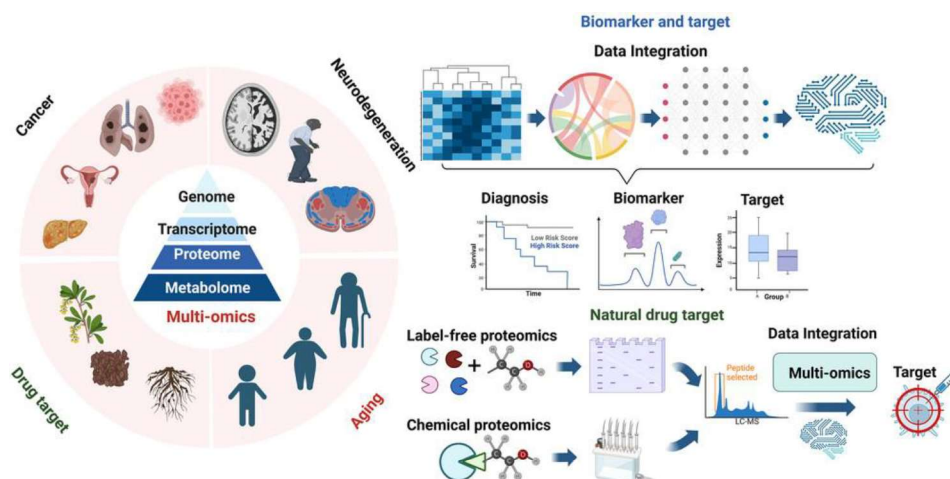


Figure 1. The application of multi-omics in disease, aging and natural drug target identification²

In the literature, there are several works in which omics science has been successfully applied to the search for biomarkers related to various cancers, for example: large B-cell Lymphoma⁴, rectal cancer⁵, breast cancer⁶, ovarian cancer^{7,8}, pancreatic cancer⁹ and prostate cancer¹⁰. Furthermore, these techniques are also applied to find biomarkers for other diseases, such as stroke¹¹, obesity^{12,13}, cardiovascular diseases¹⁴, Alzheimer's disease¹⁵, diabetes¹⁶ and so on.

In the following paragraphs, the most commonly used omics techniques will be described, explaining their applicability for understanding biological systems.

1.1.1 Genomics

Genomics is the application of omics to entire genomes, which aims to collect traits and quantify all genes in an organism, to discover their interrelationships and their influence on the organism. Few years ago, scientists used to study single genes at time. Today, technological innovations make it possible to sequence the entire genome quickly and at a reasonable cost. The possibility of sequencing DNA, the nucleic acid responsible for storing genetic information in almost all living organisms, has revolutionized biological research and led to great advances in the area of research and development¹⁷. A typical approach in genomics is genome-wide association studies (GWAS), which analyze hundreds of thousands of genetic variants in different genomes to find something statistically associated with a specific disease or treatment. In GWAS studies, millions of genetic variants are tested to identify associations between genotype and phenotype. Although GWAS can identify new disease-associated genes, biological pathways and translate these findings into clinical

treatments, most of the variants and acquired genes have no direct biological relevance to the disease^{18,19}.

Genomics has also made several changes in the pharmaceutical industry, possibly enabling the identification of protein targets and accelerating drug discovery^{20,21}. In the drug discovery concept, genes have been classified as disease genes, disease-modifying genes and genes that can be used as drugs²². This field has seen rapid expansion, with models and methods developed to analyze genome rearrangements, gene duplication, phylogenetic networks and gene clustering.

1.1.2 Transcriptomics

Transcriptomics refers to the study of gene expression patterns of the entire set of RNA molecules in an individual. Sequencing technologies (e.g. Illumina, Ion Torrent, PacBio SMRT and Oxford Nanopore) make it possible to quantify the number of times a given sequence is present in a sample.

First, in transcriptomics analyses, RNA is isolated from tissue samples and then prepared to enrich specific types of RNA such as: messenger RNA (mRNA), small RNA (sRNA), long non-coding RNA (lncRNA), circular RNA (circRNA), etc. The data obtained represent a snapshot of the abundance of enriched RNAs from the set of cells in the sample. These analyses provide an average representation of gene expression within a cell population²³.

Different RNA types are associated with different diseases, such as diabetes, cancer and others^{24,25}. In particular, circular RNAs have been linked to cardiovascular diseases²⁶, central nervous system (CNS) diseases²⁷ and cancer. Currently, with the evolution of technologies, single-cell RNA sequencing (scRNA-seq) is gaining great attention, as it allows the detection of transcriptomes of specific cell types involved in diseases such as cancer²⁸, Alzheimer's²⁹ and others. This technology helps to understand the transcriptome status of heterogeneous cell populations. For example, single-cell transcriptome analysis identified distinct transcriptional responses in lung cancer (CCL) cell lines, distinguishing those that were sensitive from those resistant to receptor tyrosine kinase inhibitors. The study also revealed specific transcriptional modules that may be linked to early drug resistance³⁰.

1.1.3 Proteomics

Proteomics studies the interactions, functions, compositions and structures of proteins and their cellular activities. This technique provides a deeper understanding of the structure and function of the organism than genomics, but, it is more complicated than omics techniques described above, because the expression of proteins varies with time and environmental conditions^{31,32}. Proteomics is a multi-step analysis where each step must be very well controlled to avoid non-biological factors

interfering with protein interaction and expression; sample preparation is the crucial step to obtain reliable, accurate and reproducible results³³.

Large-scale protein analysis can be performed using various techniques, including mass spectrometry, affinity-based proteomics, protein chips, and reverse-phase protein microarrays^{34,35}. Among these, mass spectrometry-based proteomics is one of the most widely used approaches in contemporary biomedical research and can be classified into stable isotope labeling proteomics and label-free proteomics. In particular, labeled proteomics allows for a significant reduction in mass spectrometry analysis time while also minimizing batch effects between samples³⁶.

Moreover, it can provide information on the molecular mechanisms of diseases and enable comparisons between two groups, such as patients and healthy controls³⁷ studying a set of modified proteins. Quantitative proteomics is capable of offering an in-depth understanding of disease mechanisms, cellular functions³⁸, and biomarker identification³⁹. There are a lot of works which study proteome changes to understand the progression of several diseases such as: different types of cancer^{37,40}, diabetes⁴¹, Alzheimer's disease⁴², multiple sclerosis⁴³, and so on.

1.1.4 Epigenomics, microbiomics and radiomics

Epigenomics investigates reversible modifications of DNA and histones, such as DNA methylation, that regulates gene expression without altering the nucleotide sequence. These modifications have important roles to regulate gene expression and cellular processes, and they are influenced by environmental or genetic factors and sometimes may be lasting or heritable⁴⁴. Those modifications have been associated with several diseases, including type 2 diabetes⁴⁵, cardiovascular disorders⁴⁶, and cancer⁴⁷. Epigenetic biomarkers are tissue-specific, the Next Generation Sequencing (NGS) is the most common methodology for epigenomics analysis.

Microbiomics focuses on the analysis of the ecological community of microorganisms inhabiting the human body, particularly the gut microbiota, or living symbiotically or pathologically on plants and animals (bacteria, fungi, viruses, protozoa and archaea)⁴⁸. Since the microbiome composition is predominantly shaped by environmental factors rather than genetics, its study has proven valuable in explaining phenotypic variability and associations with conditions such as neurological disorders⁴⁹, renal failure⁵⁰, and cancer⁵¹. To study microbiome the scientists mostly use macro-genome and macro-transcriptome, instead, they use 16S rRNA gene sequencing for microbial diversity analysis.

Radiomics enables the extraction of quantitative information of lesion areas and key information (Biomarkers) from radiological images (e.g., CT, MRI, and PET) using machine learning (ML)

methods, supporting diagnosis and treatment response assessment⁵². Although it faces challenges such as class imbalance and the risk of overfitting, radiomics has shown great potential in biomarker identification and in advancing personalized medicine. The results obtained from PET imaging are superior to conventional measures such as tumor volume, diameter, metastases, and other clinical tests, as PET provides higher-quality scans⁵³.

The techniques of metabolomics and lipidomics will be described in greater detail in the following paragraphs, as they represent the main focus of this work.

1.2 Metabolomics

Metabolomics is a newly emerging field of “omics” research concerned with the high throughput identification, characterization and quantification of the small molecules characterized by their high structural diversity: sugars, lipids, hormones, bile salts, free amino acids and others⁵⁴. The term “metabolome” was introduced to the scientific literature by Oliver et al. in 1998^{55,56} while he and his team were studying how microbial cells varied the concentration of their constituent metabolites in order to maintain the fluxes through the metabolic networks at a relatively constant level⁵⁶. In fact, the metabolome can be defined as: “the complete complement of all small molecule (<1500 Da) metabolites found in a specific cell, organ or organism”⁵⁴, analysing several biological matrices: serum, saliva, exhaled air, urine, tissue and other. Metabolomics is the last “omics” platform in the omics cascade (genomics-transcriptomics-proteomics-metabolomics). Metabolites are small molecules with the most various cellular and biological functions; they can not only work as building blocks for all the cellular components such as DNA (nucleotides) and proteins (amino acids), but also they can act as intermediates in energy metabolism and have an effect as signalling molecules activating cellular pathways. Metabolome includes all the major classes of biological molecules (i.e. nucleotides, sugars, lipids, amino acids, nucleic acid and other biochemical pathways), and, as mentioned, it is home to all the other little molecules that are produced and/or metabolised in the human body or any other organism. Metabolites are primarily classified into two categories: primary metabolites (carbohydrates, lipids, proteins and nucleic acid) and secondary metabolites (terpenes, phenolics, alkaloids and steroids). The first category is directly involved in essential functions such as energy production, protein synthesis and the construction of cellular membranes and is vital for life. These compounds are generally found in all living organisms. In contrast, secondary metabolites, although not essential for survival, play important roles in environmental adaptation and defence against pathogens. The distinction between primary and secondary metabolites is not always clear-cut and some compounds may have overlapping roles in both categories. It is noteworthy that both internal and external factors, alone or in combination, have an important role in modulating the profile of a given metabolome, which also has a very significant chance to vary from sample to

sample⁵⁷. In addition to this, metabolites can derive from microorganisms as well as from xenobiotic, dietary and other exogenous sources. As a matter of fact, metabolome is an amazing reflection of how the genome of a given organism is interacting with the surrounding environment and, consequently, can be easily exploited as an excellent enquiry for the organism's phenotype and reaction to xenobiotics^{58,59}. Indeed, metabolome is dynamic and can vary within a single organism and among organisms of the same species because of many factors such as changes in diet, stress, physical activity, pharmacological effects and disease⁶⁰. This technique is a close counterpart to genomics, transcriptomics and proteomics and together these four omics constitute the building blocks of systems biology^{54,61–63}. Compared to genetic and protein profile alterations, metabolic profile changes can be more easily observed for cancer cell states and are therefore a promising source of biomarkers for the detection of tumorigenesis⁶⁴. Moreover, the response of metabolome to pathophysiological alterations is much more sensitive than gene or protein response and the alterations in metabolome are closely related with the observed phenotype⁶⁵.

Metabolomic studies are based on differential analysis of metabolic profiles from various cases: healthy versus disease state, treated versus untreated or mutant versus wild-type strain. Research in the field of metabolomics has grown significantly in the last decades, with over 75,000 citations in PubMed. This expanding body of work has led to discovery of novel biomarkers and provided insights into disease mechanisms at a systems biology level, spanning conditions such as obesity⁶⁶ and diabetes⁶⁷, various form of cancer⁶⁸, neurodegenerative diseases⁶⁹ and infectious diseases⁷⁰. Beyond biomedical research, metabolomics has also found valuable applications in agriculture^{71,72} and food chemistry⁷³, serving as quantitative tool to enhance crop yield and ensure food safety.

Figure 2 illustrates a typical workflow used in metabolomic research, outlining the sequential steps involved from sample collection, through data acquisition, to data processing, statistical analysis and biological interpretation. This structured approach ensures comprehensive metabolic profiling and enables the identification of potential biomarkers or pathways associated with specific biological conditions.

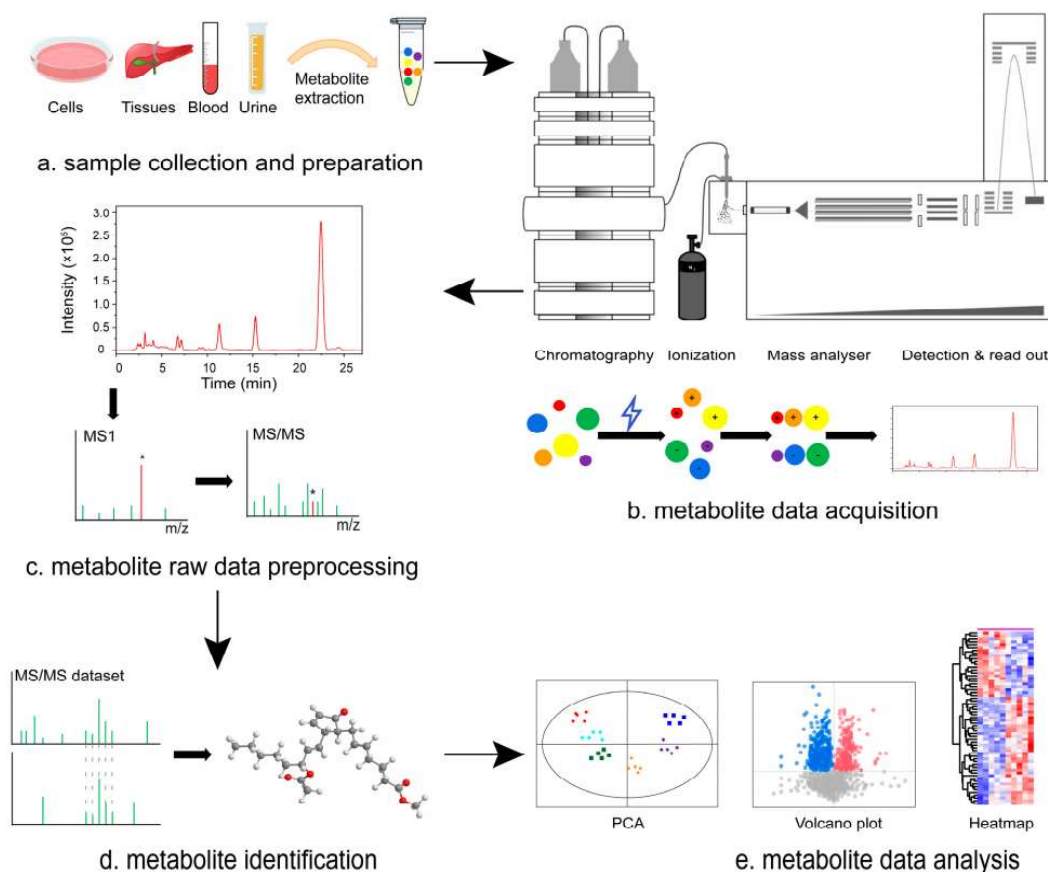


Figure 2. The basic workflow of metabolomics researches²¹⁸

1.2.1 Human Metabolome Database (HMDB)

There are several metabolic pathways database such as: KEGG, Reactome, Cyc database and general spectral databases like: BioMagResBank, Metlin, MassBank or Human Metabolome Database (HMDB). The last one is not only a spectral database, but it is an online encyclopaedia covering almost all that is known about human metabolism and metabolites. The Human Metabolome Database (HMDB) is the largest and most detailed metabolomic database dedicated to human organism; this tool was first launched in 2007, and the last version, HMDB 0.5, was released in 2022. It provides in-depth, carefully verified and extensively referenced information on all currently known human metabolites. This includes information on their chemical structure, names or identifiers, detailed description, references, chemical taxonomy, biological roles, physiological concentration, tissue/biofluids locations, diseases associations, genetic associations, chemical and enzymatic reactions, metabolic pathways and referential MS/MS (tandem mass spectrometry), GC-MS (gas chromatography mass spectrometry), NMR (nuclear magnetic resonance) spectra. One of the main challenges in metabolomic studies is the identification of m/z features in data obtained through mass spectrometry (MS). In untargeted analysis, less than 2% of m/z features can be confidently identified

and, even in targeted studies, more than 900 metabolite (1% of the known human metabolome) are rarely identified. This indicates that the coverage of metabolites and MS spectra in database has so far been insufficient. To improve the situation, the HMDB team conducted a thorough review of the scientific literature between 2018-2021, adding over 100.000 new metabolites to the database. Another key strength of this database lies in its extensive collection of metabolite description. Each compound listed in the HMDB is accompanied by a detailed textual summary that explains the metabolite's function or its location within the body or cell. Additionally, many metabolites include further information such as their presence in various biofluids or tissues, normal and abnormal concentration levels, links to diseases, MS and/or NMR spectral data, known metabolic pathways, cross-references to external databases, and associated enzymes or transporters. HMDB helps researchers to find out metabolic data through text, structure, mass or spectra matching⁷⁴.

1.2.2 Analytical techniques for metabolomic studies

The study of metabolic profiling has transitioned from the use of smell and/or taste to the application of advanced spectrometric methods such as nuclear magnetic resonance (NMR) or mass spectrometry (MS), with their respective advantages and disadvantages⁷⁵. In metabolomic analysis the choice of analytical technique is a critical step, this choice will restrict the metabolites detected and the obtained results. The researcher must consider all the instrumental characteristics like: sensitivity, resolution, limits of detection, sensibility etc; but also the characteristics, properties and abundance of the samples and of the metabolites of interest⁷⁶. On one hand, NMR offers high reproducibility and automation and does not require derivatization or sample pretreatment, making it suitable for high-throughput untargeted metabolomics. However, NMR introduces challenges in its relatively low sensitivity and pervasive signal overlap within the NMR spectrum of biological specimens, constraining the identification of metabolites and the revelation of biomolecular alterations and biomarkers^{77,78}. On the other hand, MS has high sensitivity and specificity and can be coupled with Gas Chromatography (GC) or Liquid Chromatography (LC), offering advantages in untargeted and targeted metabolomic analysis⁷⁹. Both of these chromatographic techniques can be coupled to different analyzers such as triple quadrupole mass spectrometry, time-of-flight mass spectrometry or orbitrap (GC/Q-MS; GC-TOF-MS; HPLC/Q-MS; HPLC-TOF-MS; HPLC-Q-Orbitrap-MS)^{80,81}. Indeed, the analyses of metabolome are more and more often carried out through high resolution mass spectrometry, which enables accurate mass measurements within the ppm accuracy range: this accuracy greatly improves the quality of metabolome data and allows the analysis of complex mixtures⁸². Metabolomics refers to large-scale studies where up to thousands of metabolites (known as *metabolome*) can be detected and quantified at the same time in each sample. The most commonly used approaches for the analysis of a metabolome are untargeted and targeted metabolomics^{83,84}. Even if both of them are quantitative methods, neither targeted nor untargeted metabolomics is sufficient to explain the molecular mechanism the altered metabolites

concentrations are based on^{57,59}. Metabolomic analysis employs several data analysis methods for statistical interpretation of results including bioinformatics, enrichment analysis, pathway analysis and generation of metabolic networks. To facilitate these analyses, numerous software tools, commercial and open source, are available (MetaboAnalyst, Mzmine, XCMS, etc). All of these types of analysis will be discussed and explored in detail in the paragraph 1.5.

1.3 Lipidomics

Lipidomics is the subarea of metabolomics focused on the qualitative and quantitative profile of the lipid species in biological samples (plasma, serum, urine, tissue, cells, organism, etc...). This technique was first introduced in 2003 and only in the last decade have lipid profiling methods have improved⁹⁰. The ultimate goal of lipidomics analyses is to provide a comprehensive identification and quantification of all lipids, as well as a characterization of their interactions with other lipids, proteins or gene expression⁹¹. Lipids have been defined as biological substances that are generally hydrophobic in nature and often soluble in organic solvent and they are fundamental to a wide range of cellular functions, including survival, proliferation, and cell death. They are actively involved in energy storage, cellular signalling, membrane structure and intercellular communication within tissues; the lipid profile is dynamic and is subject to endogenous and exogenous factors including genetics, nutrition and inflammatory processes. Lipid metabolism dysregulation is closely associated with the onset and progression of various diseases, including cardiovascular diseases⁹², type 2 diabetes⁹³, Alzheimer's disease⁹⁴ and several forms of cancer^{10,95,96}. Notably, lipidomic profiling captures the biochemical effects of both genetic and lifestyle factors, making it particularly valuable in the context of complex pathologies⁹⁷. Indeed, lipids are closely to carcinogenic processes, particularly in relation to cellular transformation, tumor progression and metastasis⁹⁵. Lipid metabolism is essential to understanding cancer development and progression for several reasons: 1. de novo phospholipid synthesis fuels tumor proliferation; 2. fatty-acid β -oxidation supports cellular energetics and redox balance; 3. lipids drive essential signalling pathways; 4. lipids dynamic nature mirrors physiological, pathological and environmental changes. These facets together underscore the complexity of the lipidome, establishing lipidomics as a distinct branch of metabolomics while highlighting the cancer-associated lipid fingerprints that position lipids as promising biomarkers and therapeutic targets⁶⁵.

Clinical lipidomics has emerged as a promising sub-discipline that seek to bridge this gap by enabling both clinical and consumer access to in-depth lipidomic analysis. The data generated from such analysis have the potential to support disease prediction, diagnosis and personalized management strategies. Over the past six decades, the primary lipid measurements employed in clinical practice

have consisted of total triglycerides, total cholesterol, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C). While the clinical relevance of these parameters, both in terms of their association with disease onset and progression and their diagnostic utility, is well established; they provide only a limited representation of the comprehensive lipidomic profile. Therefore, a substantial amount of metabolic information remains underexploited in routine clinical settings. Recent advances in lipidomics research platforms now allow for the identification and quantification of hundreds of distinct lipid species in human matrices, spanning dozens of molecular classes and subclasses. Despite this remarkable analytical capacity, a significant disparity persists between the capabilities of lipidomics in the research domain and the tools currently available for clinical applications. To address this, considerable international efforts are focused on translating research protocols into clinically viable assays. A particularly promising avenue within this translational effort involves the integration of statistical modelling, epidemiological analysis and machine learning approaches to develop predictive models. These models aim to identify individuals at elevated risk and to stratify pathology severity in already diagnosed patients, thereby enhancing the precision of clinical decision-making⁹⁷.

As shown in Figure 2, the workflow for lipidomics can be summarized in a similar manner to that of metabolomic. It normally involves several stages: sample collection and preparation, lipids data acquisition, raw data processing, lipids identification, data statistical analysis and biological interpretation.

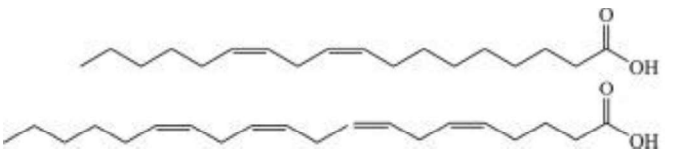
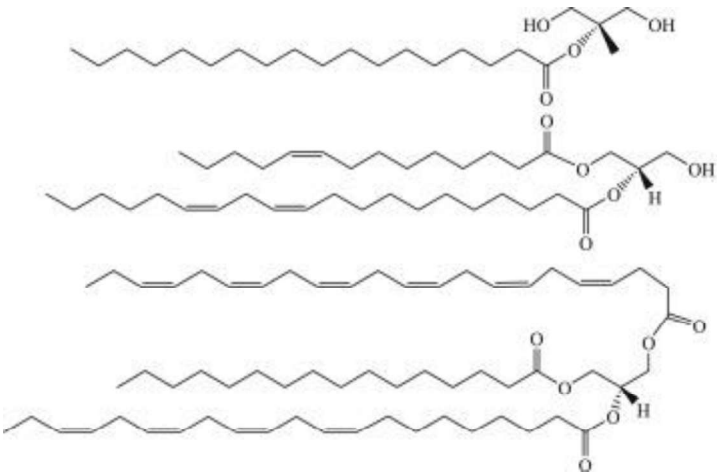
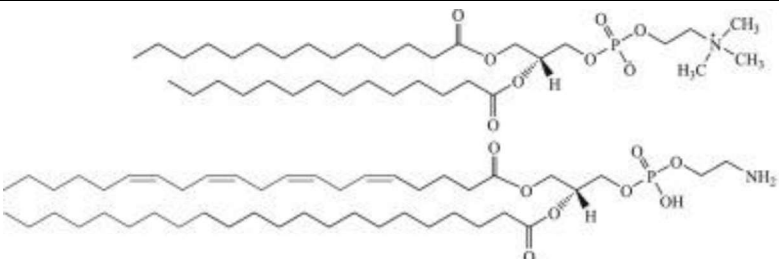
1.3.1 Classification system for lipids

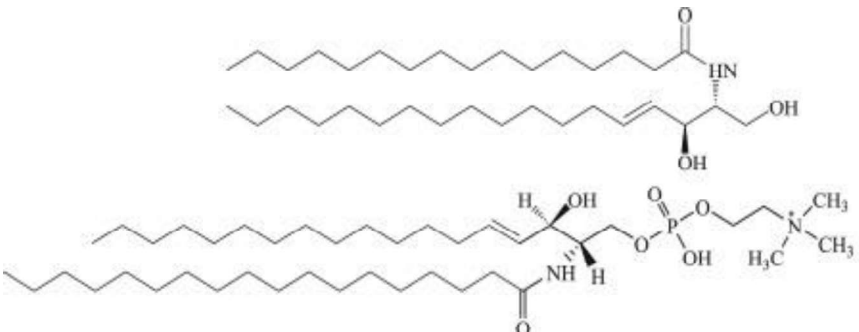
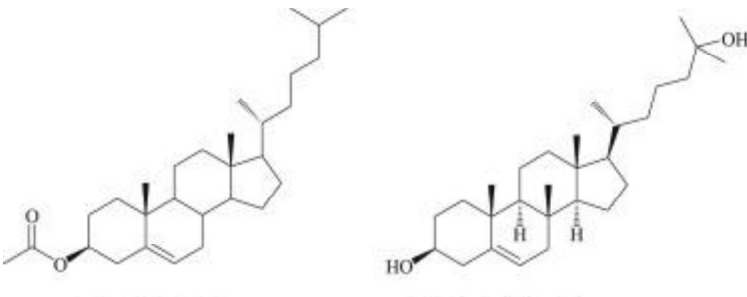
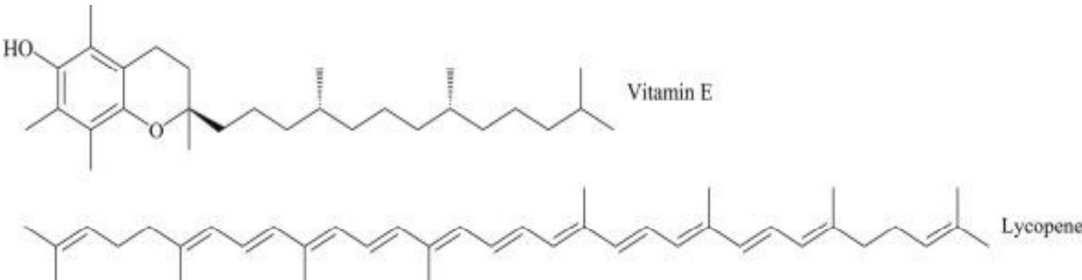
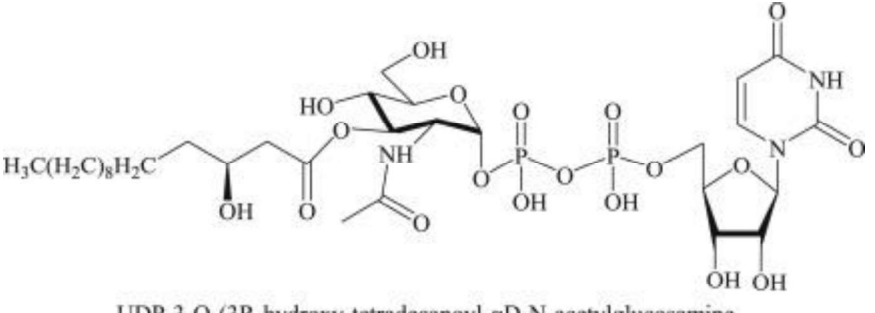
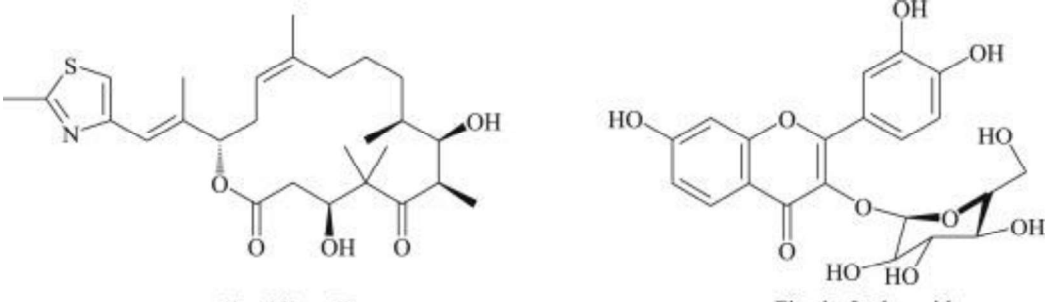
One of the last lipid nomenclature was addressed in detail by the International Union of Pure and Applied Chemistry and the International Union of Biochemistry and Molecular Biology (IUPAC-IUBMB) Commission on Biochemical Nomenclature in 1976⁹⁸. Then a number of additional documents relating to the naming glycolipids (1997)⁹⁹, prenols (1987)¹⁰⁰ and steroids (1989)¹⁰¹ have been released by IUPAC-IUBMB. Over the past three decades, numerous new lipid classes have been identified, many of which had not previously been systematically classified. The following classification system now includes these lipids and adopts a standardized nomenclature.

According to LIPID MAPS[®], lipids can be classified into 8 different categories: Fatty Acyls (FA), Glycerolipids (GL), Glycerophospholipids (GP), Sphingolipids (SP), Sterol lipids (ST), Prenol lipids (PR), Saccharolipids (SL) and Polyketides (PK) containing distinct classes and subclasses of molecules (some examples are reported in Table 1). The classification is chemically based and driven by the distinct hydrophobic and hydrophilic elements that compose the lipid. Fatty acyls (FA) represent a broad and diverse class of molecules formed through the elongation of an acetyl-CoA starter unit by the addition of malonyl-CoA or methylmalonyl-CoA units. These structures can feature cyclic elements or substitutions with heteroatoms. Lipids that include a glycerol backbone

are grouped into two main categories: glycerolipids (GL), which include acylglycerols as well as their alkyl and 1Z-alkenyl variants, and Glycerophospholipids (GP), defined by the presence of phosphate or phosphonate group esterified to one of the hydroxyl groups of glycerol. Sterol lipids (ST) and prenol lipids (PR) share a common biosynthetic origin, derived from the polymerization of dimethylallyl pyrophosphate and isopentenyl pyrophosphate, although they diverge significantly in structure and biological roles. Another clearly defined group is that of sphingolipids (SP), whose core structure consists of a long-chain base. The category of saccharolipids (SL) has been introduced to describe lipids in which fatty acids are directly attached to a sugar backbone. The final class, polyketides (PK), includes a wide variety of secondary metabolites derived from plants and microorganism. It's worth noting that glycolipids do not constitute a separate category in this classification but are instead assigned to one of the above groups depending on their core lipid structure¹⁰².

Table 1.Examples of eight categories of lipids¹⁰³.

Lipid classification	Representative species
Fatty acyls	 Linoleic acid Arachidonic acid
Glycerolipids	 MG(0:0/18:0/0:0) DG(14:1(9Z)/20:2(11Z,14Z)/0:0) TG 16:0/18:3/22:6
Glycerophospholipids	 PC(14:0/14:0) PE(20:4(5Z,8Z,11Z,14Z)/22:0)

Lipid classification	Representative species
Sphingolipids	 Ceramide (d18:1/16:0) SM(d18:1/18:0)
Sterol lipids	 Cholesteryl acetate 25-Hydroxycholesterol
Prenol lipids	 Vitamin E Lycopene
Sacharolipids	 UDP-3-O-(3R-hydroxy-tetradecanoyl)-αD-N-acetylglucosamine
Polyketides	 Epothilone D Fisetin-3-glucoside

LIPID MAPS has also introduced a unique 12-character code (LIPID ID) for each lipid, based on the classification described above. The format of this code is outlined in Table 2, allowing for a total of

1.68 million of possible combinations. If the lipid structures are obtained from other databases such as LipidBank or LIPIDAT, the corresponding IDs are included to enable cross-referencing. In fact, the first two characters of the code identify the source database. In addition, lipids can be effectively represented using a shorthand notation, where abbreviations denote the backbones structure, head group and sugar component. The radyl substrate are described using a code that specifies their carbon length and degree of unsaturation, some examples are reported in Table 3¹⁰².

Table 2. Format of 12-character LIPID ID¹⁰²

Characters	Description	Example
1–2	Fixed database designation	LM
3–4	Two letter category code	FA
5–6	Two digit class code	03
7–8	Two digit subclass code	02
9–12	Unique four character identifier within subclass	7312

Table 3. Examples of shorthand notation for lipids¹⁰²

Category	Abbreviation	Class or Subclass	Example
GP	GPCho	Glycerophosphocholines	GPCho (16:0/9Z,12Z-18:2)
SP	Cer	Ceramides	Cer (d18:1/9E-16:1)
SP	SM	Phosphosphingolipids	SM (d18:1/24:0)
GL	MG	Monoradyl glycerols	MG (16:0/0:0/0:0)
GL	DG	Diradyl glycerols	DG (18:0/16:0/0:0)
GL	TG	Triradyl glycerols	TG (12:0/14:0/18:0)

1.3.2 Analytical techniques for lipidomics studies

As with metabolomics, the selection of the analytical technique in lipidomics studies represents a critical step, as it directly influences lipid identification and the quality of the resulting data. To choose the most appropriate method, researchers must carefully consider the characteristics, abundance and physicochemical properties of the target compounds, as well as the advantages and limitations of each available analytical technique. TLC (thin layer chromatography) and 2D-TLC were the first methods settled for the separation of different lipid classes. After extraction, lipids were spotted onto a silica plate and then developed using a single solvent or a mixture of solvents (such as chloroform, methanol and ammonia). Lipid classes can be identified simply by comparing them with reference compounds. Although TLC does not allow for the identification of specific individual lipids, it can still be considered a useful technique for purification^{104,105}. Gas chromatography (GC)

offers higher resolution compared to TLC, but its main limitation lies in being restricted to volatile compounds. Prior to GC analysis, a derivatization step is required to enhance the thermal stability of analytes and reduce their boiling points. It is therefore common practice to perform transesterification of fatty acids and glycerolipids to increase their volatility. However, this process may lead to a loss of structural information, as it becomes impossible to determine the original position of the fatty acids on the glycerol backbone^{106,107}. The main detectors used in GC-based lipid analysis are: the flame ionization detector (FID) and single quadrupole mass spectrometers equipped either electron ionization (EI) or chemical ionization (CI) sources. Mass spectrometers can operate in different acquisition modes: scan mode, in which the quadrupole sequentially transmits ions to generate a full mass spectrum and single ion monitoring (SIM) mode, which allows the selection of a specific m/z value thereby increasing specificity and improving sensitivity¹⁰⁸. The high reproducibility and extensive source fragmentation characteristic of EI enables the construction of comprehensive spectral libraries, containing hundreds of thousands of reference spectra. Even higher resolution can be achieved using time-of-flight (TOF) mass spectrometers, which are well suited for determining the elemental composition of the ions generated. However, these instruments require systematic external calibration throughout the analysis and are significantly more expensive than single quadrupole system¹⁰⁹. Analyses that do not require prior chromatographic separation are particularly well-suited to the use of MALDI (matrix-assisted laser desorption/ionization) ion source. In this approach, the sample is mixed with an excess of matrix and deposited onto a metal target, where the mixture is cocrystallized. Under vacuum conditions, the sample is then irradiated with a laser pulse, and the generated ions are introduced into a TOF analyser. MALDI exhibits high salt tolerance and is considered a robust and reliable technique for qualitative lipid analysis^{110,111}. The main drawback of shotgun lipidomics is the ion suppression effect that can bias quantification. This effect is a phenomenon where the presence of matrix components in a sample reduces the ionization efficiency of the analyte of interest. The best way to reduce the ion suppression effect is to combine ultra performance liquid chromatography (UPLC) coupled with mass spectrometry (MS) capabilities. UPLC utilizes stationary phases with sub-2 μm particles (normally 1.7-1.8 μm), which significantly enhances chromatographic resolution, sensitivity and analytical speed. This technique also offers excellent reproducibility, with retention time deviations typically below 0.03 minutes, thereby minimizing the need for chromatographic alignment during multivariate statistical analyses and facilitating clearer interpretation of mass spectra while improving detection limits¹¹². Lipid separation via UPLC can be performed using either normal-phase (NPLC), reverse-phase (RPLC) or hydrophilic interaction liquid chromatography (HILIC) stationary phases, depending on the chemical properties (polar or apolar) of the lipid classes being analysed. This last mode has proven particularly effective for the lipidomic profiling of a wide range of biological matrices, including plasma¹¹³, serum¹¹⁴, bile¹¹⁵, cerebrospinal fluid¹¹⁶ and other matrices. Owing to its robustness, precision and versatility, it is considered the method of choice for comprehensive and high-throughput lipidomics

workflows. Nevertheless, special attention must be paid to potential carryover effects, which may lead to the unintended detection of residual lipid species in subsequent blank injections.

As in metabolomics, three different approaches based on HPLC-MS(/MS) can also be employed in lipidomic analyses: untargeted, semi-targeted and targeted. Moreover, high-resolution mass spectrometry (HRMS) coupled with liquid chromatography has also been introduced in this context. High-resolution mass analyser such as time-of-flight (TOF) or orbitrap allow for the comprehensive characterization of the lipid composition of a sample without prior knowledge of its constituents (untargeted analysis).

Lipidomic analyses rely on various computational and statistical tools to interpret complex dataset, including bioinformatics pipelines, lipid classification frameworks, pathway analysis and network reconstruction. To support these tasks, a wide array of software solutions, commercial and open source, are available (LipidSearch, Lipid Data Analyzer, MS-Dial, etc), specifically designed for the identification, quantification and annotation of lipid species. All these analytical approaches, along with the HPLC-MS_TOF methodology, will be described in detail in the paragraph 1.5.

1.4 Biological matrices

As stated in the previous sections, the selection of the biological matrix is a critical aspect in metabolomic and lipidomics studies aimed at identifying biomarkers of various diseases. Whole blood, plasma/serum, urine, saliva and feces are the most frequently used and critical sources for comprehensive analysis. All these biological matrices offer a rich reservoir of metabolic and lipidomic information which allows researchers to collect valuable information about metabolome that help to find out biomarkers for several pathologies⁸⁵. The following paragraphs will describe in detail conventional biological matrices used in this study (whole blood, urine, oral fluid and keratin matrix).

1.4.1 Whole blood, plasma and serum

Blood, as it circulates throughout the body and reaches equilibrium with organs and tissues is generally considered to provide information on instantaneous internal exposure¹²⁴. Whole blood is the biological matrix of choice in both clinical and forensic contexts, as it allows for the assessment of recent intake of exogenous substances (drugs or medications) and for correlating their concentrations with the individual's psychophysical state at the time of sampling. Moreover, it can be used to determine blood alcohol concentration, support various laboratory investigations, monitor disease progression and pharmacological treatments. Blood has four main components: plasma, red blood cells, white blood cells and platelets; it consists of approximately 55% plasma and 45% cellular

elements (Figure 3)¹²⁵. Blood collection is an invasive procedure that requires the involvement of qualified personnel to ensure biological safety¹²⁶.

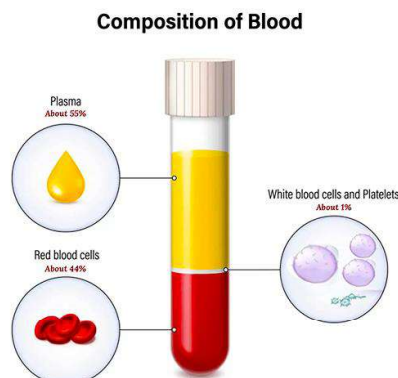


Figure 3. Composition of whole blood: 55% plasma, 44% red blood cells and 1% white blood cells and platelets (buffy coat)¹²⁵

Plasma is the liquid component of blood (92% H₂O) that transports blood cells throughout the body along with nutrients, waste products, antibodies, proteins and chemical messengers such as hormones¹²⁷. Plasma performs several vital functions such as transporting oxygen and releasing carbon dioxide, maintaining blood pressure and carrying hormones, nutrients, proteins where they are needed. It also removes waste products through the liver and kidneys. As shown in Figure 3, plasma can be obtained by separating the components of whole blood through centrifugation immediately after collection¹²⁸.

Serum is the fluid fraction of blood obtained after coagulation and subsequent removal of cellular elements and clotting factors. Unlike plasma, it lacks fibrinogen and most coagulation proteins, as these are consumed or separated during the clotting process (Figure 4). Its composition includes water (90%), albumin, immunoglobulins, electrolytes, hormones, metabolites and other low-molecular-weight solutes¹²⁹. Serum is extensively utilized in clinical diagnostics, biochemical and immunological assays, pharmaceutical research and as supplement in cell culture media due to its rich content of growth-supporting factors.

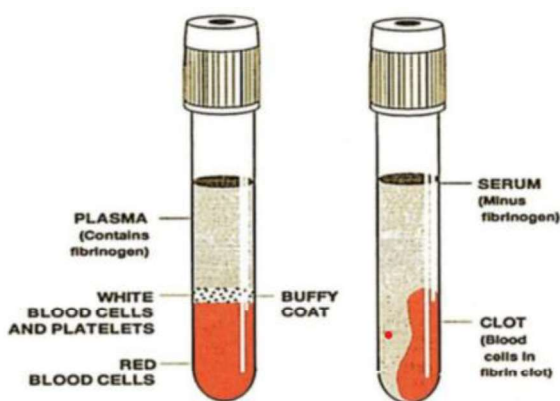


Figure 4. Differences between plasma and serum.

Plasma or blood serum are interesting biological matrix for metabolomic and lipidomic studies due to the abundance of measurable hydrophilic and hydrophobic metabolites they contain¹³⁰. Indeed, these matrices are widely used in clinical and biological studies, but attention must be paid to the sampling phase and the coagulation cascade, as they influence the concentration of both proteins and metabolites present. Yu et al.⁸⁶ demonstrated that serum exhibits greater sensitivity than plasma in biomarker detection, likely due to its higher metabolite concentration and lower total protein content (pre-treatment), which can be advantageous for small molecules analysis by reducing ion suppression and enhancing detection sensitivity. Unlike plasma, which contains more components, serum retains proteins that may interfere with analytical performance. On the other hand, plasma does not undergo blood clotting process, and the results are easier to replicate. At the end both serum and plasma can be used for these studies, but sampling should be consistent¹³¹. There are several metabolomic studies using these biological matrices for the identification of biomarkers identifying different diseases such as: diabetes¹³², cancers^{133,134} and neurodegenerative diseases¹³⁵. Dried blood spots¹³⁶ and whole blood¹³⁷ were also used for this type of analysis. Whole blood is a complex matrix that is not easy to work with, yet it is still used in metabolomics and lipidomics analyses, particularly in ¹HNMR-based metabolomics¹³⁸, but there are several studies that describe the use of this biological matrix is used in HPLC-TOF-MS untargeted metabolomics too¹³⁹. All these blood-derived matrices are now widely used to support diagnosis and disease monitoring^{140,141}, personalize pharmacological treatments¹⁴², identify specific biomarkers that enable more accurate and less invasive diagnostic approaches. They are also employed in the study of metabolic and lipidomic pathways^{143,144}, nutritional research and the assessment of athletic performance¹⁴⁵.

1.4.2 Urine

Urine is primarily composed of by-products of ongoing metabolism and reflects the body's need to maintain fluid and electrolyte balance¹⁴⁶. Historically, it has been regarded as a mere waste product, with no significant biological role in an individual's health. However, as early as 1491, Johannes de

Ketham's publication described how the color and consistency of urine could be used to formulate a diagnosis, marking the beginning of its use as diagnostic tool¹⁴⁷. Macroscopic examination of urine (uroscopy) was already practiced in antiquity and in the Middle Ages, while microscopic analysis developed during the 19th and 20th centuries. In 1933, R.F. Pitts introduced the use of urinary markers to evaluate kidney function¹⁴⁸. In recent decades, urine has increasingly been recognized as an accessible source of biomarkers for monitoring human health¹⁴⁹. It is also widely used in forensic toxicology to assess drug and substances abuse, medication use and in post-mortem analysis¹⁵⁰. Thanks to advanced techniques such as mass spectrometry, researchers have identified and catalogued exosomes, cells, proteins and other small molecules (including lipids and metabolites) present in urine.

Urine is one of the most informative body fluids in metabolomic studies; indeed, compared to other biological matrices such as blood, urine offers several advantages: it can be collected non-invasively, it is easily accessible and stable too. However, urine composition can vary due to several external factors, like diet, smoking habits, genetic factors, microbiota, diurnal cycles, diabetes, and other diseases which can affect urine metabolome. It contains a wide variety of metabolites originating from different organs such as kidneys, liver and gut thus providing a comprehensive overview of the body's metabolic state. As told above, this kind of analysis can be used to detect alterations in metabolic pathways associated with pathological conditions, to identify potential biomarkers for early diagnosis, to monitor treatment efficacy and to detect possible side effects of therapies. For example, urine metabolomics has been used to identify biomarkers for the early detection and diagnosis of renal diseases (acute kidney injury and chronic kidney disease¹⁵¹), for different types of cancer (bladder^{149,152}, prostate⁶⁵, and renal cell carcinoma) and intestinal cystitis¹⁵³ which can aid in early diagnosis and prognosis. Urine metabolomics has also been pivoted to investigate metabolic disorders (diabetes and obesity). Finally, researchers have used urine metabolomics to understand the metabolic effects of different diets and nutritional interventions. Moreover, Li et al.¹⁵⁴ studied the phenomenon of acute exacerbation of asthma in pediatric patients using untargeted metabolomics. Sometimes urine and blood are analyzed simultaneously for more comprehensive metabolomic studies¹⁵⁵.

Urine, like blood, is also increasingly used in lipidomics studies. In recent years, significant research efforts have focused on developing urinary lipidomics as a tool for the early diagnosis, monitoring and therapeutic management of both acute and chronic kidney diseases (CKD). Despite these advancements, our understanding of lipidomics alterations in urine associated with CKD remains limited¹⁵⁶. Urinary lipids have occasionally been proposed as diagnostic markers in particularly promising candidates for the early detection of prostate¹⁵⁷ and breast cancers¹⁵⁸. Furthermore, recent studies have shown that profiling lipid mediators in urine can serve as a non-invasive method for the molecular phenotyping of diseases such as asthma and atopic dermatitis¹⁵⁹. These findings support

the potential role of urinary lipidomics in identifying biomarkers across a wide range of conditions, providing valuable insights into disease mechanisms and supporting the development of personalized therapeutic approaches. However, broader clinical application of urinary lipidomics is currently limited by insufficient knowledge regarding baseline reference values and the origin of urinary lipid species. Nevertheless, due to its non-invasive nature, urinary lipidomics and metabolomic profiling represents a particularly appealing strategy for investigating metabolic alterations driven by genetic mutations or complex pathological states¹¹⁸.

1.4.3 Oral fluid

The term “oral fluid (OF)” refers to exocrine biological matrix excreted by the major salivary glands (submandibular, parotid and sublingual) and by the multitudes of minor salivary glands (300-1000 units) distributed into the oral mucosa. Oral fluid is a slightly acid secretion (pH 5.8-6.8), clear, hypotonic and mucoserous; it is produced by healthy humans in a range between 500 mL to 1.5L¹⁶⁰⁻¹⁶². The composition of OF can vary significantly due to a range of factors, including circadian rhythm, pathological conditions and external influences such as oral hygiene, physical activity, diet and substance use¹⁶³. Generally, OF is composed of 98.8% to 99.5% water, while the remaining portion includes both resting and stimulated saliva, food debris, drug metabolites, microorganism, gingival crevicular fluid and several electrolytes (calcium, magnesium, sodium, chloride, phosphate and other)¹⁶⁴⁻¹⁶⁶. This complex composition allows to distinguish OF from pure saliva, which refers to the secretion collected directly from a specific salivary gland and lacks the additional components typically present in oral cavity¹⁶⁷. Among the salivary components, mucins, glycoproteins and immunoglobulins play a key role in protecting the oral cavity by inhibiting bacterial growth, plaque formation and tooth erosion¹⁶⁸. As mentioned above, salivary secretion is influenced by multiple factors. It is essential to note that even in the absence of external stimuli, basal saliva is continuously produced to lubricate the mouth and exert antibacterial action. However, in response to stimuli such as food or exogenous substances, the salivary flow increases to support digestion, dilute various compounds, enhance taste perception and promote the mouth’s self-cleaning mechanisms (Figure 5). It is also worth highlighting that stimulated saliva is compositionally closer to blood than unstimulated saliva^{163,169}. Distinguishing between unstimulated and stimulated saliva is important due to their different roles in oral physiology, particularly in relation to salivary pH regulation. Stimulated saliva, produced at a high flow rate, passes rapidly through the excretory ducts, which limits the time for electrolyte reabsorption. This results in higher bicarbonate levels and a more alkaline pH (up to 7.8), enhancing its buffering capacity. At the same time, the fast secretion rate leads to a lower protein concentration, creating an inverse relationship between flow rate and protein content. In contrast, unstimulated saliva flows more slowly, allowing more extensive electrolyte exchange within the ducts. This leads to reduce bicarbonate concentration, a more acidic pH (around

5.3) and lower buffering ability, but a higher protein content^{166,170,171}. Oral fluid is often regarded as a direct ultrafiltrate of blood due to the dense vascularization of the salivary glands¹⁷². The primary pathways through which molecules transfer from bloodstream into the oral cavity include passive diffusion (lipophilic compound) and ultrafiltration, which applies to small, hydrophilic molecules¹⁷³.

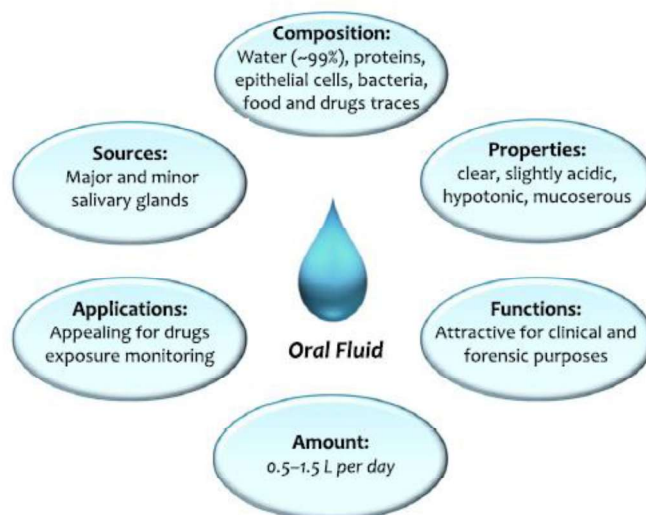


Figure 5. Main characteristics of oral fluid¹⁶²

A variety of internal and external factors can affect the salivary flow rate and the composition of oral fluid, potentially disrupting its normal physiological balance. One notable factor is aging, which is linked to histological alterations in the salivary glands, often resulting in a reduction in saliva production. People over the age of 60 are particularly prone to xerostomia, a condition characterized by low salivary output, increased evaporation, reduced clearance through swallowing and reabsorption by the oral mucosa¹⁷⁴⁻¹⁷⁷. Although aging plays a central role xerostomia can affect younger individuals due to underlying health conditions or the use of various pharmaceutical or recreational substances. Additionally, several systemic diseases, in particular autoimmune disorders such as sarcoidosis, rheumatoid arthritis and Sjögren's syndrome, are associated with impaired salivary gland function and reduce secretion¹⁷⁸. When saliva production decreases, the oral cavity tends to become more acidic, compromising the protective functions normally provided by whole saliva. This shift in pH can heighten susceptibility to dental caries, periodontal infection, halitosis and opportunistic mucosal infection^{179,180}. On the other hand, excessive salivation, sialorrhea, can also occur, most notably in individuals with neurodegenerative disorders such as Parkinson's diseases¹⁸¹.

As previously discussed, a wide range of systemic and local diseases can influence the composition, pH and flow rate of whole saliva. Consequently, oral fluid has emerged as a valuable diagnostic matrix for identifying such conditions, either through the detection of pathological biomarkers

produced locally or those that migrate from systemic circulation into the oral cavity¹⁸². Salivary biomarkers have also shown promise in the early detection of systemic cancers, including those located far from the salivary glands such as: lung¹⁸³, pancreatic¹⁸⁴ and breast cancers¹⁸⁵. For these reasons, oral fluid is currently used as a biological matrix in metabolomic and lipidomics studies.

There are several advantages to using oral fluid as a matrix in metabolomic research. First, a positive correlation between metabolite levels in plasma and saliva has been observed, indicating that the metabolic profile of saliva contains biological information. Secondly, the metabolic profile of each individual's saliva is subject to variation based on diet as is urine. Saliva is also a very available, easy-to-sample, inexpensive and non-invasive matrix¹⁸⁶. Several metabolomic studies have employed saliva as biological matrix to identify biomarkers and monitor therapeutic response in various oral disorders¹⁸⁷ such as oral cancer, periodontally healthy, gingivitis, caries and others^{188,189}. In recent years, salivary metabolomic analyses have also been applied to the investigation of diseases not directly related to the oral cavity, like: Sjögren's syndrome¹⁹⁰, breast cancer, gastric cancer, pancreatic cancer¹⁹¹.

For the same reasons discussed above in the context of metabolomics, oral fluid is also considered a key biofluid for investigation disease-related changes in the lipid profile through lipidomics studies. It has proven valuable in various conditions, including oral cancer¹⁹², diabetes¹⁹³ and chronic oral inflammatory diseases (periodontitis). The predominant salivary lipids include cholesterol, cholesteryl esters, mono-, di- and triglycerides and fatty acids. Phospholipids, on the other hand, constitute only a minor fraction of the total salivary lipid content¹⁹⁴.

1.4.4 Keratin Matrix

Hair analysis can be used to determine the concentration of many licit or illicit drugs in their parent or metabolized form such as nicotine, the biomarker of tobacco exposure, ethyl glucuronides (EtG) and total fatty acid ethyl esters (FAEEs), which are biomarkers of ethanol intake, cannabis, cocaine, amphetamines and NPS, including phenethylamines, piperazines, synthetic cathinones and synthetic cannabinoids^{195,196}. The main advantage is the possibility of tracing the intake history of the subject over a long period of time, proportional to the length of the hair. It also has additional advantages over more conventional matrices, including the ease and non-invasiveness of sampling, the simplicity of storage and transport, the stability of the analytes within the matrix and, the possibility of searching for both the substance as such and its metabolites. Furthermore, it is possible to evaluate chronic drug use through segmental analysis, in which hair is cut into smaller pieces and analyzed separately^{197,198}. It is necessary, however, to highlight the disadvantages that arise when this type of matrix is used, such as the low concentrations of the analytes, in the range of pico- or nano- grams

per milligram (pg/mg, ng/mg) of hair, which is why it is necessary to use accurate and sensitive methods and the cost of analysis is higher than that of other biological samples¹⁹⁹. Moreover, the detection of recent drug use (within 7 days) is not possible and there is the possibility of obtaining false negatives due to cosmetic treatments. Hair analysis is suitable for accurately monitoring relative changes in drug intake in the same individual. In several studies, it has been shown that a doubling of drug dose in the same individual results in a doubling of the drug content of the hair, which is not the case for blood and urine drug level.

Hair is a product of differentiated organs in mammalian skin, composed of protein (65% to 95% essentially keratin), water (15% to 35%), lipids (1% to 9%) and minerals (<1%). The hair shaft consists of an outer cuticle surrounding a cortex, the one that in some hair types surrounds a central pith. The hair shaft begins in a hair follicle and grows cyclically, alternating between periods of growth (anagen phase) and periods of dormancy (catagen and telogen phases) (Figure 6.a). About 1 million hair follicles in the adult scalp, about 85% of the hair is in the growth phase and the remaining 15% is in the dormancy phase. Hair follicles are embedded in the dermis of the skin and contain networks of arterial capillaries that nourish the growing hair bulb (root). Associated with most hair follicles is a sebaceous gland that secretes sebum, a waxy substance that coats the hair strand. In addition to the hair of the head, hair follicles in other parts of the body, such as the axilla, have apocrine glands that release an oily substance that also coats the hair strand. Eccrine sweat glands abound near hair follicles. Although the sweat ducts exit directly onto the skin, their proximity causes the hair to be frequently bathed in this fluid. The primary structure of hair consists of two or three α -keratin chains wrapped in strands called microfibrils. Keratins are high molecular weight polymers and consist of long chains of hydrophobic amino acids, which is why they are poorly soluble. The primary structure of keratin consists of amino acids, mainly cysteine, that interact in a head-to-tail arrangement. Two cysteine molecules bind through the formation of disulfide bridges between two sulfhydryl residues, a reaction catalyzed by the enzyme sulfhydryl oxidase²⁰⁰. The formation of axial keratin filaments (microfibrils) occurs when multiple intermediate keratin alpha filaments coil together. The microfibrils are organized into larger bundles of macrofibrils that make up most of the cortex, the internal structure of the hair. The cortex comprises most of the stem and contains melanin pigment granules and air bubbles: it is the density of the pigment and the amount of air bubbles that determine hair color. The diversity in hair pigmentation comes mainly from the amount and ratio of two types of melanin pigments, black and brown eumelanin and red-brown and yellow pheomelanin²⁰¹. A central hollow area, the medulla oblongata, may also be present. A protective layer of epithelial cells, called the cuticle, surrounds the cortex. The cuticle cells overlap and act as a protective barrier to the environment. Without the cuticle, the cortex degenerates, frays, and breaks down.

The unique physiology and structure of hair allows multiple pathways for drug incorporation and loss. Blood, sweat, sebum, and skin may be potential drug pools from which drug can be transferred to hair. Three models for incorporation have been proposed, drugs can enter the hair through: 1. active or passive diffusion from the bloodstream feeding the dermal papilla; 2. diffusion from sweat and other secretions bathing the growing or mature hair fiber; 3. external drug from vapors or powders that diffuse into the mature hair fiber. Indeed, a combination of these routes is probably the most realistic model to choose (Figure 6.b). From an interpretive viewpoint, the most important route is via the bloodstream, for example when we are interested in answering questions about the time of intake or even the dose taken²⁰². Several hair components have been suggested as possible molecular sites for drug binding and interaction. The discovery that drugs such as cocaine, heroin, and 6-acetylmorphine are stable in hair and can be detected for many months after ingestion indicates that hair binding sites provide significant protection from the various chemical challenges that these relatively unstable molecules must endure. The three components of hair that are most likely to provide this protection are proteins, melanin, and lipids. Evidence to date indicates that proteins and melanin are the primary binding components. Indeed, both neutral and charged species have the ability to bind to melanin, highlighting the efficiency of melanin as an *in vivo* toxin absorber. The remarkable ability of melanin to bind to various chemicals has emerged as one of the strongest body retention mechanisms²⁰³. Additionally, it is likely that proteins in hair have specific groups that serve to bind drugs through electrostatic and van der Waals forces similar to those found for melanin.

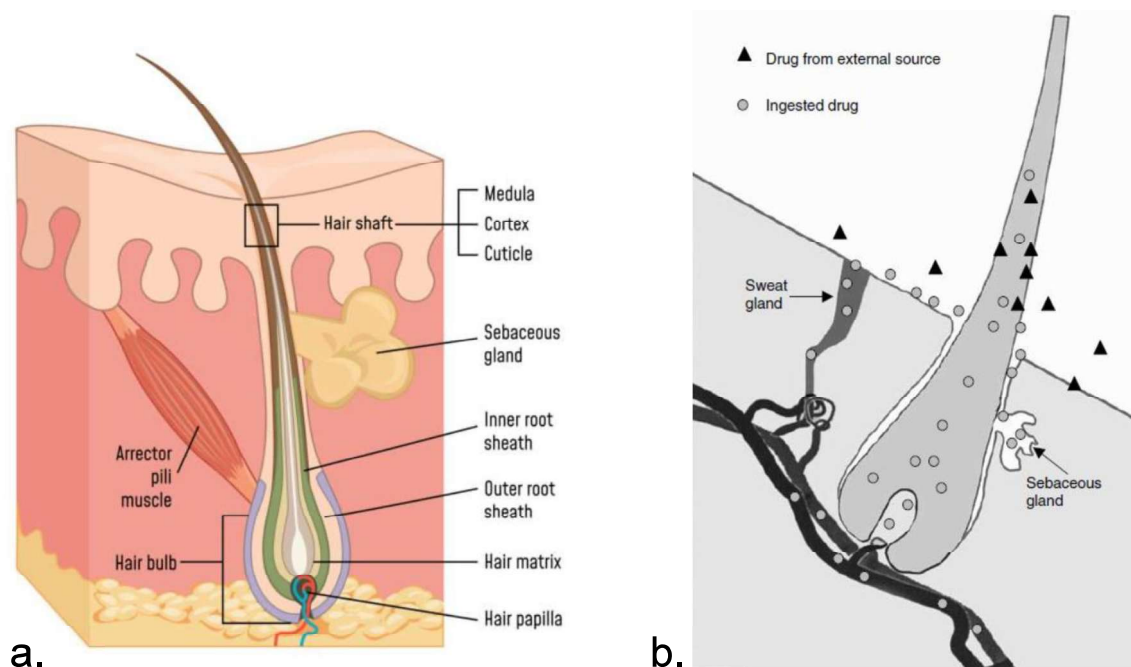


Figure 6. a. schematic view of hair follicle; b. pathways of drug incorporation into the hair.

1.5 Analytical techniques

As discussed in section 1.2.2 and 1.3.2, various analytical techniques have been developed over the centuries and are currently employed in lipidomic and metabolomic analyses. Among the most commonly used methods are nuclear magnetic resonance (NMR), gas chromatography (GC) and liquid chromatography (LC) each of which can be coupled with different types of mass spectrometer (triple quadrupole (MS/MS), time-of-flight (TOF) and orbitrap) depending on the specific objectives of the research. Lipidomic and metabolic studies can be conducted using two main strategies: targeted and untargeted approaches. In the following paragraphs, these two strategies will be described in detail, followed by a focus on liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (LC-Q-TOF-MS), the analytical technique employed in this study.

1.5.1 Targeted and untargeted approaches

Metabolomic and lipidomic strategies are generally divided into two main approaches: untargeted and targeted analyses. Untargeted approaches involve a broad, comprehensive examination aimed at detecting as many metabolites or lipid species as possible within a sample, including those that are unknown or unexpected. Conversely, targeted strategies focus on the quantitative analysis of a predefined set of known and biochemically characterized compounds. Each method has its own advantages and limitations; typically, the strengths of one corresponds to the weakness of the other. Untargeted techniques offer greater discovery potential, while targeted ones provide higher sensitivity, specificity and quantification accuracy for selected molecules. Importantly, the choice between these techniques necessitates careful consideration of the researcher's goals.

Going into more detail, the untargeted approach represents an exploratory strategy aimed at hypothesis generation and the discovery of novel biological mechanisms. This method allows for the qualitative identification and relative quantification of thousands of endogenous compounds present in biological samples, without the need for prior knowledge. Due to its broad metabolic coverage, untargeted analysis has played a fundamental role in biomarker discovery and in deep understanding of both physiological and pathological processes. In contrast, the targeted strategy is generally employed at a later stage, with the aim of validating preliminary results obtained from untargeted studies. By leveraging prior knowledge of metabolic pathways and molecular mechanisms, the targeted approach enables the absolute quantification of a limited number of selected metabolites (~20), making it particularly useful for quantitative comparisons between healthy and diseased conditions. Considering the disparities between these strategies, they also differ significantly in their procedural workflows. Specifically, sample preparation for targeted approach involves extraction protocols designed for specific compounds and typically requires the use of internal standards to

absolute quantification. In contrast, untargeted analysis employs global extraction procedures aimed at capturing a broad spectrum of metabolites without prior selection. As mentioned in previous sections, both approaches commonly utilize analytical platforms such as nuclear magnetic resonance (NMR), gas chromatography (GC) and liquid chromatography (LC) often coupled with various types of mass analyser to enhance sensitivity, resolution and analytical coverage. However, due to the high complexity and large volume of data generated, particularly because of the presence of numerous unidentified compounds, untargeted strategy requires more extensive data processing compared to targeted one. To interpret the data, both methodologies utilize a range of computational approaches such as: bioinformatic, enrichment analysis, pathway analysis and metabolic network reconstruction, to extract meaningful biological insights from complex metabolomic datasets²⁰⁴. Table 4 provides a concise comparison of the main advantages and disadvantages of these two approaches in metabolomic and lipidomic analysis.

Table 4. Advantages and disadvantages of targeted and untargeted approaches^{205–207}

	Targeted approach	Untargeted approach
Advantages	- Higher analytical accuracy (ISTD) - Absolute quantification - Optimized sample preparation - Focused analysis allows for precise comparisons between control and experimental group	- Flexible sample preparation - Systematic measurement of a large number of metabolites - Ability to detect both known and unknown compounds - Broad coverage
Disadvantages	- Limited number of compounds analysed - Increase risk of missing metabolites/lipids of interest - Requires prior knowledge of metabolic pathways	- Lack of reference standards - Unpredictable fragmentation patterns - Low precision (relative quantification) - Higher demand for time and resources - Detection bias toward high-abundance compounds

1.5.2 High/Ultrahigh-performance liquid chromatography (HPLC/UHPLC)

Liquid chromatography was first introduced in early 1900s by the botanist Mikhail S. Tswett, who separated plant derived compounds using a solvent through a packed column. Later, in 1970s, Csaba Horváth coined the term high-pressure liquid chromatography (HPLC; Figure 7), which was subsequently redefined as high-performance liquid chromatography in recognition of ongoing improvements in performance and instrumentation. In 2004, further advancements in column technology and instrumentation (reduction in particle size and the ability to operate at higher pressures) led to significant gains in resolution, speed and sensitivity. Today, ultra-high-performance liquid chromatography (UHPLC or UPLC) systems represent the evolution of HPLC, utilizing even smaller particle columns and capable of operating at much higher pressures, offering enhanced analytical efficiency. This technique is one of the most powerful tools in analytical chemistry, allowing for the separation, identification and quantification of compounds present in a sample dissolved in a liquid phase. It has been successfully applied to a wide range of samples type, including pharmaceutical products, food and nutraceuticals, environmental matrices, forensic samples and industrial substances²⁰⁸.



Figure 7. HPLC/UHPLC system

Figure 8 illustrates the basic components of an HPLC/UPLC system. The mobile phases (up to four) are delivered at the specific flow rate (mL/min) by one or more high-pressure pumps, ensuring a continuous and consistent flow through the packed particles within the chromatographic column. The sample, which contains the compounds of interest, is introduced into the continuous mobile phase stream by an injector (autosampler), which transports it into the column which is packed with stationary phase, essential for achieving separation. Following sample injection, the analytes are gradually separated due to the competition between the mobile and stationary phases for interaction

with each analyte, based on their specific physico-chemical properties. A detector is required to monitor the separated compound bands as they elute from the HPLC column. The detector is connected to a computer workstation, which records the electrical signal necessary to generate the chromatogram displayed on-screen and to identify and quantify the concentrations of the sample components. Since analytes may exhibit different chemical characteristics, various types of detectors have been developed. For example, if a compound is capable of absorbing ultraviolet light, a UV absorbance detector is employed. If the compound is fluorescent, a fluorescence detector is used. Additionally a mass spectrometer (MS) can be employed for further characterization. The most effective analytical approach often involves coupling multiple detectors in series. This allows HPLC to provide more comprehensive information about an analyte from a single injection²¹⁰

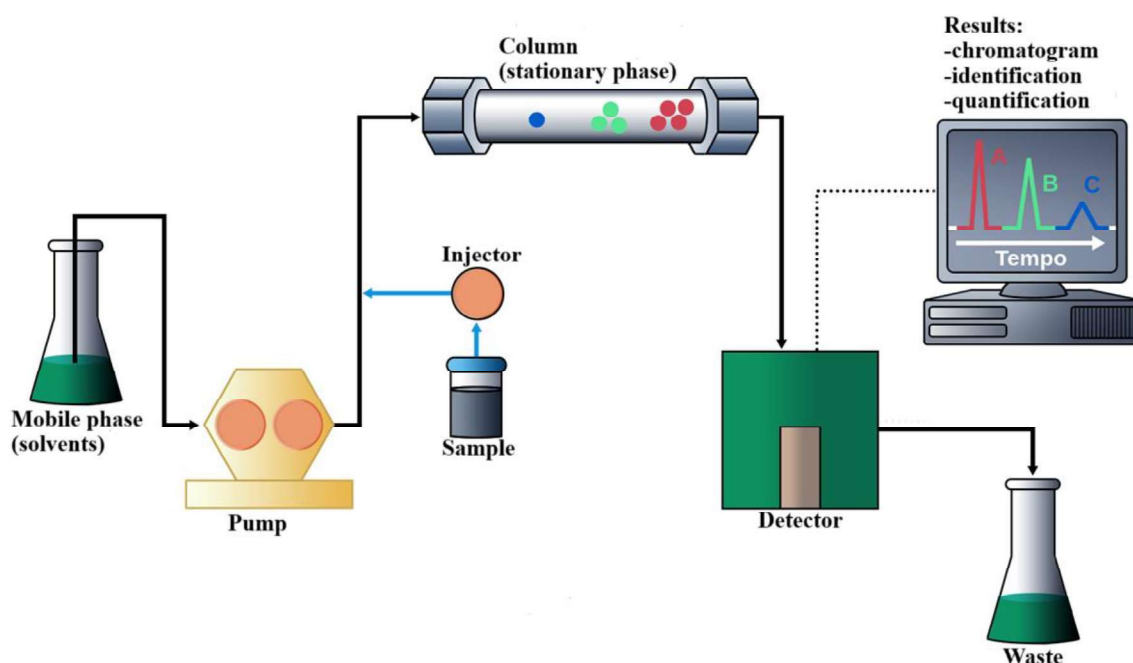


Figure 8. HPLC/UPLC scheme²⁰⁹

HPLC separations can be based on three main chemical properties of compounds: polarity, electrical charge and molecular size. Polarity is a key factor in two primary chromatographic modes: normal-phase chromatography (NPC) and reverse-phase chromatography (RPC). In designing a chromatographic system, a “competition” is established between the sample components by selecting mobile and stationary phases with differing polarities. Compounds with polarity similar to the stationary phase interact more strongly and migrate more slowly, while those with polarity closer to the mobile phase move faster due to weaker interaction. In normal-phase chromatography, the stationary phase is polar and the mobile phase is non-polar; typically, silica is used as the stationary

phase and the mobile phase is composed entirely of organic solvents, without water. Reverse-phase chromatography, on the other hand, uses a non-polar stationary phase and a polar mobile phase, usually a mixture of water and a water-miscible polar organic solvent such as acetonitrile or methanol. This setup facilitates the interaction of analytes with the hydrophobic surface of the stationary phase. The most common stationary phase in RPC is C18-bonded silica. A third polarity-based approach is hydrophilic interaction liquid chromatography (HILIC), which is considered a variant of NPC. In HILIC, polar analytes strongly interact with the polar stationary phase and may not elute unless water is added to the typically aprotic organic mobile phase. Increasing the water content (< 20%) raises the polarity of the mobile phase, allowing elution of strongly retained polar compounds. Buffer or salts are often added to maintain analytes in a consistent ionization state. Another technique, based on polarity, is hydrophobic interaction chromatography (HIC), used primarily to separate large biomolecules like proteins under aqueous conditions that preserve their native structure. HIC uses moderately hydrophobic stationary phase instead of strongly hydrophobic materials like C18 and exploits hydrophobic interactions between the biomolecules and the stationary phase. Separations based on charge are achieved using ion exchange chromatography (IEC), where the stationary phase contains acidic or basic groups that attract oppositely charged ions. Cation exchange retains positively charged ions on a negatively charged phase, while anion exchange retains negatively charged ions on a positively charged phase. The retention and selectivity depend on the nature and density of the ion-exchange sites. Size-based separations can be performed using size exclusion chromatography (SEC) or gel permeation chromatography (GPC), where molecules are filtered through a porous stationary phase such as hydrophilic dextran (GPC) or controlled-porosity silica (SEC). The mobile phase must dissolve the analytes effectively while minimizing interaction with the stationary phase. Larger molecules elute first, as they are excluded from the pores, whereas smaller molecules diffuse in and out of the pores and elute later, resulting in a separation based on decreasing molecular size²¹¹.

In light of this information, two different separation approaches were employed in this study depending on the analysis of interest. For lipidomic analyses, a reversed-phase chromatography was chosen using a CSH C18 column (Waters®). Conversely, for metabolomic analyses a hydrophilic interaction liquid chromatography (HILIC) approach was adopted using an Atlantis BEH Z-HILIC (Waters®). In both cases, however, the separation was based on polarity. High performance liquid chromatography was coupled with a time-of-flight mass spectrometer, which will be discussed in the following sections.

1.5.3 Mass spectrometry

Mass spectrometry (MS) is a powerful analytical technique widely used for the characterization of chemical compounds and biological molecules. It measures the exact molecular mass of a sample by breaking the original compound into smaller, charged fragments by ion source. It provides both qualitative and quantitative information and is capable of identifying and quantifying a broad range of clinically relevant analytes²¹². MS is not only applied in clinical field, but it is also used in various study area such as: toxicology, pharmaceutical research and chemical analysis, due to its high sensitivity, specificity and versatility. Mass spectrometry data are typically expressed in terms of the mass-to-charge ratio (m/z), where m represents the molecular mass of the ion (in Daltons) and z corresponds to the number of charges on the ionized molecule. For low molecular weight compounds (generally below 1000 Da), ions usually carry a single positive charge, making the m/z value effectively equal to the molecular mass. In contrast, larger biomolecules such as peptides and proteins tend to acquire multiple charges during ionization, resulting in m/z values that reflect both their mass and charge state, with z being an integer greater than one²¹³. This technique can be employed either to identify unknown compounds or to confirm the identity of product obtained from synthetic process²¹⁴. Although mass spectrometry can be used as a standalone technique, it is most commonly coupled with chromatographic methods (GC, LC), to enhance the separation and detection of complex mixture²¹⁵.

Figure 9 shows a schematic representation of a mass spectrometer, highlighting its three fundamental components: ion source, mass analyzer and detector. As previously mentioned, the sample can originate from a chromatographic separation or be directly injected into the ion source. Once introduced into the instrument, the sample is ionized using various ionization technique, which can generate either positive or negative ions depending on the specific analytical objectives. The resulting ions are then separated according to mass-to-charge (m/z) ratio through the application of electric and magnetic fields. These charged fragments are accelerated by the fields and pass rapidly through the mass analyzer. Upon exiting the analyzer, they collide with the detector, where their m/z values are recorded and converted into a mass spectrum. In this spectrum the y-axis represents the relative abundance of the detected ions, reflected by the intensity of each peak; while the x-axis corresponds to the mass-to charge ratio. For a given compound, the most abundant ion is referred to as the base peak, which is set to 100% intensity and all other peaks are expressed relative to it^{209,213}.

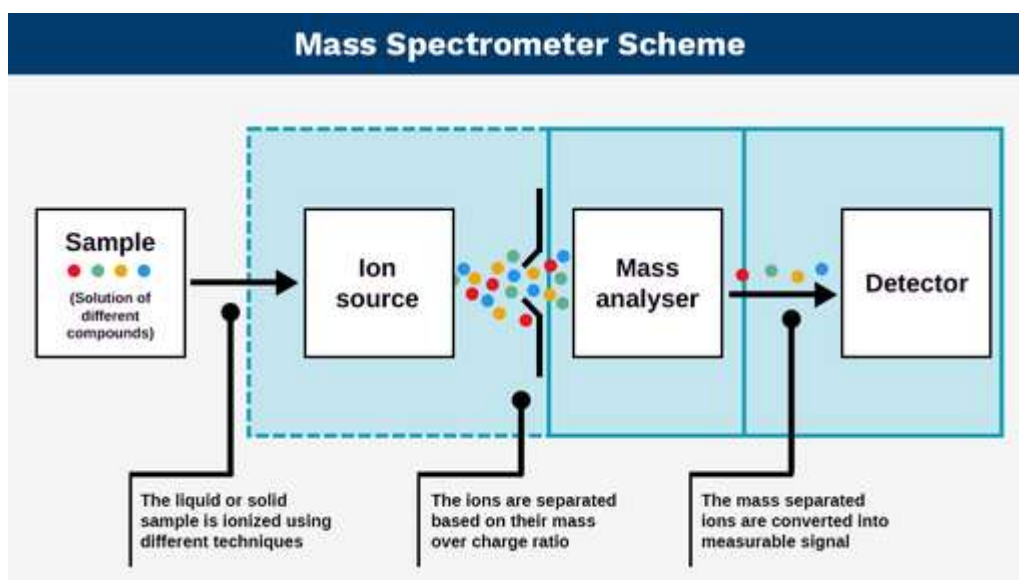


Figure 9. Mass spectrometer scheme²¹⁴

1.5.3.1 Ionization sources

Several ionization sources are available, and their selection depends on the specific analytical objectives and experimental conditions. Under vacuum conditions, electron ionization (EI) and chemical ionization (CI) are commonly employed, particularly in commercially available GC-MS system. For atmospheric pressure ionization, electrospray ionization (ESI) and atmospheric pressure chemical ionization (APCI) are widely used, especially in LC-MS applications²¹⁶. Another ionization technique, matrix-assisted laser desorption ionization (MALDI), generates ions by exposing the sample to a pulse of ultraviolet laser light²¹⁷. Table 5 summarizes the main characteristics of the ionization sources commonly used in mass spectrometry.

Table 5. Mass spectrometry ionization source types. GC-MS (gas chromatography mass spectrometer); LC-MS (liquid chromatography mass spectrometer); CE-MS (capillary electrophoresis mass spectrometer) and MS (mass spectrometer)²¹⁸.

Ionization Source Type	Characteristics	Applicable Compound	Instrument Type
Electron Ionization (EI)	Hard ionization; generates molecular ions	Thermally stable, volatile substances	GC-MS
Chemical Ionization (CI)	Soft ionization	Volatile, thermally stable substances	GC-MS
Electrospray Ionization (ESI)	Soft ionization source at atmospheric pressure	Less volatile, thermally unstable compounds	LC-MS or CE-MS
Atmospheric Pressure Chemical Ionization (APCI)	Soft ionization; ionization of oxygen or nitrogen with corona needle	Volatile, thermally stable substances	LS-MS

Ionization Source Type	Characteristics	Applicable Compound	Instrument Type
Matrix-Assisted Laser Desorption Ionization (MALDI)	Soft ionization; the matrix cocrystallizes with the compound, and the compound ion is produced by laser hitting the matrix	Large molecules	MS

Electron ionization (EI) is a widely used technique in which neutral molecules in the gas phase are ionized through interaction with high-energy electrons, typically accelerated at 70 eV. These electrons are emitted from a resistively heated filament and directed toward an anode, often following spiral trajectories under the influence of a magnetic field to maximize their interaction with the sample. When sufficient kinetic energy is transferred, an electron is removed from the analyte molecule, generating a positively charged molecular ion whose mass corresponds closely to the molecular weight of the original compound. This ionization process often imparts excess energy, leading to extensive fragmentation and the formation of a distinct pattern of fragment ions. These fragments provide valuable structural information; however the molecular ion itself may be weak or absent due to the high degree of fragmentation, which can complicate direct molecular weight determination. The ion source includes components such as extractor and focusing plates, which accelerate and direct the ions toward the mass analyzer for subsequent detection²¹⁶.

Chemical ionization (CI) is a soft ionization technique in which sample molecules are ionized through ion-molecule reaction in the gas phase, rather than direct interaction with high-energy electrons. A reagent gas, typically present in large excess (methane), is first ionized by electron impact. The resulting reagent gas ions react with the sample molecules, leading to the formation of pseudo-molecular ions through processes such as proton transfer, proton abstraction or adduct formation. Due to the relatively low energy involved, fragmentation is minimal, allowing for accurate determination of molecular mass but providing limited structural information. For this reason, CI is often used as a complementary approach to electron ionization, particularly when analyzing compound that are prone to extensive fragmentation under hard conditions²¹⁶.

Electrospray ionization (ESI) is a widely adopted atmospheric pressure ionization (API) technique, particularly in LC-MS applications. This source typically comprises a capillary through which the liquid sample flows and a counter-electrode positioned to generate an electric field (2000-4000 V). When a high voltage is applied between these components, electrical charges accumulate at the tip of the capillary, inducing the formation of charged droplets as the liquid exits. A nebulizing gas may be introduced to facilitate the formation of these droplets, while a drying gas promotes solvent evaporation. As the solvents evaporates, the droplets shrink and the surface charge density increases until Coulombic repulsion exceeds surface tension, causing the droplets to undergo successive fission events. This process continues until individual ions are introduced into the vacuum system of the

mass spectrometer for analysis. Like chemical ionization, ESI is classified as a soft ionization technique due to the limited fragmentation of analytes. However, unlike CI, ESI often generates multiply charged ions, making it particularly suitable for the analysis of high-molecular weight and thermally labile compounds, such as proteins and other large biomolecules²¹⁶.

Atmospheric pressure chemical ionization (APCI) is another soft ionization technique frequently used in LC-MS system, utilizing an interface setup similar to that of ESI. In APCI, the liquid effluent from the chromatographic column is introduced into a pneumatic nebulizer, often assisted by a flow of nitrogen gas, which generates a fine aerosol. This aerosol is then directed into a heated chamber where rapid solvent evaporation and vaporization of analytes occur. Ionization takes place via a corona discharge, which initiates electron ionization of the nebulizing gas. The resulting primary ions react with solvent molecules to generate secondary reagent ions, which subsequently transfer ionization with minimal fragmentation, allowing for reliable molecular ion detection, particularly for small to moderately polar compounds²¹⁶.

Matrix-assisted laser desorption ionization (MALDI) is a soft ionization technique introduced in the early 1990s, particularly effective for the analysis of large biomolecules such as proteins, peptides and polymers. In this method, the analyte is co-crystallized with a solid matrix, typically an organic compound possessing specific physico-chemical properties. These include strong absorption in the UV range (commonly at 337 nm), acidity to facilitate proton transfer, high water solubility and the ability to evaporate easily without degradation prior to analysis. Upon irradiation with a short and intense UV laser pulse, from a nitrogen laser, the matrix absorbs the energy and transfers it to the analyte. This induces both desorption and ionization, releasing gas-phase ions, typically carrying a single charge. The process allows for the formation of quasi-molecular ions through the gain or loss of a proton, with minimal fragmentation of the original molecule. The matrix plays a crucial protective role by absorbing the laser energy and mediating a gentle energy transfer, thus preventing decomposition of thermally labile analytes. Due to its high sensitivity and soft ionization characteristics, MALDI is frequently coupled with time-of-flight (TOF) mass analyzer, which are well suited to detect the broad mass range of ions generated by this technique²¹⁷.

1.5.3.2 Mass analyzer

After ionization, the fragment ions are accelerated and directed into the mass analyzer, where they are separated based on their mass-to-charge ratio (m/z). Various types of mass analyzers have been developed, each differing in ion separation mechanisms, resolution, transmission efficiency and detectable mass range. Depending on their resolving power, mass spectrometry systems are generally categorized into high-resolution (HRMS) and low-resolution (LRMS) instruments (quadrupole or triple quadrupole). HRMS, with resolution values typically exceeding 10,000, includes technologies such as time-of-flight (TOF), Fourier transform ion cyclotron resonance (FTICR) and Orbitrap

analyzers. These instruments enable accurate determination of exact mass and isotopic patterns, which is particularly advantageous in metabolite identification and structural elucidation. When combined with chromatography techniques, mass spectrometry becomes especially effective for analyzing complex mixtures. Chromatography enhances selectivity by reducing matrix interferences and allowing partial separation of isomers prior to ionization, thus improving both qualitative and quantitative performance^{216,218}. In Table 6 the characterization of different mass analyzers is reported.

Table 6. Characterization of different mass analyzers. a) in hybrid/reflectron configuration b) working resolution (FWHM)²¹⁹.

Analyzer	Quadrupole	Ion Trap	Time-Of-Flight	Orbitrap
Acquisition speed (Hz)	2-10	2-10	10-100	1-18
Mass accuracy (ppm)	Low	Low	1-10 ^a ppm	1-5 ppm
Mass range (m/z)	<3000	<6000	<100.000 ^a unlimited	<6000
Resolution	Unit	Unit	<50.000 ^a	<500.000 ^b
Advantages	Low cost, easily interfaced to various ionization techniques higher dynamic range	Low cost, easily interfaced to various ionization techniques, MS ⁿ	Fast scanning, high mass range and mass accuracy	High mass accuracy, fast polarity switch
Disadvantages	Low resolution, mass accuracy, mass range and scanning speed, MS/MS requires multiple analyzers	Low resolution, mass accuracy, mass range and scanning speed	High cost, lower dynamic range than quadrupole	Lower scanning rate than QTOF, high cost, lower dynamic range than quadrupole

The *single quadrupole (Q)* mass analyzer comprises four parallel metallic rods arranged within a vacuum chamber. By applying a combination of direct current (DC) and radiofrequency (RF) voltages to the rods, an oscillating electric field is generated. This field selectively stabilizes the trajectories of ions with specific mass-to-charge ratio (m/z) allowing them to pass through the analyzer to the detector. Ions with unstable paths are deflected and not detected. Before entering the quadrupole, ions are accelerated through a small orifice by a low-voltage potential. Within the analyzer, the applied voltages cause ions to oscillate in the x and y directions. Only those with stable oscillations, matching the set m/z range, successfully reach the detector, while others are filtered out. Quadrupole mass spectrometers operate in two main modes. Scan and selected ion monitoring (SIM).

In scan mode, the system incrementally varies the applied voltages to sequentially analyze a specified m/z range, producing a comprehensive mass spectrum. In SIM mode, the instrument selectively monitors predetermined m/z values, significantly enhancing sensitivity and minimizing interference from background noise or co-eluting compounds. Thanks to their operational simplicity, moderate vacuum requirements and effective performance up to 2000 m/z , quadrupole analyzers are widely used in routine analytical workflows²²⁰.

The *ion trap (IT)* mass analyzer is designed to capture and manipulate ions using oscillating quadrupolar electric field. Two main configurations exist: the three-dimensional ion trap (3D-IT), also known as the quadrupole ion trap and the two-dimensional ion trap (2D-IT) or linear ion trap. Linear traps offer greater ion storage and faster scanning compared to 3D configurations, though both operate at relatively low resolution. In both cases, helium gas employed to reduce ion kinetic energy and improve trajectory control during MS^n experiments. Ions are introduced in pulses and confined by applying a radiofrequency (RF) voltage to the ring electrode, while the end-cap electrodes are grounded. As the RF voltage increases, ions of specific mass-to-charge (m/z) ratios reach instability thresholds and are selectively ejected for detection. Unlike quadrupole analyzers, which transmit ions with stable trajectories, ion traps function by destabilizing and expelling ions sequentially. Although limited in dynamic range due to their pulsed nature, ion traps provide high sensitivity and enable multistage fragmentation (MS^n), making them particularly useful for detailed structural characterization in complex biological analyses^{219,220}.

The *time-of-flight (TOF)* mass analyzer (Figure 10) operates by measuring the time it takes for ions to travel through a field-free region within high-vacuum flight tube. Upon ionization, all ions are accelerated by a high-voltage electric field, imparting them with equal kinetic energy. Since velocity is inversely proportional to the square root of the ion's mass-to-charge ratio (m/z), lighter ions reach the detector more quickly than heavier ones (Equation 1-2). By correlating flight time with m/z a complete mass spectrum can be generated without the need for scanning.

Equation 1:

$$KE_{ion} = \frac{1}{2}mv^2 = zeV$$

Equation 2:

$$T = \frac{distance}{velocity} = \sqrt{\frac{m}{z}} \times \frac{L}{\sqrt{2eV}}$$

TOF instruments offer several advantages over scanning analyzers such as quadrupoles and ion traps. Notably, they provide high mass resolution and accuracy with no theoretical upper limit on mass range, making them particularly suitable for the analysis of large biomolecules, including intact proteins. Resolution can be further enhanced by extending the flight tube or employing a reflectron,

an ion mirror that corrects for differences in ion kinetic energy, thereby sharpening mass peak separation. Moreover, TOF analyzers are inherently compatible with pulsed ionization techniques, such as MALDI, enabling rapid spectral acquisition and supporting high-throughput applications. Recent technological improvements, such as delayed ion extraction and reflectron configurations, have significantly increased the resolving power of TOF instruments, enabling their use in high-resolution mass spectrometry for applications in proteomics, metabolomics and structural biology^{219,220}.

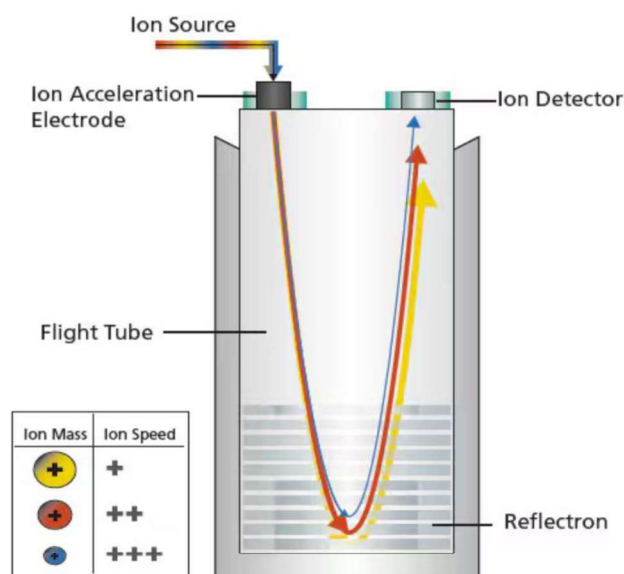


Figure 10. Schematic of a TOF-MS²²⁰

In *Orbitrap* mass spectrometry, ions produced by electrospray ionization are transferred through a series of quadrupoles and accumulated in a linear ion trap. This storage phase allows ion cooling and spatial focusing before synchronized injection into the Orbitrap analyzer, which functions in a pulsed mode. Within the trap, ions are temporarily confined in an axial potential well, where low-pressure bath gas (helium) is used to reduce their kinetic energy and spatial dispersion. The ions are accelerated and directed by ion optics system into the Orbitrap, where they are injected off-axis into an electrostatic field between a central spindle-shaped electrode and an outer barrel-like electrode. These oscillations generate image currents on the split outer electrodes, which are amplified and digitalized. The resulting axial motion induces an image current on the split outer electrodes. This signal is amplified, digitized and processed using a Fourier transform algorithm to generate a high-resolution mass spectrum. The accuracy and resolution of the Orbitrap are maintained by preserving spatial and phase coherence of the ion packets throughout the detection period. Although some signal loss may occur due to ion dephasing or collisions with residual gas molecules, the Orbitrap remains one of the most powerful analyzers in terms of mass resolution (up to 500,000 FWHM) and mass accuracy (sub-ppm with internal calibration) making it ideal for complex mixture analysis and structural elucidation²²¹.

To enhance mass resolution and accuracy, mass analyzers can be combined using tandem mass spectrometry (MS/MS) techniques. In a typical tandem set up, ions are first selected based on their mass-to-charge ratio (precursor ions), fragmented, usually via collision-induced dissociation (CID) in a collision cell, and the resulting product ions are then analyzed. MS/MS can be conducted using various instrumental configurations, including hybrid systems and ion trap, depending on the analytical goal. Among the most widely used instruments for targeted quantification is the *triple quadrupole* (QqQ) mass spectrometer (Figure 11), which consists of three quadrupole sections arranged in series. In this configuration, the first quadrupole (Q1) selects the precursor ion, the second (Q2) acts as the collision cell and the third (Q3) scans for the resulting fragment ions. This setup is particularly well-suited for sensitive and selective detection of known analytes in complex matrices, making it ideal for quantitative applications.

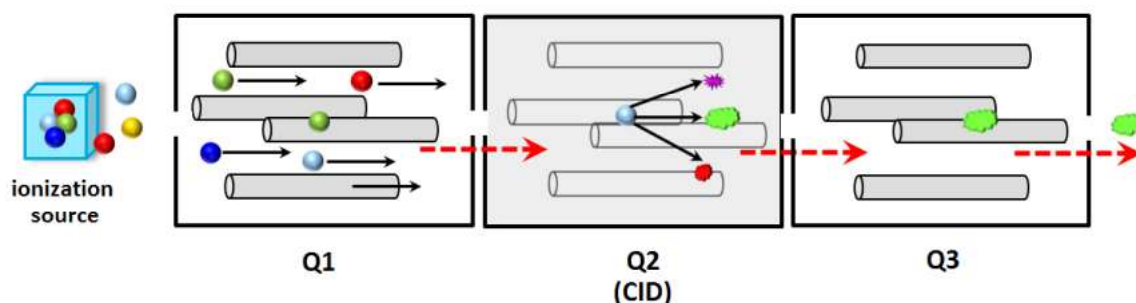


Figure 11. The tandem mass spectrometry based on triple quadrupole operation²¹⁹.

In addition to QqQ systems, other hybrid analyzers such as *quadrupole time-of-flight* (QqTOF) and *quadrupole-Orbitrap* instruments combine the specificity of quadrupole selection with the high resolution of TOF or Orbitrap detectors, allowing for both targeted and untargeted workflows. Ion trap instruments also support MSⁿ experiments, where sequential stages of fragmentation and analysis are performed within a single trap, further enhancing structural elucidation capabilities. Several MS/MS scan modes are available, each tailored to specific analytical needs. 1) product ion scans involve selecting a precursor ion and scanning for all resulting product ions (structural characterization). 2) precursor ion scans, on the other hand, identify all precursor ions that generate a specific product ion (screening of compound classes). 3) Neutral loss scans detect ions that undergo the loss of a characteristic neutral fragment during fragmentation, offering insights into shared structural features. For quantitative purposes, 4) selected reaction monitoring (SRM) and multiple reaction monitoring (MRM), are widely employed. These methods involve tracking specific precursor-product ion transitions with high sensitivity and reproducibility. Due to its superior selectivity and signal-to-noise performance compared to single ion monitoring (SIM), MRM has become the gold standard for quantitative targeted analysis, particularly in clinical and bioanalytical applications²¹⁹.

1.6 Data processing and identification of compounds

Metabolomic and lipidomic research generate complex datasets comprising hundreds to thousands of compounds. Proper data handling is essential, as it significantly influences the reliability and interpretability of the results. Yet, data processing and metabolite identification remain among the most challenging aspects of the workflow. This complexity arises from the inherent characteristics of metabolomics data, which are often noisy and involve a high number of intercorrelated variables relative to the number of biological samples. To address these challenges, a variety of data analysis tools are available, ranging from commercial software (e.g. Agilent Technologies, ABSciex) to open-source platforms such as MS-Dial, XCMS, Mzmine, MetAlign, MetaboAnalyst, MeltDB and the more recent Workflow4Metabolomics (W4M). These tools assist in the separation of meaningful biological variation from technical variability introduced during the experimental process. A robust and tailored data analysis is therefore critical and typically involves specialized software capable of integrating chemometric approaches, statistical analysis and bioinformatics. The general workflow for data analysis in metabolomic and lipidomics comprises four key stages: raw data processing, data pre-processing, data pre-treatment and data treatment (Figure 12). In untargeted studies, where a broad range of metabolites and lipids are measured simultaneously, careful consideration must be given to both biological variability and technical sources of error as these can introduce significant bias into the results²¹⁹.

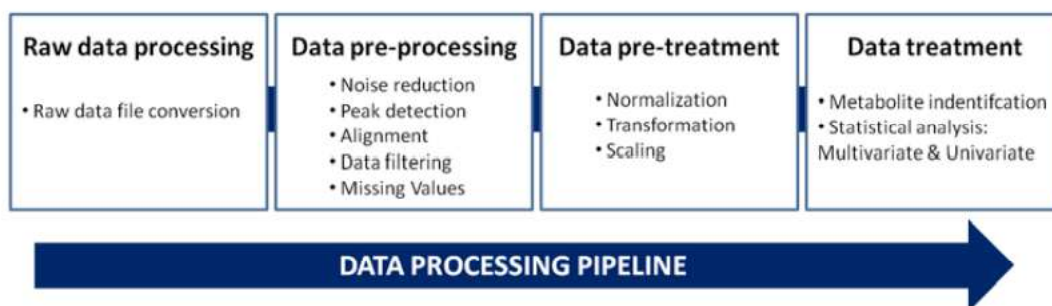


Figure 12. The main steps in the metabolomic and lipidomic data analysis workflow²¹⁹

Once the data have been acquired, the initial and crucial task is to transform the raw instrumental outputs into structured, interpretable scientific information. This process often involves converting vendor-specific file formats into open formats that are compatible with various third-party processing tools. However, this step becomes unnecessary when using proprietary software provided by the instrument manufacturers themselves, as these tools are already designed to work directly with the

native data format. In addition to vendor software, there are also freely available programs that can directly process raw data files generated by specific instrument platforms. For example, MS-DIAL is a widely used open-source tool capable of processing .wiff files produced by ABSciex instruments. These tools offer researchers the possibility to process and analyze complex metabolic and lipidomic data without the need for format conversion, ensuring compatibility with various data types and acquisition methods.

The data pre-processing stage encompasses all procedures applied directly to the raw data to enhance signal quality and correct for technical variation. This step is critical, as it reduces noise and improves the reliability of downstream analysis. It typically involves several operations: noise reduction to eliminate background signals, peak detection and deconvolution to identify relevant features, alignment to correct for retention time shifts, imputation of missing values and data filtration to remove irrelevant or redundant information. Following pre-processing, data pre-treatment is performed to address unwanted variation stemming from biological or experimental inconsistencies. Techniques such as normalization, transformation and scaling are applied to ensure that the observed differences in metabolic and lipidomic profiles reflect true biological variation rather than technical artifacts. Normalization is applied to correct for unwanted peak intensity differences and to stabilize the variance within the dataset. Transformation is often applied prior to statistical analysis, as compound abundances in a data matrix typically exhibit a right-skewed distribution; a common approach is the use of log transformation in stabilization variance and approximate normality. Scaling is performed to adjust for differences in fold change between metabolites which may be caused by large differences in the variation of the measured responses. Additionally, signal drift correction may be used to compensate for instrument related fluctuations over time²¹⁹.

The final step in the data analysis pipeline for both metabolomics and lipidomics is data treatment, which encompasses metabolite identification and statistical interpretation. Among these, compound identification is often the most challenging, due to the biological complexity of samples and the limitations of existing databases. In untargeted analyses, it is common for up to 50% of detected features to remain unidentified. Instead, identified compounds are typically classified into levels of confidence: tentative identifications based on database matching, refined identifications incorporating retention time and MS/MS fragmentation and definitive identifications confirmed by comparison with authentic standards under identical conditions. In metabolomics, database resources have significantly evolved in recent years. For example, The Human Metabolome Database (HMDB) has grown from 2,180 compounds in 2006 to over 42,000 entries, each with extensive data fields. Despite these advancements, the metabolomic remains less standardized than other omics, requiring researchers to cross-reference multiple online databases; over 50 are currently in use. Metabolomics databases are generally categorized as pathway-centered or metabolite-centered, the latter of which may further subdivide into compound- or spectral-based resources. Though many are metabolomics

specific, general platforms like KEGG and PubChem are also widely used. Instead, in lipidomics, identification is normally performed through manual data inspection, assisted by accurate mass and fragmentation data. Specialized resources such as LipidBank, LIPIDATA and LIPID MAPS provide valuable support for lipid structure annotation. To manage lipidomic data, mass spectrometer vendors have developed proprietary software tailored to specific acquisition methods, including: LipidView™ (ABSciex) for neutral loss and precursor ion scans and LipidSearch™ (Thermo Scientific) for LC-MS based workflow on Orbitrap instruments. Additionally, several open-source tools have gained traction in the research community. LipidXplorer and ALEX are optimized for shotgun lipidomics using high-resolution MS; LipidBlast enables MS/MS-based annotation of polar lipids across resolution levels; and MS-DIAL supports both data-dependent and data-independent acquisition modes. These tools enable qualitative and quantitative analysis across different MS platforms and acquisition strategies. Following identification, lipidomic data are typically normalized and subjected to statistical and data analyses using several approaches aligned with those employed in metabolomics including multivariate statistics and pathways analysis²¹⁹.

More specifically, before being used, compound identification lists must be carefully curated, with the aim of eliminating or consolidating redundant or conflicting assignments. In techniques such as LC-MS or CE-MS, several factors must be taken into consideration, including adducts and multiply charged species, fragments (neutral losses, degradation products etc.), isotopic peaks and noise signals. A critical revision of the identifications is also essential in order to discard implausible or incorrect assignments. Two main criteria can be adopted to filter out unreliable identifications: 1) knowledge of the relationship between the physicochemical properties of the putatively identified compound (polarity, charge, adduct formation) and the experimental condition (extraction solvent, mobile phase, ionization parameters); 2) understanding of the experimental design, including the organism treatment and sample type. Once the list has been curated, the identifications, in some cases their relative abundances, can be subjected to further statistical analysis and bioinformatic processing in order to evaluate the biochemical significance of the observed changes²¹⁹. Statistical and data analysis are discussed in detail in the following paragraphs.

1.6.1 MS-DIAL (Mass Spectrometry - Data Independent AnaLysis software)

In recent years, data-independent acquisition (DIA) approaches in LC-MS/MS have gained increasing attention for untargeted biomolecular analyses. Unlike traditional data-dependent

acquisition (DDA) methods, DIA enables the simultaneous collection of fragment ions for all precursor ions, thereby improving molecular coverage and reducing false negatives. However, the wider precursor isolation windows typically used in DIA (10-25 Da or more) can lead to spectral contamination and loss of the direct association between precursor and fragment ions, complicating compound identification. In proteomics, tools such as OpenSWATH have been developed to address these issues, but their direct application to metabolomics remains limited. In contrast, gas chromatography-mass spectrometry (GC-MS), which commonly uses DIA-type fragmentation under hard electron ionization, benefits from well-established data-processing pipelines. Inspired by these systems, the MS-DIAL (Mass Spectrometry-Data Independent AnaLysis) software was developed to process untargeted metabolomics data from both DIA and DDA LC-MS/MS experiments²²².

MS-DIAL begins by converting raw vendor data or mzML files into its proprietary Analysis Base Files (ABF) format for efficient data handling. It then performs peak detection (“peak spotting”) by examining retention time and accurate mass dimensions. Each detected feature undergoes deconvolution through the MS2Dec algorithm, which reconstructs clean MS/MS spectra from overlapping signals. This method, adapted from established GC-MS algorithms, applies least-squares optimization and accurate mass information to separate coeluting metabolites and lipids and minimize background noise. Compound identification in MS-DIAL integrates multiple criteria, including retention time, mass accuracy, isotope pattern and spectral similarity matching against public databases such as MassBank and LipidBlast. The software further supports essential untargeted metabolomic and lipidomic functions such as peak alignment, filtering and missing-value imputation. It is compatible with major vendor formats (Agilent Technologies (.D), ABSciex (.wiff), Thermo Fisher Scientific (.RAW), Bruker Daltonics (.D) and Waters (.RAW)) and is optimized for large-scale studies through sequential data access that minimizes memory usage²²².

The most recent release, MS-DIAL 5, introduces major algorithmic and interface improvements. It now supports additional data types, including direct infusion MS (DI-MS), ion-mobility-coupled MS (IM-MS), and mass spectrometry imaging (MSI). A key enhancement is the ability to load and prioritize multiple spectral libraries (MSP files), including in house standards, public or commercial databases (e.g. MassBank, NIST) and in silico predictions (e.g., CFM-ID). This flexible library management system improves annotation accuracy and reduces false identifications, making MS-DIAL 5 a comprehensive and user-friendly platform for advanced untargeted metabolomics and lipidomic workflows²²³.

1.7 Statistical and data analysis

1.7.1 Statistical analysis

After obtaining the cleaned data matrix containing the list of potential compounds and their abundances in each sample, the next step involves applying statistical chemometrics tools, which provide model-based descriptions of the biological variation in the system and enable the detection of meaningful patterns and changes in metabolite or lipid levels across different experimental conditions. Both univariate and multivariate approaches are commonly employed to explore the dataset comprehensively and to identify features that exhibit statistically significant variations. To further narrow down the list of biologically relevant compounds, advanced data mining techniques are often integrated into the analysis workflow. Nevertheless, traditional statistical tools typically rely on mathematical relationships among variables, often disregarding the biological context in which these variables interact; an important limitation when studying highly interconnected biological systems²²⁴. To mitigate this, the combined application of multiple statistical approaches is strongly recommended, as it improves both the robustness and interpretability of the results. A critical aspect of this process is the selection of an appropriate p -value threshold to rank significantly altered metabolites or lipids. The choice of this threshold can significantly influence which molecular changes are deemed biologically relevant, ultimately affecting the conclusions drawn from the study²²⁵. Depending on the study design and objectives, a wide range of statistical and data mining techniques can be adapted and applied. In the following paragraphs will be described an overview of the most commonly used univariate and multivariate methods in metabolomic, which are equally applicable to lipidomics datasets.

Univariate statistical analysis is often employed as an initial step to characterize the dataset and highlight features that may differ significantly across experimental conditions. For comparisons between two groups, commonly used tests include the Student's t -test (for normally distributed data) and its non-parametric counterpart, the Mann-Whitney U test. These methods evaluate whether the means or medians of two independent groups differ significantly, providing a simple yet effective approach for identifying potential biomarkers. Once a t -value is determined, a p -value can be used to determine whether this distinction is statistically significant. To visually integrate both statistical significance and magnitude of change, volcano plots are widely used. These plots combine the p -value from the statistical test (y-axis, as $-\log_{10}(p)$) with the fold change (FC) (x-axis, as $\log_2(FC)$), facilitating the identification of metabolites or lipids that are both significantly altered and biologically relevant between a control group and pathological subjects. These tests can support both paired and unpaired analyses, the first one is used when the same individuals are measured before and after an intervention and the second is used when individuals randomly are assigned to two groups^{226,227}. For experiments involving more than two groups, one-way analysis of variance (ANOVA) is used to assess whether there are significant differences among group means. When a significant ANOVA result is obtained, post hoc test (e.g. Turkey's HSD or Fisher's LSD) are necessary to determine which specific groups differ from each other. Correlation analysis may also be performed to examine the relationship between metabolite abundances and continuous variables,

such as clinical or phenotypic measurements. Given that metabolomic datasets typically include hundreds to thousands of variables measured across a relatively small number of samples, multiple hypothesis testing presents a significant risk of false positives. To address this, *p*-value adjustment methods such as Bonferroni, Holm-Bonferroni and Benjamini-Hochberg corrections are applied. Among these, the Benjamini-Hochberg procedure, which controls the false discovery rate (FDR), is often preferred in omics studies because it offers a balance between stringency and sensitivity²²⁷.

Since univariate analyses assume that only one factor influences the response of each variable, they may be inadequate when investigating complex pathologies where multiple biological pathways are simultaneously affected and regulated by several interacting variables. In such contexts, multivariate data analysis (MVDA) provides a more suitable statistical framework. Indeed, MVDA plays a pivotal role in metabolomics and lipidomics by enabling the simultaneous evaluation of numerous metabolites and facilitating the identification of those most significantly associated with biological variation. Prior to the application of this approach, data-pretreatment steps (scaling and transformation) are essential to enhance comparability across variables and optimize the extraction of relevant patterns. Commonly used MVDA techniques include unsupervised methods, such as principal component analysis (PCA) and supervised approaches like partial least square discriminant analysis (PLS-DA) and its orthogonal variant OPLS-DA. These methods reduce the dimensionality of complex datasets by summarizing multiple variables into a smaller number of components, thereby simplifying interpretation and revealing latent structures. Multivariate data analysis is particularly effective for exploratory data, as it uncovers associations, trends and grouping that might remain undetected using univariate approaches alone^{219,227}.

More specifically, PCA, first introduced by Pearson in 1901, is an unsupervised multivariate statistical technique widely employed for dimensionality reduction and data visualization. By utilizing orthogonal transformations, PCA converts potentially correlated variables into a set of linearly uncorrelated variables known as principal components (PCs). These components capture the maximum variance in the data in descending order of importance, with PC1 accounting for the greatest variance, followed by PC2 and so forth. PCA serves two primary purposes in omics research: it enables the compression of high-dimensional data into a simplified form while preserving essential variance and it allows for an initial assessment of the biological replicates' quality, thereby facilitating the identification of outliers that may compromise downstream analyses. Additionally, PCA helps to identify the main sources of variability within the dataset, such as biological factors or treatment effects. In contrast, PLS-DA is a supervised extension of PCA that incorporates known group information to optimize the separation between predefined classes. This method has been extensively used in chemometrics and omics research for over two decades, particularly for its ability to combine dimensionality reduction with classification and feature selection. PLS-DA facilitates the identification of key variables contributing to differences among experimental groups, making it

especially valuable for the screening of differential metabolites. Building upon PLS-DA, OPLS-DA further enhances model interpretability by integrating orthogonal signal correction (OSC). OPLS-DA decomposes the predictor matrix (X) into components that are predictive of the response variable (Y) and those that are orthogonal, or unrelated, to Y. This separation of systematic variation enables the exclusion of noise or confounding factors, such as minor environmental fluctuation, that might obscure biologically relevant signals. As a supervised method, OPLS-DA focuses on the predictive component and improves the identification of statistically significant and biologically meaningful variables. It is particularly effective in omics contexts (metabolomic, spatial metabolomic and proteomic) where it aids in identifying key metabolites, lipids or protein biomarkers, distinguishing tissue-specific molecular patterns and integrating multiple layers of omics data. Together, PCA, PLS-DA and OPLS-DA represent a powerful suite of multivariate analysis tools that not only reduce data dimensionality but also enhance the interpretability of complex biological dataset, supporting robust biomarker discovery and hypothesis generation in a wide range of omics studies²²⁸. In table 7 these statistical approaches are compared.

When developing one of the statistical models described above, two fundamental parameters (R^2 and Q^2) are typically employed as preliminary indicators of model quality and serve as the bias for initial validation. R^2 quantifies the proportion of variance in the training data explained by the model. It indicates how well the model fits the observed data, with higher values reflecting better explanatory capability and reproducibility. Conversely, Q^2 evaluates the model's predictive accuracy by estimating its ability to generalize to new, unseen data. A high value denotes strong predictive performance. For a model to be deemed robust and suitable for diagnostic applications, particularly in the context of biological data, both R^2 and Q^2 should be relatively high and the difference between them should not exceed 0.2-0.3. A substantial discrepancy between these values may suggest overfitting, where the model adapts too closely to the training data and fails to capture generalizable patterns. Commonly accepted thresholds for biological datasets are $R^2 > 0.7$ and $Q^2 > 0.4$ ²¹⁹.

Table 7. Method comparison: PCA vs PLS-DA vs OPLS-DA²²⁸

Feature	PCA	PLS-DA	OPLS-DA
Type	Unsupervised	Supervised	Supervised
Advantages	Data visualization, evaluation of biological replicates	Identify differential metabolites, build classification models, assessing the statistical significance of PLS-DA results is essential for reliable conclusions	Improve accuracy and reliability of differential analysis with OPLS-DA model

Feature	PCA	PLS-DA	OPLS-DA
Disadvantages	Unable to identify differential metabolites	May be affected by noise	Higher computational complexity. Internal cross validation is crucial to prevent overfitting in OPLS-DA models
Risk of overfitting	Low	Medium	Medium-High
Suitable for	Exploration	Classification	Classification + clarity
Common in	All omics	Metabolomics, proteomics	Proteomics, multi-omics

Another important aspect in the application of PLS-DA and OPLS-DA models is the variable importance in the projection (VIP) score, which serves as a key metric for assessing the relevance of each variable within the model. The VIP score indicates how much each predictor contributes to the model's ability to make accurate and reliable classifications. Higher values suggest a stronger influence in explaining the dependent variable. To build a robust model, variables (metabolites, lipids) with a VIP score greater than 1 are commonly selected, as they are considered especially relevant for distinguishing between classes. Analyzing VIP Scores thus supports the identification of the most informative features, streamlines the model by reducing dimensionality and enhances the interpretability of the results^{219,229}.

To avoid overfitting the statistical model needs to be validated. The validation is essential to objectively assess a model's performance and stability. Two widely used techniques are the permutation test and cross-validation. The first one evaluates the significance of a classification by randomly permutating class labels multiple times and building models for each permutation. The performance of these models is then compared to the original one. It is best suited for large dataset (more than 50 samples). Instead, cross-validation is ideal for small to medium sized datasets, this method involves repeatedly partitioning the data into training and testing subsets. A typical approach is the "leave-1/3-out" method, where one-third of the data is left out to test the model trained on the remaining two-thirds. This process is repeated until all samples have been used for validation. A model is considered valid if it consistently and accurately predicts the excluded data²¹⁹.

Another commonly used tool in statistical analysis is the heatmap, widely recognized as an effective visualization technique in omics research, particularly in the fields of proteomic and metabolomic. Its strength lies in the ability to represent complex, high-dimensional data in an intuitive and

interpretable way. Beyond its traditional exploratory role, heatmaps are now increasingly employed for integrating heterogeneous datasets, generating and testing hypotheses and exploring complex molecular interactions. The integration of different omics layers (transcriptomic, proteomic and metabolomic) allows researchers to identify novel relationships among biological components and gain more comprehensive understanding of cellular processes. Techniques such as dataset concatenation and correlation mapping are often used to support this integration. However, several challenges must be addressed, including ensuring high data quality, avoiding over-interpretation of visual patterns and rigorously validating results. From scientific communication perspective, it is essential to follow best practices in data visualization, such as using clear labeling, appropriate color scales, context-specific annotations and simplifying graphic elements to highlight the most relevant findings. Ultimately, a well-designed heatmap serves not only as a visual summary of the data but also as a narrative tool that can guide scientific discovery, facilitate interdisciplinary collaboration and enhance the understanding of complex biological systems²³⁰.

1.7.2 Data analysis

Following the identification and curation process, the resulting list of compounds (lipids, metabolites, proteins...) with their relative abundances, serves as a foundation for data analyses. These analyses aim to explore the biological relevance of the detected changes and are typically carried out using a combination of statistical approaches and specialized bioinformatic tools. These last tools related to biochemical pathway analysis can be grouped into two main categories: pathway database, which are similar to compound databases but contain information on entire metabolic pathways rather than individual molecules; pathway analysis tools, which apply mathematical algorithms to assess the significance of observed changes, based on signal enrichment and the number and relevance of the affected metabolites.

Biochemical pathway analysis is a fundamental tool for interpreting metabolomic data within a biologically meaningful framework. A pathway can be defined as a sequence of biochemical reactions that convert a set of substrates into specific products. However, this definition remains somewhat arbitrary and non-standardized, as the inclusion of metabolites and lipids in a given pathway often varies across databases. Moreover, pathways differ in size, frequently overlap and a single metabolite may participate in multiple pathways. Despite these limitations, pathway databases provide a rich source of biological information by linking metabolites to genes, proteins and diseases, while also offering interactive tools for metabolite, lipid mapping and visualization across different species. Among the most widely used databases are KEGG (Kyoto Encyclopedia of Genes and Genomes), Recon 2, SMPDB (Small Molecule Pathways DataBase) and PathWhiz, which allow the exploration of complex biological functions through detailed metabolic maps. In particular, KEGG

serves as a comprehensive resource for understanding the systemic functions of biological systems, including cells, organisms and ecosystems, based on molecular-level information. KEGG integrates genomic, chemical (metabolite and compounds) and systems-level data (molecular interaction and reaction networks) alongside information related to diseases and pharmaceuticals. Currently, KEGG includes over 508 metabolic pathway maps, 17931 compounds 11015 glycans and 10476 annotated biochemical reactions. Metabolomics pathway analysis typically employs two complementary strategies: enrichment analysis, which assesses whether biologically meaningful groups of metabolites (e.g. associated with particular pathways or disease states) are statistically overrepresented among those that show significant changes; and topological analysis, which incorporates the structural context of each metabolite within the metabolic network, considering factors such as its connectivity and centrality. Several bioinformatic tools have been developed to support these analyses. For example, iMet-Q (intelligence metabolomic quantitation) provides an automated pipeline for metabolite quantification in LC-MS data, including noise filtering, peak detection and alignment. Tools such as: MBRole (Metabolite Biological Role), BiNChE, IMPaLA, MPEA (Metabolite Pathway Enrichment Analysis) and MSEA (Metabolite Set Enrichment Analysis) offer various approaches for enrichment analysis, ranging from simple over-representation to multi-omic data integration and customizable metabolite sets. MSEA, in particular enables the exploration of metabolite concentration changes in the context of pathways, disease associations and tissue localization, supporting both qualitative and quantitative analyses through user-friendly visual outputs. Instead, for topological analysis, where the structure of the metabolic network is taken into account, tools like MetaboAnalyst represent a robust and freely accessible platform widely used in the metabolomic community. MetaboAnalyst incorporates KEGG-based pathways maps and supports a range of statistical and topological methodologies to assess the impact of metabolite changes based on their position in the network. Its interactive, web-based visualization interface helps users to interpret complex results more intuitively²¹⁹. In conclusion pathways and enrichment analysis provide essential interpretative frameworks that transform complex metabolic datasets into biologically coherent insights, enhancing understanding of metabolic alterations in health and disease.

Once relevant pathways or metabolite/lipid sets have been identified through enrichment and topological analysis, the next step is to assess their potential as biomarkers capable of distinguishing between experimental conditions. When a single metabolite, or more commonly a panel of compounds, is proposed as a discriminative signature, it becomes necessary to validate its predictive performance through a target, quantitative experiment conducted on a larger, independent cohort of samples. Ideally, this validation phase should be carried out on individuals not included in the initial discovery phase, in order to avoid overfitting and ensure the generalizability of the findings. To evaluate the diagnostic or classification performance of these biomarkers, one of the most robust and widely accepted approaches is the analysis of Receiver Operating Characteristic (ROC) curves. This

statistical method allows for the construction of predictive models from one or more variables (metabolites and lipids), which can then be applied to classify new subjects into distinct categories. A ROC curve is a graphical representation that plots the true positive rate (sensitivity) against the false positive rate (1-specificity) across a range of threshold settings, providing a visual and quantitative measure of the model's discriminatory power. The area under the ROC curve (AUC) serves as a summary metric of classification accuracy, ranging from 0.5 (no discriminative ability) to 1.0 (perfect classification). In the context of biomarker validation, the goal is to achieve the highest possible AUC with the smallest and most biologically meaningful set of metabolites. Among the available tools for ROC analysis, RocCET (now integrated into the MetaboAnalyst platform) offers a user-friendly and statistically rigorous environment for model construction, performance evaluation and biomarker optimization²¹⁹.

1.7.3 MetaboAnalyst

There are two principal strategies for the analysis of metabolomic data: chemometric (untargeted) and quantitative (targeted) approaches²³¹ as explained before. Chemometric techniques focus on identifying statistically relevant spectral features without initially assigning compound identities. Instead, spectral patterns and signal intensities are compared across sample groups to detect features that discriminate between conditions. Only after this statistical analysis are efforts made to identify the underlying metabolites associated with those features. In contrast, quantitative metabolomics involves the prior identification and quantification of metabolites within a biosample before conducting downstream analysis. This process typically relies on comparing NMR, GC-MS or LC-MS spectra to spectral libraries or isotopically labeled standards. However, recent expansions in publicly available metabolomic databases and spectral libraries^{54,232,233} have facilitated the broader adoption of this method. Regardless of the analytical strategy employed, it is important to recognize that metabolomic datasets share considerable similarities with microarray data. Both are characterized by high-dimensional features spaces and relatively limited sample sizes and both aim to identify features associated with specific biological conditions, often for purposes of biomarker discovery or classification. Consequently, statistical methods and machine learning techniques developed for microarray analysis can be adapted for use in metabolomics. To explore this potential, Xia, J. et al in 2009, have utilized resources from the R-project and Bioconductor project²³⁴, both of which offer extensive collections of open-source tools for statistical analysis and machine learning. By integrating these tools with custom built modules for metabolite identification and pathway mapping developed in their laboratory, they created MetaboAnalyst, a comprehensive web-based platform for the analysis, visualization and interpretation of high-throughput metabolomic data²²⁶.

MetaboAnalyst was developed using Java Server Faces (JSF) technology. The R and Bioconductor packages functions allowed to build the backend statistical computing and visualization operations of this new tool. All MetaboAnalyst functions are carried out by R script and Bioconductor function. MetaboAnalyst is compatible with a wide range of data formats, including compound concentration tables, spectral binned data, NMR or MS peak lists and GC/LC-MS spectral files (e.g. NetCDF, mzMXL, mzDATA) commonly used in chemometric analyses. The platform offers a full suite of functionalities for data clustering and classification. It also supports compounds annotation and biological pathway mapping, presenting results through a variety of intuitive and visually rich graphical outputs. MetaboAnalyst is not a fully automated tool, but it operates as a guided, multi-step analysis pipeline, similar to established microarray tools such as GEPAS and CARMAweb. It is primarily designed for two-group comparative analyses (control vs experimental) and support both paired and unpaired study designs. A standard workflow includes six stages: 1) data upload, 2) data processing, 3) normalization, 4) statistical analysis, 5) data annotation and 6) summary report generation (Figure 13). The platform features an intuitive interface, with interactive navigation aids and context-sensitive guidance through each step. To support users, MetaboAnalyst also provides tutorials, sample datasets, example reports and extensive FAQ section²²⁶.

Since its initial release just described over, MetaboAnalyst has evolved substantially, reflecting rapid advances in the field of metabolomic and overcoming limitations of the first and subsequent versions. The original version (1.0) was primarily designed to support data normalization and basic statistical analysis. Subsequent versions have progressively expanded the platform's functionality in line with emerging analytical needs. Version 2.0 introduced support for functional analysis tailored to targeted metabolomics, while version 3.0 emphasized translational biomarker discovery and significantly improved performance through the integration of cloud computing and modern web technologies.

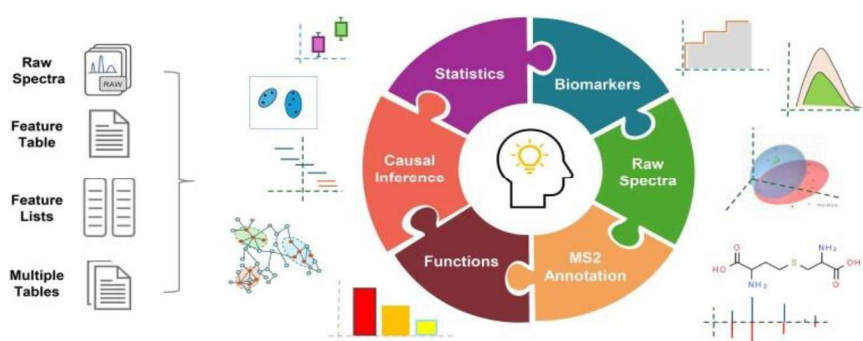
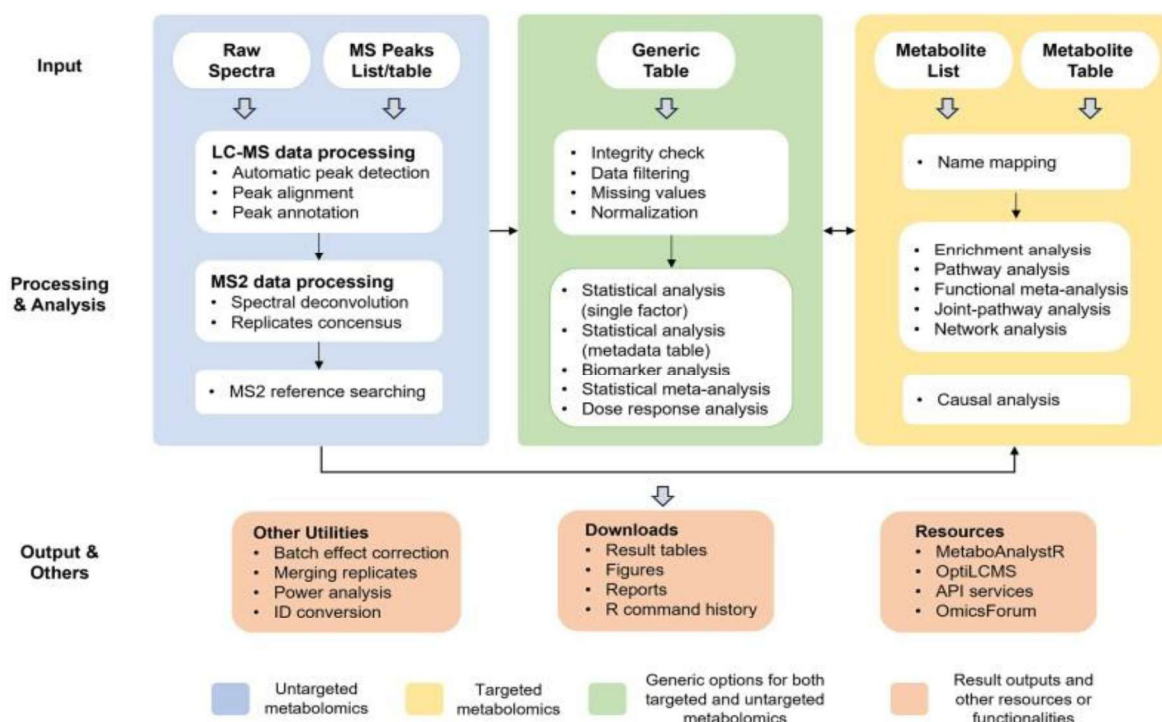


Figure 13. MetaboAnalyst workflow for targeted and untargeted metabolomic and lipidomics data²³⁵.

The release of version 4.0 marked a key translation toward more integrative and reproducible workflow, including tools for the functional interpretation of untargeted, global metabolomics datasets. For example, version 4.0 enabled direct functional analysis from LC-MS peak data, a

capability that was further enhanced in version 5.0, which incorporated an auto-optimized LC-MS spectral processing module seamlessly linked to downstream functional analysis^{235,236}. Building on this trajectory, Pang et al. in 2024, developed MetaboAnalyst version 6.0, which introduces several major enhancements. Among these is improved LC-MS spectra processing pipeline incorporating the Asari algorithm, along with support for MS2 data acquisition modes (DDA and SWATH-DIA). This version also adds new modules for MS2-based compound identification, causal inference analysis using two-sample Mendelian Randomization (2SMR) and dose-response modeling with benchmark dose (BMD) estimation. Additionally, this version supports more sophisticated statistical analyses involving complex metadata and offers improved functional interpretation by integrating MS2-based compound identification with pathway and metabolite set analyses. Updates to compound databases and enhanced visualization tools further extend the platform's analytical capabilities²³⁶.

When comparing the core functionalities of MetaboAnalyst 6.0 with other widely used metabolomic platforms as well as XCMS online, GNPS, Workflow4Metabolomics (W4M) and Met Explore, MetaboAnalyst continues to distinguish itself as the most comprehensive tool for the processing, statistical analysis and biological interpretation of metabolomic data. Its ability to support both targeted and untargeted workflow, along with recent innovations in MS2 data integration, casual inference and dose-response modeling, underscores its leadership in the field. In conclusion, MetaboAnalyst 6.0 represents a mature and user-friendly platform for high-throughput metabolomic analysis. Its extensive functionality and analytical rigor effectively meet the evolving needs of complex studies, where high-dimensional data demand integrative and scalable computational solutions. Future development will focus on enhancing metabolite annotation, facilitating multi-omics integration and leveraging generative artificial intelligence to offer more interactive and adaptive user experiences²³⁶. Accordingly, MetaboAnalyst was selected as the most suitable platform for performing the statistical and data analyses required in this study.

1.8 Applications of metabolomics and lipidomics

Metabolomics and lipidomics have rapidly evolved, as explained above, into essential tools within systems biology, offering deep insights into the dynamic biochemical processes that govern health and disease. These approaches capture the molecular phenotype, more directly than genomics or transcriptomics, rendering them uniquely sensitive to environmental, dietary, developmental and pathological influences^{237,238}. Recent methodological advancements, particularly in high-throughput and high-coverage mass spectrometry, have significantly enhanced analytical precision and enabled quantitative analysis of a vast array of metabolites and lipid species, even from small samples volumes. In the clinical, metabolomic and lipidomic platforms now support the discovery and

validation of biomarkers for disease prediction, monitoring and precision medicine applications²³⁷. Indeed, these omics platforms have been applied across a wide spectrum of biological research contexts including physiology, pathology and addiction studies. Within the physiological domain, metabolomics and lipidomics profiling has been used to identify age-associated metabolic changes and to support the development of biological age prediction tools, such as lipid-based “aging clock”²³⁹. In pathological context, integrated metabolomic and lipidomic workflows have provided insights into mechanisms underlying neurodegenerative diseases (Alzheimer’s, multiple sclerosis, dementia) as well as chronic inflammatory, cancers, diabetes and metabolic disorders^{157,189,218,240–242}. In the context of addiction, instead, emerging studies explore neurochemical alterations and metabolic disruptions associated with substance use, although targeted examples remain comparatively less represented in recent literature^{243,244}. Taken together, the synergy of metabolomic and lipidomic facilitates comprehensive investigation across cellular metabolism, disease progression, exposure phenotypes and therapeutic response. The following section examines these applications in detail: physiological studies (aging), pathological studies (Alzheimer’s disease) and addiction studies.

1.8.1 Physiological studies: Aging

Physiology, as a core discipline within the life sciences, focus on understanding the mechanisms that govern the function of living organisms, from molecular and cellular processes to the coordination of complex systems at the whole-body level. It provides essential insight into how the body maintains homeostasis, responds to internal and external stimuli and adapts to environmental and lifestyle challenges. By investigating these mechanisms under normal conditions, physiology lays the foundation for recognizing deviations associated with disease. Physiological research is inherently experimental and integrative, combining molecular, cellular and systemic approaches to uncover the dynamic interactions that sustain life. In recent years, particular attention has been given to the physiological processes underlying aging, with studies increasingly aimed at identifying biomarkers, regulatory pathways and adaptive changes that characterize the aging trajectory. Understanding these age-related changes is critical for informing strategies to promote healthy aging and prevent age-associated functional decline^{245,246}.

Aging is a complex, gradual and multifactorial biological process marked by the progressive accumulation of cellular and molecular damage, which contributes to systemic functional decline and increased susceptibility to chronic diseases. Notably, the rate and manifestation of aging vary significantly among individuals, leading to substantial heterogeneity in physical and cognitive status between people of the same chronological age. This divergence underscores the need to develop reliable metrics for assessing biological age, as opposed to merely relying on chronological age.

Biological age is increasingly recognized as more informative predictor of health outcomes, including morbidity, mortality and functional capacity. Monitoring biological aging could enable early interventions, well before the clinical onset of age-related diseases, many of which have long asymptomatic phase. In this context, the identification of robust biomarkers of aging has become a major research priority. These markers can enable the assessment of an individual's biological age, independently of chronological age and serve as early indicators of age-related decline or disease risk²⁴⁵. Traditional biomarkers have typically been selected based on their correlation with chronological age, without necessarily reflecting the underlying mechanisms driving aging or accounting for individual variability. However, current research efforts are increasingly focused on mechanism-specific and omics-based biomarkers, which offer a more nuanced understanding of aging as multifactorial and system wide process. To enhance the classification and utility of aging biomarkers, the field has increasingly adopted standardized framework such as the FDA-NIH BEST (Biomarkers, EndpointS and other Tools) classification. This taxonomy distinguishes biomarkers by modality such as molecular, physiological, histological and radiographic and aims to harmonize terminology across biomedical and translational research. Among these, molecular biomarkers, often derived from omics data or based on individuals circulating molecules, are the most widely developed. Omics technologies have opened new avenues for discovering molecular signatures that reflect both age-related physiological states and pathological trajectories. These approaches allow for a comprehensive and integrative view of biological aging, capturing alterations across multiple biological layers. While functional studies in model organisms have provided valuable insight into aging pathways, the translation of these biomarkers into clinically applicable tools remains challenging due to issues of feasibility, invasiveness and context specificity. Physiological biomarkers, on the other hand, may include objective functional measures such as gait speed, grip strength and cognitive performance, some of which have been accepted by regulatory bodies like the FDA as surrogate endpoints for disease outcomes, although they are not yet formally recognized for aging or health span trials. In addition to these categories, digital biomarkers are gaining traction. These include longitudinal, real-world measures such as sleep patterns, mobility and heart rate variability, which may provide scalable, non-invasive means to monitor biological aging over time. Although histological and radiographic biomarkers remain limitations, recent advances in imaging and computational analytics may soon make them more accessible. Overall, the development of comprehensive, validate biomarkers, particularly molecular and omics-based, is critical for advancing our understanding of aging and for enabling early interventions, personalized risk stratification and the design of clinical trials aimed at extending health span^{245,247}.

As highlighted in the review by Moqri et al. (2023), research on molecular biomarkers of aging began to gain momentum around 2011, with a predominant focus on epigenetics. This omics technique studies changes in gene expression influenced by environmental and lifestyle factors, without altering the underlying DNA sequence. Since then, numerous studies have investigated epigenetics

alterations as key indicators of biological aging, leading to the development of various epigenetics clocks and predictive models. In parallel, other omics approaches such as transcriptomics, proteomics and metabolomics have been explored to identify aging-related molecular signatures²⁴⁷. Furthermore, lipidomics has emerged as a complementary approach to investigating the role of lipid metabolism and lipid-related pathways in aging. These integrative multi-omics strategies are now at the forefront of biomarker discovery, aiming to enhance the accuracy and applicability of aging biomarkers across populations and contexts²³⁹.

Metabolomic studies started years ago from early animal studies of longevity to cellular and molecular of aging processes; but human population metabolomic studies of aging began to emerge in the late 2000s. While early studies focused on plasma, serum and urine samples from 2020s studies have expanded to more specialized contexts such as cerebrospinal fluid (CSF)²⁴⁸, saliva²⁴⁹ and muscle²⁵⁰. Despite variations in scale, analytical technologies, biological matrices and cohort characteristics, several consistent patterns have emerged across human population studies investigating the metabolic signatures of aging. As illustrated in Figure 14, these findings can be grouped into seven major metabolomic pathways associated with aging: lipid and lipoprotein metabolism, steroid hormone regulation, renal function and excretory processes, amino acid metabolism and muscle physiology, diet-related metabolites, oxidative stress and inflammatory pathways. The themes on the left of the pictures are grouped by chemical structure and the themes on the right are grouped by biological pathway. Within each pathway the most consistent changes with age are noted as an up arrow (increased with age) or down arrow (decreased with age). These interconnected processes reflect the multifactorial nature of aging and highlight the value of metabolomic in identifying potential biomarkers and mechanistic insights into age-related decline. All these seven biological pathways have several consequences to health and disease. The ability to understand these changes in human organism opens up new opportunities for diagnosis and prognosis for pathologies of old age²⁵¹.

The most prominent metabolic pathways altered with aging is lipid metabolism, encompassing various lipid and lipoproteins such as: very-low-density lipoprotein (VLDL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides (TGs), cholesterol, fatty acids (FAs) and polyunsaturated fatty acids (PUFAs). Adult individuals typically exhibit lipid profiles associated with increased clinical risk, including elevated levels of VLDL, LDL, TGs, cholesterol and FAs alongside reduced HDL levels (Figure 14)²⁵¹. Dysregulation of lipid metabolism has far-reaching effects on cellular physiology, contributing to the accumulation of oxidized lipid-rich exosomes, increased intracellular lipid droplets, impaired membrane fluidity and the development of the senescence-associated secretory phenotype (SASP). Moreover, altered cholesterol levels have been implicated in the inhibition of key membrane-bound enzymes, such as Na⁺/K⁺-ATPase, suggesting further downstream impacts on cellular homeostasis. This could be associated with several conditions such

as: coronary heart disease, ischemic heart disease, obesity, type 2 diabetes, hypothyroidism and chronic renal disease, which, in turn, represent a substantial burden of morbidity and mortality worldwide²⁵¹. Notably, of the twelve established hallmarks of aging described by López-Otín et al. (2023) (Figure 15.a), ten have direct mechanistic links to lipid metabolism and lipid oxidation (Figure 15.b). These include, but are not limited to, mitochondrial dysfunction, deregulated nutrient sensing, cellular senescence and chronic inflammation. Importantly, the hallmarks do not act in isolation; rather, they exhibit extensive interconnectivity. For instance, lipid-induced oxidative stress may promote genomic instability, which in turn can exacerbate epigenetic alterations and impair proteostasis. Similarly, disrupted autophagy can hinder the clearance of lipid peroxidation products, reinforcing a cycle of damage. This intricate network of interactions underscores the central role of lipid metabolism in the aging process and its potential as a therapeutic target for mitigating age-associated decline^{239,252}.

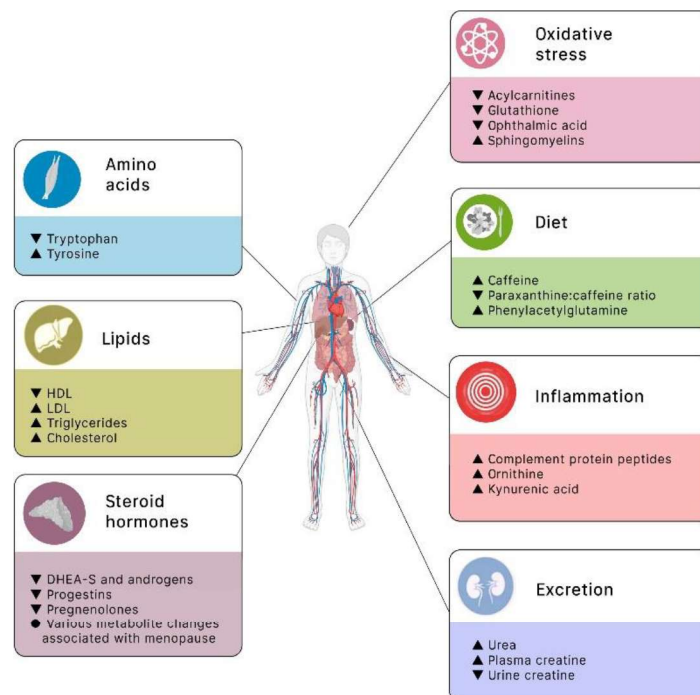


Figure 14. Overview of metabolomic associations with aging²⁵¹.

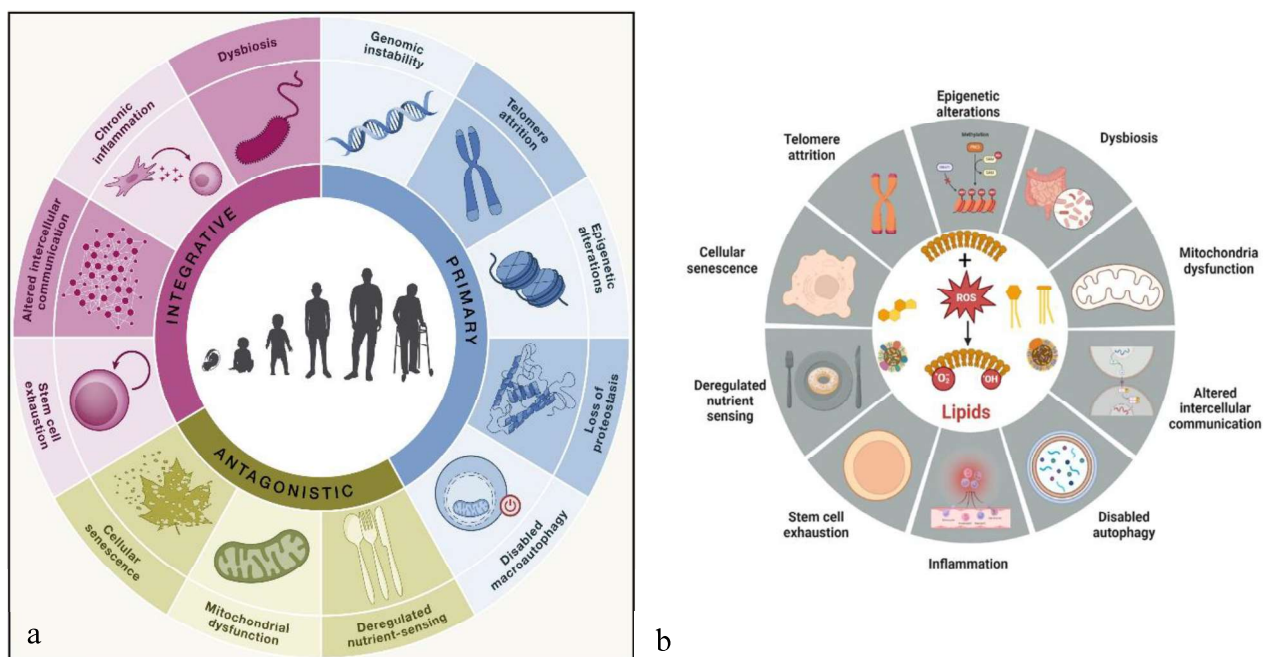


Figure 15. a) The hallmarks of aging; b) the hallmarks of aging associated with deregulated lipid metabolism and lipid peroxidation^{239,252}.

Despite substantial progress in characterizing age-related changes in the metabolome, significant limitations remain, particularly regarding population-specific differences. The metabolome is highly dynamic and influenced by numerous factors such as sex, diet, physical activity, body mass index (BMI), socioeconomic status and health conditions. However, many studies have not adequately accounted for these potential confounders, often controlling only for sex and occasionally BMI. This lack of control raises concerns about the causal nature of observed associations between age and metabolite levels, which may instead reflect dietary habits, health status or other unmeasured variables. Furthermore, the frequent use of “healthy” participants, without a clear or consistent definition of health, may introduce selection bias, especially when studying old individuals. Another major limitation is the predominance of cross-sectional study designs, which rely on single time-point samples and often group participants into broad age categories. Longitudinal studies, which are better suited to disentangle causal relationships and capture dynamic changes over time, remain scarce and typically involve small sample sizes or limited follow-up periods. Additionally, most research focuses on adults, neglecting age-related metabolic variation in children. The absence of high-resolution, longitudinal metabolomic data may obscure key temporal patterns and mechanisms of aging. Finally, while associations between age and metabolites, such as those involved in oxidative stress, are repeatedly observed, the directionality of these relationships remains unclear, necessitating further investigation to establish causality²⁵¹.

The future of aging metabolomic and lipidomic research lies in addressing current limitations while leveraging emerging opportunities. A major challenge is the lack of diversity in study populations, with most research concentrated in North America, Europe and East Asia and limited representation of other regions and young adults. This restricts the generalizability of findings and overlooks

important developmental and nonlinear metabolic changes. Methodologically, the field has been dominated by cross-sectional designs and linear models, which fail to capture the complex dynamics of aging. Future studies should prioritize high-resolution longitudinal designs and incorporate advanced analytical tools like machine learning and network-based approaches. Integrating metabolomic with other omics layers (proteomics, lipidomics, genomics etc...) will be the key to uncovering causal mechanisms and building accurate models of biological aging. These advances will ultimately support precision health strategies aimed at personalized prevention and management of age-related conditions across diverse populations²⁵¹.

1.8.2 Pathological studies: Alzheimer's disease

As discussed in previous chapters and in the sections on aging studies, the identification of metabolite or lipid variations through metabolomic and lipidomic approaches can be highly valuable for the diagnosis of diseases, the investigation of their progression and the evaluation of potential therapeutic interventions. Indeed, dysregulation of lipids and metabolites has been increasingly recognized as a central feature in the pathophysiology of numerous metabolic and chronic diseases, including components of the metabolic syndrome as well as neurodegenerative disorders, obesity, atherosclerosis, stroke, hypertension and diabetes. In the context of the nervous system, lipids are particularly critical due to the high lipid content of the brain, where they are involved in myelination, synaptic function, neurotransmitter release and neuroinflammation²⁵³.

Alongside lipidomics, metabolomics has emerged as a powerful approach also to study neurodegenerative diseases, offering a broader view of the small-molecule alterations occurring in disease states. Metabolomic analyses allow for the detection of metabolic shifts in pathways such as amino acid metabolism, energy production, oxidative stress and mitochondrial function, pathways commonly disrupted in neurodegeneration^{88,254}. Recent studies have demonstrated that both lipidomic and metabolomic signatures can distinguish between disease stages and patient subgroups, providing insight into pathogenesis as well as offering potential for early diagnosis and monitoring of therapeutic response. For example, alterations in sphingolipids, phospholipids and bile acids have been consistently reported in Alzheimer's and Parkinson's diseases and are now being explored as candidate biomarkers^{255,256}. These neurodegenerative conditions are increasingly viewed as systemic diseases with strong metabolic underpinnings, in which aberrant lipid and metabolite profiles contribute not only to neuronal dysfunction, but also to disease onset and progression. Characterizing this molecular alteration through high-throughput omics approaches is essential for understanding the complex biochemical landscape of neurodegeneration and holds significant promise for the identification of novel biomarkers and therapeutic targets aimed at disease prevention, early intervention and personalized treatment strategies.

Alzheimer's disease (AD) is a progressive neurodegenerative disorder and the most prevalent form of dementia in old adults. It is estimated to affect more than 35% of individuals aged 85 and older and currently impacts over five million people in the USA, ranking as the sixth leading cause of death nationally²⁵⁷. Instead, in Italy, according to the Dementia Observatory coordinated by the Istituto Superiore di Sanità (ISS), approximately 1.100.000 individuals are affected by dementia, with Alzheimer's disease accounting for 50-60% of these cases corresponding to around 600.000 old adults²⁵⁸. Despite decades of research, the etiological mechanisms underlying AD remain incompletely understood. While genetic predisposition plays a central role, particularly in early-onset familial AD, the vast majority of cases are sporadic and influenced by complex interaction between genetic, environmental and lifestyle factors²⁵⁹. Environmental risk factors include traumatic brain injury, low educational attainment, high-fat diets, obesity, Type II diabetes and cardiovascular disease²⁶⁰. Additionally, exposure to environmental toxins such as pesticides, metals and industrial surfactants has been implicated in sporadic AD^{257,259}. Among genetic factors, ApoE4 remains the most well-established risk allele, contributing to more than 99% of late-onset AD cases. In Figure 16 is reported the multifactorial and complex nature of neurodegenerative diseases. AD can be classified into two main forms: early-onset, which occurs between the ages of 30 and 65, and late-onset, which develops after age 65. Early-onset AD often has a clear familial genetic component, while late-onset cases are more frequently sporadic and influenced by a wide range of risk factors²⁵⁹.

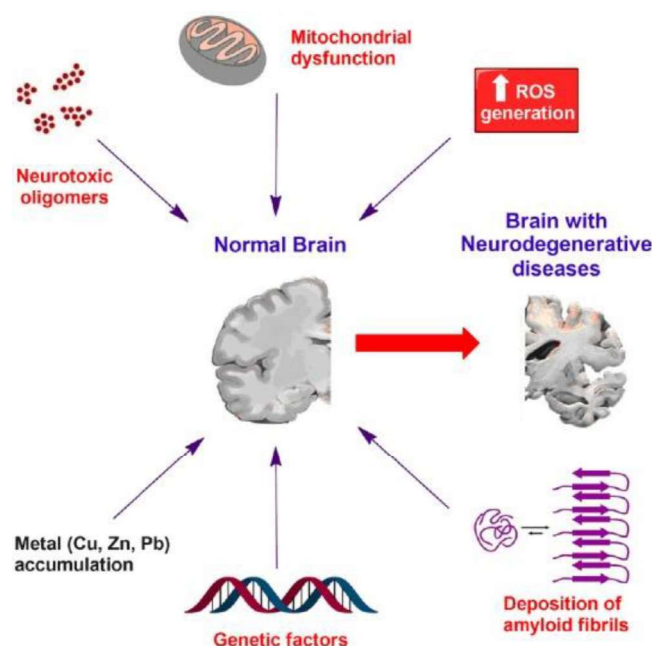


Figure 16. The multifactorial and complex nature of neurodegenerative diseases²⁶⁴.

Clinically, AD is characterized by a gradually worsening loss of memory and cognitive function, affecting higher-order intellectual abilities and ultimately leading to complete dependence^{257,260}. From a neuropathological perspective, AD is defined by the extracellular deposition of amyloid-beta ($A\beta$) in senile plaques and the intracellular accumulation of hyperphosphorylated Tau protein,

forming neurofibrillary tangles, especially in the hippocampus and cerebral cortex^{257,260,261}. These pathological features disrupt synaptic communication and intracellular transport, contributing to widespread neuronal loss. A β is thought to contribute to neurotoxicity by interfering with synaptic function, while Tau tangles impede axonal transport, preventing the movement of essential nutrients and molecules within neurons. Beyond these core mechanisms, abnormalities in lipid metabolism and protein regulation also contribute significantly to AD pathogenesis. The apolipoprotein E (ApoE) gene, particularly the ϵ 4 allele, has been strongly implicated in promoting A β and Tau pathology²⁶⁰. Additionally, presynaptic proteins such as α -synuclein, typically associated with Parkinson's disease, have also been found in AD brains, where they aggregate into Lewy bodies, further impairing neuronal function²⁶⁰. A definitive diagnosis of AD can only be made post-mortem through histopathological examination of brain tissue. However, clinical and neuropsychological assessments conducted in specialized centers achieve diagnostic accuracy rates of approximately 90%. Currently available pharmacological treatments provide only modest and temporary symptomatic relief, with no curative or disease-modifying therapies available. As the disease advances, individuals often require full-time care, placing an immense emotional and economic burden on families and healthcare systems. With an aging global population, the prevalence of AD is expected to triple by 2050, with projected healthcare costs exceeding \$50 billion annually²⁶². Importantly, while AD affects individuals across all racial and ethnic backgrounds, differences in prevalence and disease progression among subpopulations remain underexplored. Notably, women appear to have a higher incidence of AD than men and age remains the most significant risk factor, with prevalence increasing sharply between the ages of 65 and 85 and reaching up to one-third of the population beyond 85^{260,263}.

The pathological features of AD extend beyond protein aggregation. Mounting evidence implicates chronic gliosis and neuroinflammation, dysregulation in redox homeostasis, mitochondrial dysfunction and abnormal accumulation of metal ions in contributing to neuronal damage and disease progression^{263–265}. These interconnected processes reflect the multifactorial nature of AD and present significant challenges for the development of effective therapies. Despite considerable advances in delineating the molecular and cellular pathways involved, a complete understanding of AD pathogenesis remains elusive, thereby limiting the identification and implementation of successful therapeutic intervention. This highlights the pressing need for more integrative and multidimensional approaches to research. This gap continues to hinder the identification of effective disease-modifying strategies and highlights the urgent need for further integrative research combining genomics, metabolomics and lipidomics to uncover novel therapeutic targets²⁶⁶. Multi-omics strategies allow for a comprehensive examination of biological networks and may provide novel insights into the systemic alterations associated with AD. Importantly, pathological changes in AD begin decades before clinical diagnosis, suggesting that early metabolic shift could serve as predictive biomarkers for disease onset and progression. Indeed, metabolomic disturbances, particularly in lipid and energy

metabolism, are among the earliest physiological changes observed in patients with mild cognitive impairment (MCI) due to AD²⁶⁷. Beyond this well-established metabolic disruption, alteration have also been reported in neurotransmitter metabolism, the urea cycle, purine and polyamine metabolism and bile acid pathways²⁶⁸. Although current symptomatic treatments, such as cholinesterase inhibitors and memantine, aim to mitigate cognitive decline by targeting neurotransmitter deficit, these interventions do not address the underlying disease mechanisms²⁶⁹. Therefore, a deeper understanding of AD-related metabolic alteration through multi-omics approaches may not only enhance early diagnosis but also aid in the discovery of more effective therapeutic targets. In this context, in recent years, several studies have emphasized the value of employing diverse metabolomic platforms to investigate the pathophysiological mechanisms of AD, both in human cohorts and in various murine models. Among the most widely used animal models are those involving the overexpression of mutated human amyloid precursor protein (APP). Additionally, to accelerate amyloid pathology, certain models incorporate mutations in the presenilin 1 (PS1) gene, leading to the development of double transgenic lines like APP x PS1 and TASTPM^{270–272}. To capture the broad metabolomic alteration associated with AD, multiple biological matrices have been explored. Brain tissue remains one of the most informative sources, as it allows direct assessment of the molecular and biochemical changes occurring in the affected regions. Cerebrospinal fluid (CSF) also represents a valuable sample type, given its close proximity to the central nervous system and its ability to mirror brain-specific metabolic activity²⁷³. Beyond these, the investigation of more accessible and non-invasive specimens, such as blood (serum or plasma)^{273,274}, urine²⁷⁵ and saliva^{276,277}, has gained interest due to their potential for clinical translation, offering simpler and more cost-effective biomarker discovery.

Nonetheless, current diagnostic limitations, particularly in identifying individuals at the earliest stages of the disease, present a significant obstacle. Inaccurate classification may lead to the inclusion of undiagnosed, preclinical AD cases within control groups of clinical studies, thereby compromising the reliability and reproducibility of identified metabolic biomarkers²⁷⁸. Another critical limitation observed in many previously published metabolomic studies is the insufficient validation of discriminant metabolites identified during the discovery phase. In most cases, findings are not corroborated using larger and independent patient cohorts, which undermines the robustness and generalizability of the results. To enhance the clinical relevance and specificity of candidate biomarkers, it would be particularly valuable to include other types of dementia in comparative analyses. Despite its importance, this aspect has been largely overlooked in current research. Limiting the potential for distinguishing Alzheimer's disease-specific metabolic alterations from those common to other neurodegenerative conditions²⁶⁸.

Forensic toxicology is a multidisciplinary field that has undergone significant advancements over the past two decades. It focuses on the detection, identification and quantification of drugs, poisons and their metabolites, collectively referred to as xenobiotics, which are substances introduced into the body from external sources. As a specialized branch of analytical toxicology, forensic toxicology plays a vital role in both legal and administrative contexts by analyzing complex biological and non-biological samples collected either ante- or post-mortem. Originally developed to investigate the presence or misuse of psychotropic substances, forensic toxicology integrates principles from toxicological chemistry and applies scientifically validated methodologies to ensure reliable and reproducible results. The field contributes significantly to forensic science, which itself is inherently multidisciplinary, by providing critical insights into the cause of death, the diagnosis of poisoning and the detection of drug use in various scenarios such as driving under the influence of drugs (DUID), workplace drug testing, familiar legal disputes and anti-doping investigations^{279,280}. Toxicological investigations rely on the analysis of specific markers or metabolites in biological matrices such as blood, urine, hair or other tissues. These analyses aim to establish the presence of psychoactive or toxic compounds and are typically conducted using a two-step analytical approach. First, a broad screening is performed to detect the potential presence of substances of abuse. This is followed by confirmatory testing using highly sensitive and specific techniques such as gas and liquid chromatography coupled with tandem mass spectrometry (GC-MS/MS and LC-MS/MS), which allow for both qualitative and quantitative determination of the compounds of interest. Through its rigorous analytical framework and interdisciplinary applications, forensic toxicology provides essential information for public health, clinical diagnosis, legal proceedings and regulatory enforcement^{281,282}.

Addiction is currently defined as a chronic, relapsing disorder marked by compulsive drug seeking and continued use despite the occurrence of adverse consequences. It is recognized as a brain disorder due to the persistent functional changes it induces in neural circuits involved in reward processing, stress regulation and executive control. These neuroadaptations can persist long after drug use has ceased, contributing to the high rates of relapse observed in individuals with substance use disorders²⁸³. Similar to other chronic medical conditions such as cardiovascular disease, addiction disrupts the normal functioning of vital organs, in this case the brain, and leads to harmful health, psychological and social outcomes. Importantly, like many chronic diseases, addiction is both preventable and treatable, although if left unaddressed, it can persist throughout life and result in premature death. The motivation behind drug use is multifaceted and often includes the desire to experience pleasure, alleviate emotional or psychological distress, enhance performance or out of curiosity and social influences. The development of addiction is influenced by a complex interplay of individual risk and protective factors, which can be broadly categorized into biological and environmental domains. Environmental factors span multiple contexts including the family environment, peer influences, educational settings and the broader community. Instead, biological

factors that influence susceptibility to addiction include genetic predisposition, neurodevelopmental stage and even ethnicity. Genetic influences, including epigenetic modifications resulting from environmental exposures are estimated to contribute approximately 40-60% to an individual's overall risk of developing a substance use disorder²⁸⁴. Furthermore, adolescents and individuals with co-occurring mental health disorders are particularly vulnerable to substance misuse and addiction. A comprehensive understanding of these intersecting biological and environmental influences is essential for the development of targeted prevention strategies and personalized treatment approaches for individuals affected by addiction²⁸⁵.

Unlike other omics approaches, metabolomic offers a distinctive advantage in capturing the dynamic interplay between genetic and environmental factors. As previously discussed, metabolomic and lipidomic approaches are widely employed across various clinical disciplines to find biomarkers to diagnose easily pathologies. Although their application in forensic science is still emerging, metabolomics has already demonstrated significant potential in addressing key forensic challenges. Notably, it has been utilized to estimate the postmortem interval (PMI) and to identify novel biomarkers with enhanced diagnostic precision compared to traditional methodologies^{286,287}. In the context of forensic toxicology, metabolomic analyses of biochemical pathways provide valuable insights into patterns of substance use too. These approaches facilitate the differentiation between acute and chronic drug intake and help elucidate the underlying mechanisms of toxic action²⁴⁴. Importantly, they also offer a promising strategy for the detection of novel psychoactive substances (NPS) and their metabolites, particularly in cases where targeted screening techniques may prove insufficient. For example, untargeted metabolomic has been employed to identify previously unrecognized metabolites of gamma-hydroxybutyric acid (GHB). In a randomized, double-blind, placebo-controlled crossover study, Steuer et al. analyzed urine samples and successfully identified several novel GHB-related compound: GHB-carnitine, GHB-glycine and GHB-glutamate. Given GHB's typically short urinary detection window (less than 12 hours), these newly identified biomarkers may extend the timeframe for reliable detection²⁸⁸. Furthermore, metabolomics has proven effective in identifying biomarkers associated with synthetic cannabinoids (SCs) and stimulant-type NPS. In a study conducted by Bijlsma et al., saliva samples were collected from healthy volunteers both before and after smoking herbal mixture and analyzed using high-resolution mass spectrometry. Statistical analysis revealed two discriminative markers: scopoletin and 2-hydroxyethyl dodecylamine, whose relative concentrations successfully distinguished users from non-users²⁸⁹.

Building upon its demonstrated potential in identifying drug metabolites and distinguishing patterns of substance use, recent advancements in metabolomics and lipidomics²⁹⁰ have expanded its scope beyond acute drug detection. Emerging research now focuses on exploring biomarkers associated with drug addiction severity, patterns of dependency and the physiological interpretation of

intoxication levels. Rather than limiting the investigation to indicators of recent substance intake, these novel approaches aim to capture the broader biochemical disruption linked to chronic drug use and addiction pathways. To date, metabolomic studies in this area primarily concentrated on substances: methamphetamine²⁹¹, cocaine²⁹², crack cocaine²⁹³, and heroin²⁴³. A growing subset of this investigation is particularly concerned with elucidating the mechanism of drug action and identifying metabolic perturbations that may underlie addictive behaviors²⁹⁴. These insights not only deepen the understanding of biochemical impact of drug use but may also pave the way for development of targeted interventions or diagnostic tools for addiction management. Both human (blood, saliva and urine) and animal (rat and monkey) models have been utilized to identify potential metabolite biomarkers associated with substance use and addiction-related contributes to more comprehensive view of addiction as a complex, multifactorial condition influenced by both physiological and environmental variables.

In this context, the application of metabolomics and lipidomics continues to reinforce their relevance in forensic and clinical toxicology, offering novel perspective for monitoring addiction, assessing intoxication and ultimately enhancing the diagnostic, therapeutic and preventive strategies in the field of substance abuse²⁹⁵.

1.9 Aim of the study

Omics sciences represent a branch of analytical and biological research aimed at the simultaneous detection, characterization and quantification of large sets of bioactive molecules, with the objective of understanding biochemical pathways and system-wide functions rather than focusing on individual components. These disciplines employ high-throughput analytical methods that enable efficient and rapid exploration of biological processes in both health and disease¹. The omics fields include genomics, transcriptomics, proteomics, epigenomics, metabolomics and lipidomics²⁹⁶. Among these, the present study specifically focused on metabolomics and lipidomics. Metabolomics focuses on the comprehensive study of small molecules, such as sugars, lipids, hormones, bile acids and amino acids, that play key roles in biological systems⁵⁴. Metabolites act as building blocks for macromolecules (DNA, proteins), serve as intermediates in energy metabolism and function as signaling molecules regulating numerous cellular pathways. Lipidomics, a specialized subfield of metabolomics, is dedicated to qualitative and quantitative profiling of lipid species in biological matrices. Lipids, generally hydrophobic molecules, are essential for a broad range of cellular processes, including energy storage, membrane structure, signal transduction and intracellular communication⁹⁰. Both lipidomic and metabolic profiles are highly dynamic and influenced by endogenous and exogenous factors such as genetics, nutrition, inflammation, stress, physical activity, pharmacological treatments and disease states. These approaches not only describe normal

physiology but also capture the molecular alterations associated with aging and disease progression, providing critical insights for biomarkers discovery and improving diagnostic and prognostic accuracy.

Different biological matrices can be used in omics research, each providing unique information, such as blood (plasma and serum), urine, tissue, cell cultures and oral fluid. In this study, oral fluid was selected as biological matrix due to its recognized diagnostic potential and several practical advantages over blood and urine, including non-invasive, stress-free and straightforward collection and reduced risk of sample alteration. Nevertheless, saliva is a complex biofluid whose composition can be affected by various physiological and environmental factors, including age, gender, diet, health status and ongoing treatments.

The general aim of this research was to evaluate variations in salivary metabolic and lipidomic profiles under different physiological and pathological conditions. As a first step, salivary profiles from healthy and young individuals were characterized and compared with those from matched blood samples to identify shared and distinct molecular features and to assess the feasibility of using oral fluid as a non-invasive alternative to blood in clinical and forensic contexts. Considering that salivary composition changes with physiological factors, the study also investigated the influence of aging on lipidomic and metabolic signatures, providing insight into age-related metabolic and lipidomic remodeling.

Subsequently, the potential of saliva as a diagnostic tool for systemic diseases was explored, with particular attention to Alzheimer's disease (AD). This phase aimed to assess the reliability of oral fluid as a source of biomarkers for neurodegenerative disorders, extending its application beyond oral diseases, by comparing the salivary lipidomic and metabolic profiles of AD patients with those of cognitively healthy, age- and gender- matched controls. The study sought to identify disease-specific alterations while accounting for age-related variability. This focus is supported by the well-established bidirectional communication between the brain and salivary glands, suggesting that salivary composition may reflect central nervous system alterations²⁹⁷. Finally, the investigation was extended to substance abuse, evaluating how chronic exposure to psychoactive compounds affects salivary metabolic and lipidomic patterns. The cohort included individuals with a documented history of prolonged use of cocaine, cannabinoids, methamphetamine, 3,4-methylenedioxymethamphetamine (MDMA), ketamine, alcohol and benzodiazepines.

All salivary samples were analyzed using high-performance liquid chromatography coupled with time of flight mass spectrometry (HPLC-QTOF-MS) in both positive and negative ionization modes at the OMICs facility of the University of Milan. Raw data were processed with MS-DIAL software, allowing the identification of lipids and metabolites through multiple reference libraries. The

resulting datasets were subjected to comprehensive statistical analyses to derive meaningful biological interpretation, using MetaboAnalyst 6.0 software.

Overall, this work aimed to advance the understanding of saliva as a versatile and informative biofluid, capable of reflecting both physiological variations and pathological alterations, thereby supporting its potential role in clinical, neurodegenerative and forensic research.

2. MATERIALS AND METHODS

2.1 Volunteer's information and samples collection

The biological samples analyzed in the different phases of the study were provided by the Biobank of the Policlinico Hospital of Milan (first three phases) and by the Forensic Toxicology Laboratory of the University of Milan (final phase), following standardized collection and storage procedures to ensure methodological consistency. All samples were collected in the morning from fasting participants. Specifically, saliva samples were obtained by expectoration into a sterile tube, while blood samples were collected via standard venipuncture. All samples were immediately stored at -80°C until analysis.

Samples for the characterization of salivary lipidomic and metabolomic profiles, and their comparison with blood, were collected by Prof. Gianluca Tartaglia's group (Department of Biomedical, Surgical and Dental Sciences, University of Milan) (Appendix A, Table A). Saliva samples used in the aging and neurodegenerative disease studies were collected by Prof. Daniela Galimberti's group (Department of Biomedical, Surgical and Dental Sciences, University of Milan) at the Policlinico Hospital (Appendix A, Table B, C, D). Finally, saliva samples used to investigate lipid and metabolite variations associated with drug addictions were collected at the Forensic Toxicology Laboratory of the University of Milan (Appendix A, Table E). All samples will be described in detail in Sections 3.1, 3.2, 3.3 and 3.4.

2.2 Chemicals

Ethanol, methanol, acetonitrile, pure water, chloroform, isopropanol, dichloromethane, n-heptane, ethyl acetate, hexane, buffer solution (pH 6.88-pH 9) and ammonium acetate were acquired from Supelco (Merk, Darmstadt, Germany). As an internal standard in metabolomics analyses, methionine-d5 (1 mg/mL) was used, which was purchased from Sigma-Aldrich (Milan, Italy). BHT is acquired from Alfa Aesar (Fisher Scientific, Milan, Italy). Cocaine-d3 (0.1 mg/mL), BEG-d3 (Benzoylcegonine-d3, 0.1 mg/mL), MDMA-d5 (3,4-Methylenedioxymethamphetamine-d5, 0.1 mg/mL), MDA-d5 (3,4-Methylenedioxyamphetamine-d5, 0.1 mg/mL), methamphetamine-d5 (0.1 mg/mL), Methadone-d9 (0.1 mg/mL), EDDP-d3 (2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine-d3, 0.1 mg/mL), ketamine-d4 (0.1 mg/mL), norketamine-d4 (0.1 mg/mL), codeine-d3 (0.1 mg/mL), dihydrocodeine-d6 (0.1 mg/mL), oxycodone-d6 (0.1 mg/mL), Norbuprenorphine-d3 (0.1 mg/mL), morphine-d3 (0.1 mg/mL), Δ^9 -THC-d3 (Δ^9 -tetrahydrocannabinol-d3, 0.1 mg/mL) THC-COOH-d3 (11-Nor-9-carboxy-THC-d3, 0.1 mg/mL) were obtained as internal standard from LGC (Middlesex, TW110LY, UK). Amphetamine-d5 (0.1

mg/mL), buprenorphine-d4 (0.1 mg/mL), EtG-d5 (Ethylglucuronide-d5, 0.1 mg/mL) were obtained as internal standard from Supelco (Merck (Darmstadt, Germany). Pentafluoro-propionic anhydride, hexafluoro-2-propanol, N-Methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) were acquired from Sigma-Aldrich (Milan, Italy). NaOH was acquired from Carlo Erba (Milan, Italy).

2.3 Untargeted metabolomic analysis

2.3.1 Sample preparation

To an aliquot of 100 μ L of saliva 10 μ L of internal standard (methionine d-5) were added and brought to a volume of 1 mL by the cold addition of 800 μ L of an organic EtOH:MeOH 1:1 v/v mixture. The samples were mixed for 15 minutes and then centrifugated for 10 min at 13400 RPM. Then, the organic phase was dried after nitrogen flow. The samples were reconstituted with 70 μ L of 95% of Acetonitrile. The same procedure was used for the blank sample prepared using 100 μ L of Pure Water. Finally, the a pool sample, used as a quality control (QC) during the analysis, was prepared by taking 2-5 μ L of each prepared sample. Quality control was used to normalize the results during data analysis.

2.3.2 Experimental conditions

The untargeted metabolomic analyses were performed using HPLC (1290 Infinity II LC, Agilent) connected to a mass spectrometer (ZenoTOF 7600 System, ABSciex, Darmstadt, Germany) equipped with Turbo VTM Ion Source with ESI Probe. Chromatographic separation was achieved on a Atlantis BEH Z-HILIC (WatersTM) (100 mm (length) x 2.1 mm (ID) x 1.7 μ m (Particle Size)); using as mobile phase A: Pure Water/ACN 50/50 v/v with ammonium acetate 10 mM and as mobile phase B: Pure Water/ACN 5/95 v/v with ammonium acetate 10 mM at a flow rate of 400 μ L/min. The column and autosampler temperatures were set at 45°C and 15°C respectively. The injection volume was 5 μ L. The chromatography gradient is reported in Table 8.

Mass spectrometry spectra were collected over an m/z range of 50-1000 Da, operating in IDA[®] mode (Information Dependent Acquisition). Collision energy was set at 30 (CES 15). The samples were analyzed with both positive and negative polarity. Normalization of the results was related to saliva volumes.

Table 8. Chromatography gradient used for untargeted metabolomic analyses

Time	Flow (μL/min)	%B
0.00	Run	-
0.00	400	99.0
1.00	400	99.0
20.00	400	25.0
24.00	400	25.0
24.20	400	99.0
30.00	400	99.0
30.00	Stop Run	

Blank, QC and technical replicates were included to monitor signal drift and or potential batch effects throughout the sequence run. The blank vial was injected in duplicate at the beginning of the sequence and used to calculate the fold change during data analysis. The QC vial was injected in duplicate after the blanks and again at the end of the sequence, and a single QC injection was performed after every ten injections. QC measurements were used to calculate the coefficient of variation (CV%) during data analysis. Each sample was injected in duplicate, and the mean value was used for subsequent analysis.

2.4 Untargeted lipidomics analysis

2.4.1 Sample preparation

An aliquot of 100 μL of saliva was added to 850 μL of organic mixture MeOH/CHCl₃. The samples were mixed for 1h at 4°C (800 RPM) and centrifugated for 10 min at 13400 RPM. Then, 900 μL of organic phase were dried after nitrogen flow. They were reconstituted with 75 μL of mixture IPA/ACN 2:1 v/v and 0.1 mM BHT. The same procedure was used for the blank sample prepared using 100 μL of pure water. Finally, a pool sample, used as a quality control (QC) during the analysis, was prepared by taking 2-5 μL of each prepared sample. Quality control was used to normalize the results during data analysis.

2.4.2 Experimental conditions

The untargeted lipidomic analyses were performed using HPLC (1290 Infinity II LC, Agilent) connected to a mass spectrometer (ZenoTOF 7600 System, ABSciex, Darmstadt, Germany) equipped with Turbo VTM Ion Source with ESI Probe. Chromatographic separation was achieved on a Waters[®] CSH C18 (100 mm (length) x 2.1 mm (ID) x 1.7 μm (particle size)); using as mobile phase A:

ammonium acetate 10 mM in pure water/ACN 60:40 v/v, 0.1% formic acid and as mobile phase B: ammonium acetate 10 mM in IPA/ACN 90:10 v/v, 0.1% formic acid at a flow rate of 400 μ L/min. The column and autosampler temperatures were set at 55°C and 15°C respectively. The injection volume was 5 μ L. The chromatography gradient is reported in Table 9.

Mass spectrometry spectra were collected over an m/z range of 200-2500 Da, operating in IDA[®] mode (Information Dependent Acquisition). Collision energy was set at 35 $\pm$ 15. The samples were analyzed with both positive and negative polarity. Normalization of the results was related to saliva volumes.

Table 9. Chromatography gradient used for untargeted lipidomic analyses

Time	Flow (μ L/min)	%B
0.00	Run	-
0.00	400	40.0
2.00	400	40.0
2.50	400	50.0
12.50	400	55.0
13.00	400	70.0
19.00	400	99.0
24.00	400	99.0
24.20	400	40.0
30.00	400	40.0
30.00	Stop run	-

Blank, QC and technical replicates were included to monitor signal drift and or potential batch effects throughout the sequence run. The blank vial was injected in duplicate at the beginning of the sequence and used to calculate the fold change during data analysis. The QC vial was injected in duplicate after the blanks and again at the end of the sequence, and a single QC injection was performed after every ten injections. QC measurements were used to calculate the coefficient of variation (CV%) during data analysis. Each sample was injected in duplicate, and the mean value was used for subsequent analysis.

2.5 Targeted analysis of hair samples for ethyl glucuronide (EtG)

Hair samples were analyzed for both EtG and narcotic substances using methodologies previously developed and fully validated at the Forensic Toxicology Laboratory of the University of Milan.

2.5.1 Sample preparation

Hair samples, once collected, were washed with 4 mL of dichloromethane under sonication for 10 minutes, then dried and weighed in Eppendorf tubes. Samples weighing less than 50 mg were spiked with 50 μ L of aqueous solution of EtG-d5 (100 ng/mL) as internal standard and 450 μ L of extraction solution consisting of pure water:MeOH 88:2 v/v. Samples weighing more than 50 mg were spiked with 100 μ L of the same internal standard solution and 900 μ L of the extraction solution. All samples were centrifuge up to 13400 RPM and then were left at room temperature overnight. After incubation, samples were subjected to ultrasonic bath treatment for 2 hours at room temperature, followed by centrifugation for 2 minutes at 14500 RPM. The supernatants were transferred into vials and analyzed by liquid chromatography coupled with tandem mass spectrometry.

2.5.2 Experimental conditions

The analysis of Ethyl glucuronide was performed using an HPLC system Dionex UltiMate 3000 (Thermo Fisher Scientific, Waltham, MA,USA) coupled to a triple quadrupole mass spectrometer API 4000 (ABSciex, Darmstadt, Germany), equipped with an electrospray ionization (ESI) source and an autosampler WPS-3000 SL. Chromatographic separation was carried out on a Phenomenex Luna Omega 3 μ m Polar C18 column (100 mm x 2.1 mm) with a guard column, using a mobile phase consisting of water with 0.1% formic acid (phase A) and acetonitrile with 0.1% formic acid (phase B). A 10-minute gradient elution program was applied, as reported in Table 10. The column temperature was maintained at 25°C. The analysis was performed by injecting 3 μ L of sample, operating in negative ionization mode and using multiple reaction monitoring (MRM) acquisition.

Table 10. Chromatography gradient used for targeted analysis of hair samples for EtG

Time	Flow (μ L/min)	%B
0.00	Run	-
0.00	400	2.50
2.00	400	2.50
3.00	400	20.0
4.50	400	60.0
5.50	400	100.0
7.00	400	100.0
10.0	400	2.50
10.00	Stop run	-

The quantification of EtG was performed using MultiQuant software (ABSciex, Darmstadt, Germany).

2.6 Targeted analysis of hair samples for psychoactive substances

2.6.1 Sample preparation for screening analysis

Hair samples, once collected, were first washed with 4 mL of dichloromethane under sonication for 10 minutes, then dried and weighed in Eppendorf tubes. Subsequently, 2 mL of MeOH were added, and the samples were incubated at 37°C for 6 h. Finally, 50 µL of the supernatant were collected and analyzed by HPLC-MS/MS. A blank and a control sample were also prepared for each analytical batch.

2.6.2 Experimental conditions for screening analysis

The screening analysis for determine psychoactive substances in hair was performed using an HPLC system 1290 LC Binary VL Pump (Agilent) connected to QTRAP 5500 mass spectrometer (ABSciex, Darmstadt, Germany) equipped with an electrospray ionization (ESI) source. Chromatographic separation was achieved using a Raptor Biphenyl column (100 mm, 2.1 mm, 1.8 µm), using as a mobile phase A pure water with 0.1% formic acid and as phase B acetonitrile with 0.1% formic acid. The gradient profile is shown in Table 11. The total run time was 7 minutes with an injection volume of 1 µL for hair samples. The column oven temperature was maintained at 30°C. The analysis was performed in positive ionization mode and using multiple reaction monitoring (MRM) acquisition. The MRM window was set at 60 s with the target scan time of 0.3 s.

Table 11. Chromatography gradient used for screening targeted analysis of hair samples for psychoactive substances

Time	Flow (µL/min)	%B
0.00	Run	-
0.00	500	5.00
0.50	500	5.00
1.00	500	15.0
2.50	500	30.0
4.50	500	95.0
5.00	500	100.0
5.90	500	100.0
6.00	500	5.00
7.00	500	5.00
7.00	Stop run	-

Once the samples had been analyzed for screening (MultiQuant, ABSciex, Darmstadt, Germany), those in which the presence of narcotic substances was detected were subjected to a confirmatory analysis performed by GC-MS/MS, using different methodologies for basic psychoactive substances and for Δ^9 -THC.

2.6.3 Sample preparation for confirmatory analysis

Basic psychoactive substances

For the confirmatory analysis of basic narcotic substances, the methanol extract obtained during incubation was used. Internal standards (mix solution, 1 µg/mL), selected according to the target analyte, were added to the 2 mL of methanol. From this, 1 mL was combined with 1.5 mL of buffer at specific pH (6.88-9, depending on the analyte) and with 3 mL of organic mixture consisting of chloroform (50%), n-heptane (33%) and isopropanol (17%). The samples were shaken for 10 minutes, centrifuged at 13400 RPM for 10 minutes, and the organic phase was separated and evaporated to dryness. The residues were derivatized with 50 µL of pentafluoro-propionic anhydride and 35 µL of hexafluoro-2-propanol by heating at 80°C for 15 minutes. After evaporation of the derivatization reagents, the extracts were reconstituted in 50 µL of ethyl acetate for GC-MS/MS analysis. A blank and a control sample were also prepared for each analytical batch.

Δ^9 -tetrahydrocannabinol (Δ^9 -THC)

For Δ^9 -THC confirmatory analysis, the hair material separated after extraction was subjected to cannabinoid detection. An internal standard (THC-d3, 10 ng/mL) was added and the sample was

hydrolyzed under alkaline conditions by adding 1 mL of 1M NaOH and heating at 75°C until complete dissolution of the matrix. The sample was then extracted with 5 mL of n-hexane/ethyl acetate (9:1). The organic phase was collected in a silanized tube, evaporated to dryness and the residue was derivatized with 60 µL of N-methyl-N-(trimethylsilyl)trifluoroacetamide (MSTFA) by heating 80°C for 15 minutes. The derivatized extracts were finally analyzed by GC-MS/MS. A blank and a control sample were also prepared for each analytical batch.

2.6.4 Experimental conditions for confirmatory analysis

Basic psychoactive substances

Analyses of the prepared samples for basic narcotic substances were performed using an Agilent 7890A gas chromatograph (Agilent Technologies, Palo Alto, CA, USA) equipped with a CP-SIL 8 capillary column (15 m X 0.20 mm (i.d.), 0.25 µm (film thickness)) and interfaced with a 7000 triple quadrupole detector (Agilent Technologies, Palo Alto, CA, USA). Helium was employed as the carrier gas at a constant pressure of 10 psi. The oven temperature was as follows: isothermal at 70°C for 2 minute; ramped from 70°C to 200°C at 40°C/min; from 200°C to 240°C at 10°C/min; and from 240°C to 300°C at 25°C/min. The injector temperature was set at 260°C and the detector temperature at 280°C. The mass spectrometer was operated in multiple reaction monitoring (MRM), with an electron impact (EI) ionization source.

Δ^9 -tetrahydrocannabinol (Δ^9 -THC)

Analyses of the samples prepared for Δ^9 -THC determination were performed using an Agilent 7890A gas chromatograph (Agilent Technologies, Palo Alto, CA, USA) equipped with a CP-SIL 8 capillary column (15 m X 0.20 mm (i.d.), 0.25 µm (film thickness)) and interfaced with 7000 triple quadrupole detector (Agilent Technologies, Palo Alto, CA, USA). Helium was employed as the carrier gas at a constant pressure of 10 psi. The oven temperature program was as follows: isothermal at 100°C for 2 minutes; ramped from 100°C to 180°C at 40°C/min; from 180°C to 290°C at 10°C/min; and isothermal at 290°C for 5 minutes. The injector temperature was set at 270°C and the detector temperature at 300°C. Analyses were acquired in selected ion monitoring (SIM) mode with an electron impact (EI) ionization source.

The quantification of all narcotic substances was performed using MassHunter software (Agilent Technologies, Palo Alto, CA, USA).

2.7 Statistical analysis

After the analytical phase, lipids and metabolites were identified across the different samples through data processing with specialized software (ABSciex, Darmstadt, Germany and MS-DIAL), which enabled the reprocessing of raw instrumental files using reference libraries. The summary of MS-DIAL parameters used for feature detection, alignment and compound identification in salivary metabolomics and lipidomics analyses are reported in Appendix D, Table N. In particular, for metabolomic analysis MS1 and MS2 tolerances were set at 0.01-0.02 and 0.5, respectively, whereas for lipidomics these values were 0.01 for MS1 and 0.05 for MS2. For both analytical approaches, a minimum peak height threshold of 1000 was applied. Metabolite identification was carried out using the MSMS-public-experiment-spectra-neg/pos-VS19 library, with a retention-time tolerance of 100 and a score cut-off between 70-80. For lipidomic analysis, the MS-Dial library was employed, using the same parameters as those applied to metabolomics. Finally, for both techniques, peak alignment was performed using the central QC samples, applying a retention-time tolerance of 0.1, and MS1 tolerance of 0.015, and a sample-to blank average ratio equal to 10.

The resulting compound lists, with their intensities, were subsequently subjected to a previous analysis. Fold change and CV% were calculated using blank and QC intensities to filter the compounds which were detected using MS-DIAL. The thresholds used were respectively 10 for FC and 30 for CV%, So only the compounds with a $FC > 10$ and a $CV\% < 30$ were selected. Then a statistical analysis was performed, on the remaining compounds, with MetaboAnalyst 6.0. This software enables filtering and normalization of the acquired data prior to statistical analysis. In the present study, the data were filtered using an interquartile range (IQR) threshold between 10 % and 25% and subsequently normalized by log-transformation. Following this preprocessing step, statistical analysis was performed, which revealed statistically significant differences among the groups through volcano plots (p value < 0.05 and fold change > 2). Multivariate analysis using PLS-DA (Partial Least Squares Discriminant Analysis) further highlighted clear clustering between the subject groups, while the corresponding VIP (Variable Importance in Projection) score plots indicated the variables that contributed most to this separation. To complement these findings, heatmaps were generated to visualize the changes in the intensity of the identified molecules across groups and study phases, providing an overview of the metabolic and lipidomic variations under the different conditions considered.

3. RESULTS

The initial aim of this study was to characterize the salivary metabolomic and lipidomic profile in healthy young individuals. To this end, saliva samples from healthy young volunteers were analyzed, and the resulting lipid profiles were compared with those obtained from whole blood, a biological matrix traditionally used in clinical and forensic investigations, and far more extensively studied in the fields of metabolomics and lipidomics. In this study, whole blood was employed instead of serum or plasma, which are more commonly used in metabolomics and lipidomics analyses. This choice was made because is more readily available and easier to obtain. In future investigations, however, plasma or serum will be adopted as comparative matrices, allowing for a closer alignment with existing literature and more comprehensive interpretation of the results. The subsequent goal was to explore how lipidomic and metabolic signatures may vary across different physiological and pathological conditions, including aging, Alzheimer's disease and dependence on drugs or medications. These investigations provide a preliminary framework for understanding the potential of saliva as a non-invasive matrix for metabolic and lipidomic assessment across a range of health conditions, and, more importantly, for evaluating its promise as a source of biomarkers.

3.1 Metabolic and lipidomic profile in healthy people: oral fluid and whole blood

Table 12 presents the main demographic characteristics of the healthy, non-smokers and young participants who took part in the first phase of the study. Oral fluid and whole blood samples were collected from the same individuals. A total of 16 saliva samples and 21 whole blood samples were analyzed, as the amount of saliva available was not sufficient to perform both lipidomic and metabolomic analyses for all subjects. The mean age of participants in the oral fluid group was 29.4 years (range 23-35), whereas the whole blood group had a mean age of 29.6 years (range 23-35). The difference between the two groups was not statistically significant ($p=0.88$), indicating a high degree of age homogeneity within the study population. Concerning gender distribution, the oral fluid group showed a marked predominance of women participants (93.7%, $n=15$) compared with men (6.2%, $n=1$). Similarly, in the whole blood group, women accounted for 76.2% ($n=16$) and men for 23.8% ($n=5$). Although a difference in percentages was observed between the groups, it does not appear to be clinically or statistically relevant. Overall, the analysis of demographic characteristics indicates that the two groups were comparable in terms of age and gender, ensuring adequate sample homogeneity and allowing subsequent analyses to be conducted without the influence of demographic confounding factors.

Table 12. Characteristics of healthy and young individuals included in the study of salivary lipidomic and metabolic profiles compared with whole blood. Data are reported as median (min-max) or as n (%).

	Oral fluid (n=16)	Whole blood (n=21)	
Characteristics			pvalue
Age	29.4 (23-35)	29.6 (23-35)	0.88
Gender			
Men	1 (6.2%)	5 (23.8%)	
Women	15 (93.7%)	16 (76.2%)	

3.1.1 Characterization of oral fluid metabolic profile

In oral fluid, 77 metabolites were identified by untargeted analyses, distributed across 26 distinct classes; of these, 58 metabolites, belonging to 25 classes, were consistently detected in all samples. Figure 17 reported the 11 classes containing more than one metabolite and the number of metabolites within each class. The category “Other” refers to classes represented by a single metabolite (14 classes). The complete list of these metabolites and their corresponding classes is provided in Table F (Appendix B).

Classes of metabolites in oral fluid

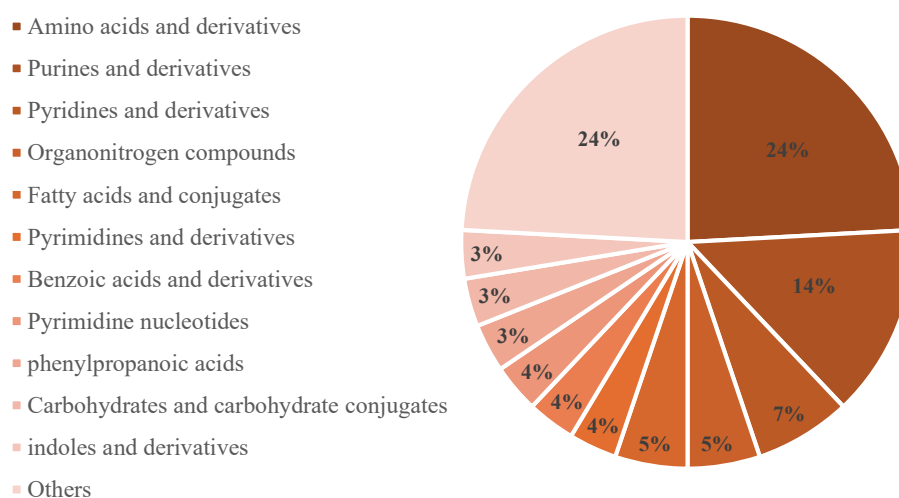


Figure 17. Classes of metabolites in oral fluid samples taken from young and healthy people.

3.1.2 Characterization of oral fluid lipidomic profile

A total of 730 lipids were consistently detected in oral fluid samples through untargeted analyses, spanning 77 distinct lipid subclasses. The distribution of these lipids was highly variable: the majority of classes (59 out of 77) contained fewer than 10 identified lipids. Figure 18 summarized the identified lipid subclasses, whereas the complete dataset was reported in Table G (Appendix B). For the sake of clarity, Figure 18 highlighted only the lipid subclasses containing more than 10 members, together with the corresponding lipid counts (right column). These subclasses can be further grouped into broader categories, namely glycerophospholipids, glycerolipids, sphingolipids and fatty acids. The category labeled “Other” grouped all subclasses with fewer than 10 detected lipids (59 classes containing 222 species). A detailed description of the abbreviations used for each lipid subclass reported, in Figure 18 and Table 14, is provided in Appendix C.

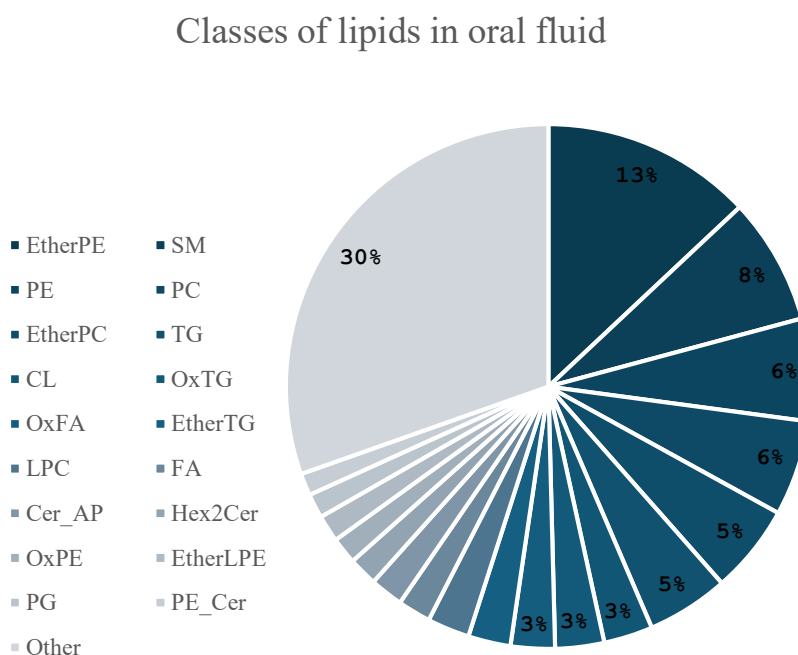


Figure 18. Subclasses of lipids in oral fluid samples taken from young and healthy people.

3.1.3 Comparison of whole blood and salivary lipidomics and metabolic profiles

In parallel with the salivary samples analyzed for the characterization of the lipidomic and metabolic profiles described in the previous sections, whole blood was also collected from the healthy volunteers (21 samples, 16 women and 5 men). These blood samples were analyzed using the same analytical approach applied to oral fluid, enabling a direct comparison of the lipidomic and metabolic profiles between these two matrices. As previously detailed, the salivary analysis revealed 77 metabolites and 730 lipids, whereas in whole blood 102 metabolites and 859 lipids were identified

across all samples. For comparative purpose, only compounds detected in both matrices were considered, resulting in a final dataset of 292 shared compounds, comprising 35 metabolites distributed across 16 classes and 257 lipids grouped into 32 subclasses classes (Summarized in Figure 19, described in detail in Table J (Appendix B)). Comprehensive lists of the metabolites and lipids identified in oral fluid, along with their respective classes and subclasses, are provided in Tables F and G (Appendix B), while the corresponding data for whole blood are reported in Tables H and I (Appendix B).

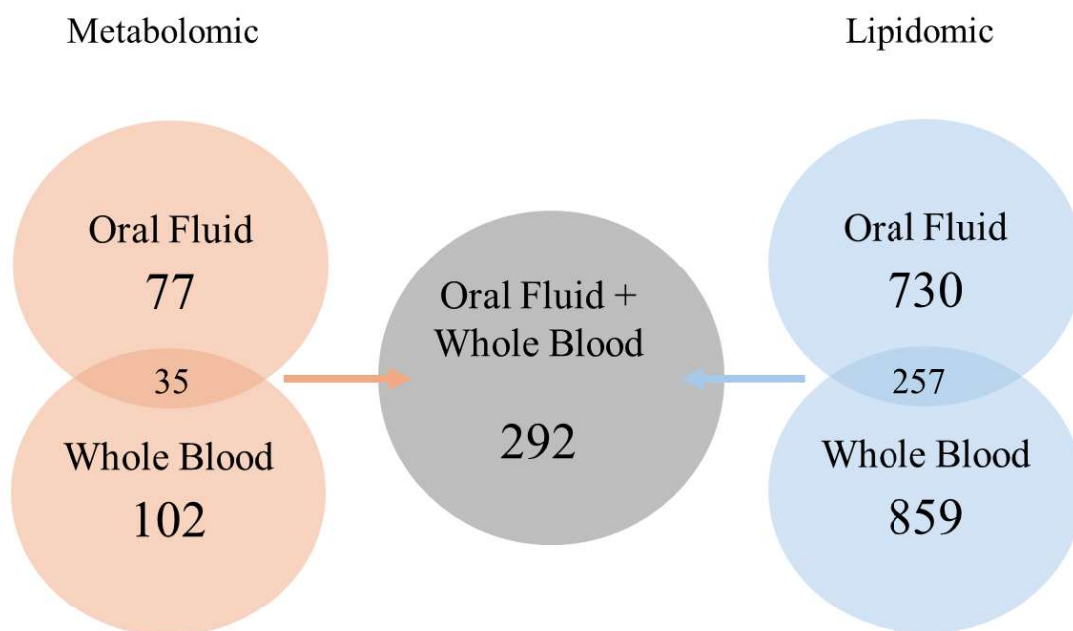


Figure 19. Summary of metabolomics and lipidomics compounds identified in oral fluid and whole blood from healthy and young individuals. A total of 77 metabolites were detected in saliva and 102 in whole blood, with 35 metabolites shared between matrices. Lipidomics analysis revealed 730 lipids in saliva and 859 in whole blood, with 257 lipids in common, for a total of 292 shared compounds.

Of the 292 initial compounds, 30 were excluded during the filtration step as they did not meet the predefined selection criteria. The remaining compounds were subjected to statistical analysis. The volcano plot, oral fluid vs whole blood (Figure 20.a), highlighted significant differences in lipids and metabolites between saliva and whole blood samples. Considering both p-value and fold change (p-value < 0.05 and fold change > 2), 138 compounds were found to be downregulated (blue) in saliva compared to blood, 44 were upregulated (red) (Appendix F, Table P) (distributed across 36 subclasses, Table 13) and 80 compounds showed no statistically significant differences between the two matrices. This analysis revealed the majority of statistical different lipids belonged to the glycerophospholipids class, which accounted for more than 65% of the detected lipid species, followed with several metabolite classes as purines and derivatives and amino acids.

Table 13. Subclasses of lipid and metabolite species found to be significantly changed in oral fluid compared with whole blood, as identified through volcano plot analysis.

Subclasses	N° of species	Subclasses	N° of species
PC	29	SHexCer	1
EtherPE	29	Pyridines and derivatives	1
EtherPC	21	Organonitrogen compounds	1
PE	20	SSulfate	1
SM	13	CAR	1
LPC	10	Ureas	1
CE	6	Indoles and derivatives	1
TG	6	Pyrimidine nucleotides	1
Hex2Cer	6	Keto acids and derivatives	1
Purines and derivatives	6	DG	1
Amino acids and derivatives	5	PI	1
Cer_NS	2	ST	1
FA	2	Piperidinones	1
PS	2	VAE	1
EtherPS	2	LNAPe	1
Fatty acids and conjugates	2	OxPE	1
EtherLPE	2	Alkaloids and derivatives	1
Steroids	1	LPE	1

Partial least squares discriminant analysis (PLS-DA) (Figure 20.b), showed, as expected, a clear clustering between oral fluid and whole blood. The model demonstrated a strong separation along component 1 between these two matrices. Variable importance in projection (VIP) plot (Figure 20.c) scored the top 15 discriminating compounds, ranked according to their contribution to the variance explained by component 1. Most of these discriminant compounds belong to the class of glycerophospholipids and their ethers, with the exception of: 2-piperidone, niacinamide, ST 27:1;O;S and FA 18:2 (linoleaidic acid). Notably, all but two of these compounds (2-piperidone and FA 18:2) were downregulated in oral fluid. Finally, Figure 20.d presents a heatmap illustrating the top 100 compounds identified through the t-test. This shows a pattern similar to that observed in the volcano plot emerges, with most compounds being downregulated in saliva compared to whole blood. This trend aligns with the known physiological distribution of lipids, which play essential roles in the body by circulating in the bloodstream to be delivered to cells or used as an energy source. In contrast, saliva has a different biochemical composition and contains substantially lower lipid levels.

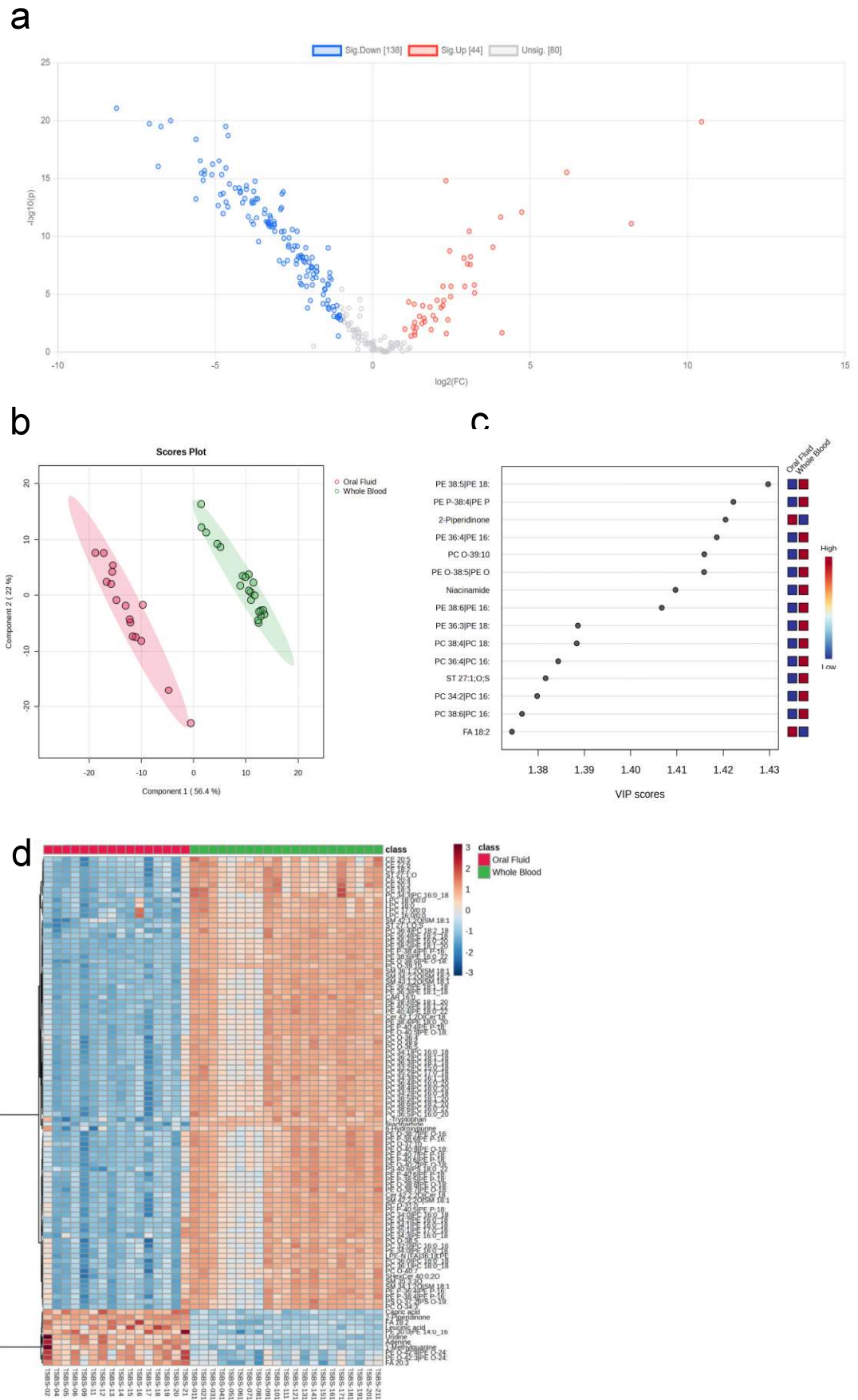


Figure 20. Statistical comparison of lipidomic and metabolic profiles between oral fluid and whole blood from healthy young individuals. Shown are: (a) volcano plot (oral fluid vs whole blood, p -value < 0.05 and fold change > 2), (b) PLS-DA score plot, (c) VIP scores plot, (d) heatmap of relative compounds abundances.

Building on the lipidomic and metabolic profiling conducted in healthy individuals, the next phases of this study explored how these salivary signatures vary under different physiological and pathological conditions, including aging, Alzheimer's disease and addictions. Such investigations will help establish the value of oral fluid as non-invasive matrix for metabolic and lipidomic assessment across a range of health context.

3.2 The impact of aging on salivary lipidomic profile

Table 14 summarizes the main demographic characteristics of the two study groups: adult (n = 27) and young (n = 20). The mean age of the adult group was 65.4 years (range 51-87), whereas the young group had a mean age of 29.3 years (range 23-35). Concerning gender distribution, the adult group included 15 men (55.5%) and 12 women (44.4%), while the young group comprised 5 men (25%) and 15 women (75%). Overall, the demographic data indicated that the two cohorts differed as expected in terms of age, while maintaining a sufficiently balanced gender representation to allow for reliable comparative statistical analyses.

Table 14. Characteristics of individuals included in the study salivary lipidomic and metabolic profile variations associated with aging. Data are reported as median (min-max) or as n (%).

	Adult (n=27)	Young (n=20)
Characteristics		
Age	65.4 (51-87)	29.3 (23-35)
Gender		
Men	15 (55.5%)	5 (25%)
Women	12 (44.4%)	15 (75%)

This design allowed for a direct comparison between the salivary metabolic and lipidomic profiles of the two groups of individuals, providing insights into how aging may influence the composition and abundance of key biomolecules in oral fluid. The samples were analyzed using high-resolution time-of-flight mass spectrometer coupled with HPLC and subsequent raw files were processed using MS-Dial software to achieve library-based identifications. As in the comparison between saliva and whole blood section described above, both lipids and metabolites were jointly analyzed in this part of the study. A total of 602 compounds (582 lipids and 20 metabolites) were identified in oral fluid, distributed across 67 distinct classes of metabolites and subclasses of lipids. The complete list of compounds with their respective classification is provided in Table K (Appendix B). More than 60 % of the identification compounds belonged to the following subclasses: EtherPE (56), PE (54), TG (45), Cer_AP (37), OxFA (35), CL (33), OXTG (29), PC (24), SM (22), FA (22) and PG (21);

individual compounds within each subclass are indicated in parentheses (legend of lipid subclasses is reported in Appendix C). These subclasses were distributed into four major classes: glycerophospholipids, glycerolipids, sphingolipids and fatty acids. After identifying the features common to both age groups, a series of statistical and data analyses was performed to evaluate age-related differences in the salivary lipidomic and metabolic profiles.

Of the 602 initially identified compounds, 151 were excluded during data filtering as they did not meet the predefined selection criteria, leaving the remaining features for statistical evaluation. The volcano plot, adult vs young (Figure 21.a), revealed 57 downregulated compounds (blue) and 3 upregulated (red) compounds in adults compared to young individuals (Appendix F, Table Q), using a threshold of $p\text{-value} < 0.05$ and of fold change > 2 . Notably, nearly all statistically significant variations involve lipids; the only metabolite identified was palmitoyl carnitine. Among the altered compound, LPC 22:4 displayed the most striking change, with a very low $p\text{-value}$ ($6.07\text{E-}24$) and a negative $\log_2(\text{FC})$ (-5.55). In addition, several glycerolipids species (TG and OxTG) were found to be downregulated (56% of compound significantly different), followed by glycerophospholipids (36 %, including EtherPE, PE, LPE, PC, EtherPC, PI, CL and EtherPG). Conversely, the three upregulated compounds were FA 22:5; O, FA 20:4 and VAE 4:0 which are grouped in fatty acids class and vitamin A fatty acid ester classes (Table 15). To further investigate group separation, a PLS-DA (Figure 21.b) was performed. The multivariate model demonstrated a clear distinction between the two groups (red $\rightarrow$ adult and green $\rightarrow$ young), primarily along the first component (61.8% of explained variance), which captured the main axis of differentiation in metabolic and lipidomic profiles. The second component (5.3%) accounted for a smaller portion of variance, reflecting interindividual variability. Although some overlap was observed in the confidence ellipses, the overall clustering pattern indicated distinct age-related signatures. VIP scores (Figure 21.c) identified the compounds driving this separation. Lysophosphatidylcholine, LPC 22:4, strongly contributed to the first component, highlighting its potential role as key discriminator between the two age groups. Other relevant contributors included NAGly 13:1;O, VAE 4:0 and several triglycerides species, with all downregulated in adult individuals except VAE 4:0, which was upregulated. Finally, heatmap analysis (Figure 21.d) provided a visual overview of abundance patterns across the two groups. The top 60 compounds selected by t-test heatmap confirmed the trend observed in the volcano plot, with the majority of compounds exhibiting lower abundance in adult individuals. Although variability within the adult group was evident, possibly due to the wide age range, diet, physical activity or other factors that can alter the metabolic and lipidomic profile.

Taken together, these results revealed consistent age-related alterations in the salivary lipidomic and metabolic profiles. The predominance of downregulated compounds in adult individuals suggests a potential link to key biological processes of aging, including altered energy metabolism,

increased oxidative stress and chronic low-grade inflammation, highlighting specific metabolites and lipid classes as promising candidates for future biomarker discovery.

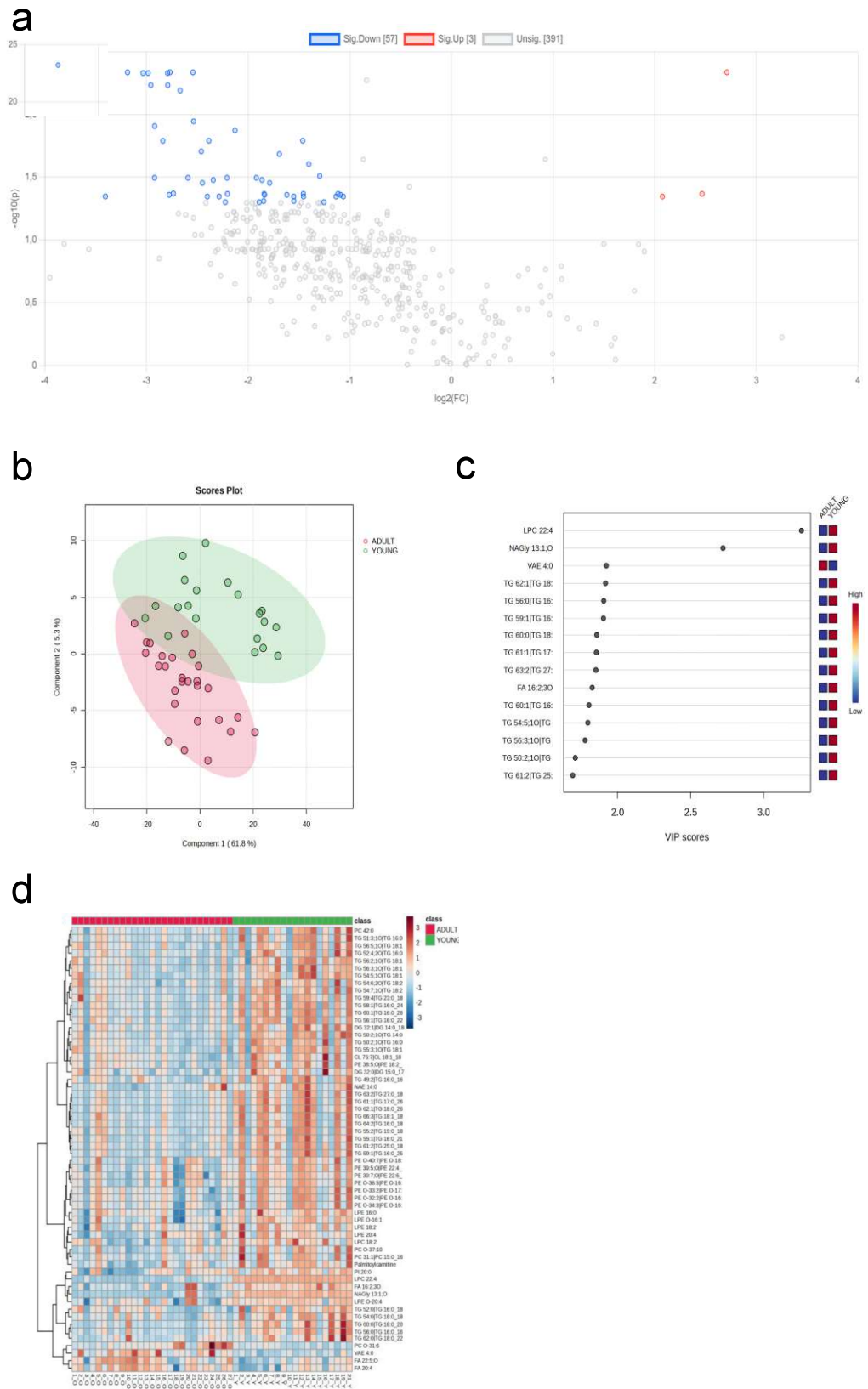


Figure 21. Statistical comparison of salivary lipidomic and metabolic profiles between the two age groups of interest. Shown are: (a) volcano plot (adult vs young, p -value <0.05 and fold change >2), (b) PLS-DA score plot, (c) VIP scores plot, (d) heatmap of relative compound abundances.

Table 15. Subclasses of salivary lipid and metabolite species found to be significantly up- or downregulated in two aging groups, as identified through volcano plot analysis.

Subclasses	N° of species
TG	20
OxTG	12
Ether PE	7
PE	3
LPE	3
DG	2
PC	2
LPC	2
FA	1
VAE	1
PI	1
Ether PC	1
Acyl carnitines	1
CL	1
NAE	1
Ether PG	1
OxFA	1

3.3 Salivary lipidomic signature as a potential biomarker in neurodegenerative pathologies: Alzheimer's disease

One of the principal aims of the study was to evaluate the reliability of saliva as a biomarker source in lipidomic and metabolomic studies. Since oral fluid is closely linked to pathologies of the oral cavity, saliva has traditionally been investigated in relation to these diseases. However, we aimed to assess whether variations in metabolic and lipidomic profiles could be associated with an independent pathology. To this end, we compared patients with Alzheimer's disease (AD) to cognitively healthy age- and gender-matched controls, taking into account that lipidomic and metabolic changes associated with aging can influence the salivary profiles as previously observed.

Table 16 reports the demographic and clinical characteristics of the control group (n=17) and the Alzheimer's disease (AD) group (n=17). The mean age of participants in the control group was 65.6 years (range 52-87), whereas the AD group had a mean age of 69.9 years (range 50-78). This difference was not statistically significant (p=0.14). Regarding gender distribution, both groups were balanced, with 9 men (52.9 %) and 8 women (47%) in each group, indicating a high degree of age and gender homogeneity within the study population. Clinical biomarkers were assessed only in the AD group. The mean concentration of β -amyloid 42 was 557.7 pg/mL (range 358-1798), total tau was 577.6 pg/mL (range 259-1097) and phosphorylated tau was 95.7 pg/mL (range 39-187).

Cognitive function, evaluated using the Mini-mental state examination (MMSE), showed a mean score of 20.7 (range 13-26.2) in the AD group compared to scores above 26 in the control group. Overall, the two groups were comparable in terms of age and gender, while the AD group exhibited the expected pathological changes in β -amyloid and tau biomarkers, along with reduced cognitive performance, consistent with the clinical diagnosis.

Table 16. Characteristics and clinical assessment of individuals included in the study of salivary lipidomic and metabolic profile variations in Alzheimer's disease. Data are reported as median (min-max) or as n (%).

	Control group (n=17)	AD (n=17)	
Characteristics			pvalue
Age	65.6 (52-87)	69.9 (50-78)	0.14
Gender			
Men	9 (52.9%)	9 (52.9%)	
Women	8 (47%)	8 (47%)	
β-amyloid 42	-	557.7 (1798-358)	
Tau	-	577.6 (1097-259)	
Phosphorylated-Tau	-	95.7 (187-39)	
MMSE	> 26	20.7 (26.2-13)	

The following section reports the results obtained from the comparison between patients with AD and cognitively healthy age-matched controls. As in the previous phases of the study, the compounds identified through lipidomic and metabolomic analyses were jointly processed. In total, 602 compounds, including lipids and metabolites, were identified in oral fluid samples and classified in 67 lipid and metabolite subclasses and classes, as reported in table K (Appendix B). The most represented subclasses, covering more than 60% of all features, were: EtherPE, PE, TG, Cer_AP, OxFA, CL, OxTG, PC, SM, FA and PG. These subclasses could be further grouped into four main lipid categories: glycerophospholipids, glycerolipids, sphingolipids and fatty acids.

Of the 602 identified compounds (582 lipids and 20 metabolites), 151 were removed during data filtering step as they did not meet the predefined criteria. The remaining compounds were then subjected to statistical analysis. The volcano plot, AD vs CTRL group (Figure 22.a), revealed 27 downregulated compounds (blue) and 29 upregulated compounds (red) in AD compared to controls (Appendix F, Table R), while 395 compounds showed no statistically significant differences between

groups (p-value < 0.05 and fold change > 2). Downregulated compounds primarily belonged to glycerophospholipids (PE, PG, CL, EtherPC, PS, EtherPE), sphingolipids (HexCer_HDS and HexCer_AP) and glycerolipids (DG and OxTG). In addition, pantothenic acid and 5-deoxy-5-methylthioadenosine were also downregulated. Conversely, upregulated features included glycerophospholipids (LPC, EtherPC, EtherLPE, PI, EtherLPC, EtherPE, PC, PS, LPE), fatty acids (NAE, OxFA, NAOra, FA) glycerolipids (DG, OxTG), sphingolipids (Cer_HS, SM) and sterol lipids (ST and CE). Among altered classes, glycerophospholipids were the most affected, with 39 features showing significant variation, followed by fatty acids (5), sphingolipids (4), glycerolipids (4) and sterol lipids (2) (Table 17).

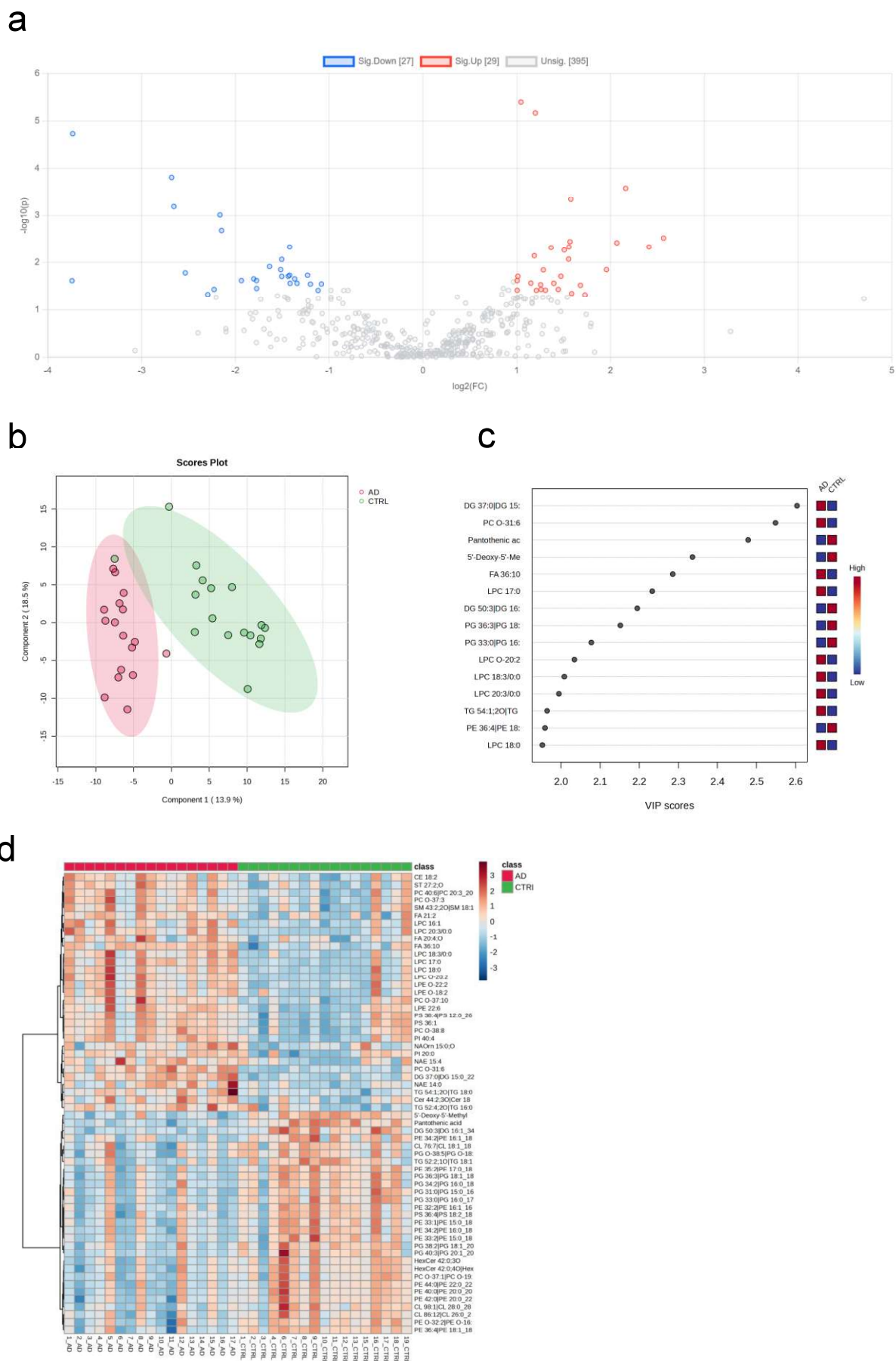


Table 17. Subclasses of salivary lipid and metabolite species found to be significantly changed in AD patients compared with a control groups, as identified through volcano plot analysis.

Subclasses	N° of species
PE	11
PG	6
EtherPC	5
LPC	5
DG	2
PI	2
OxTG	2
EtherLPE	2
PS	2
EtherPE	2
NAE	2
HexCer_HDS	1
HexCer_AP	1
CL	1
5'-deoxy-5'-thionucleosides	1
ST	1
LPE	1
Cer_HS	1
CE	1
FA	1
NAOrn	1
SM	1
OxFA	1
EtherLPC	1
PC	1

To further illustrate group separation, a PLS-DA (Figure 22.b) model was constructed. The model showed a clear distinction between Alzheimer's disease (AD) (red) and control samples (green). The compounds contributing most to this separation were identified through the VIP scores plot (Figure 22.c). This analysis highlighted several metabolites and lipids as key discriminant features, including downregulated compounds in AD such as: pantothenic acid (vitamin B), 5-deoxy-5-methylthioadenosine (MTA), DG 50:3|DG 16:1_34:2, PG 36:3|PG 18:1_18:2, PG 33:0|PG 16:0_17:0, PE 36:4|PE 18:1_18:3. Conversely, several upregulated lipids were observed in AD such as: DG 37:0|DG 15:0_22:0, PC O-31:6, FA 36:10, LPC 17:0, LPC O-20:2, LPC 18:3/0:0, LPC 20:3/0:0, LPC 18:0. Finally, heatmap (Figure 22.d) were generated to visualize the relative abundance of lipids and metabolites between the two groups. The heatmap displays the top 60 features selected by t-test (p-value < 0.05). This shows that the relative abundance of specific compounds were higher in AD patients, whereas other were abundant in controls. These variations corroborate the patterns highlighted in the volcano plot, thereby reinforcing the evidence of differential metabolic profiles between the groups under study.

3.4 Influence of drug addiction on salivary lipidomic and metabolomic profiles

Considering the interest in understanding how different physiological and pathological conditions may influence salivary composition, following the analysis of metabolomic and lipidomic alterations associated with Alzheimer's disease, it was deemed particularly relevant to also investigate the impact of chronic psychoactive substance use. Specifically, this study aimed to assess how prolonged use and addiction on such substances may modulate the salivary metabolic and lipidomic profiles. To this end, the analysis included individuals with a history of chronic consumption of cocaine, cannabinoids, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine), methadone, ketamine, alcohol and benzodiazepines.

All recruited participants (n=295) underwent targeted hair analysis, as described in paragraph 2.6, to verify drug consumption. Of these, 24 subjects tested positive for at least one of the substances listed above and were therefore included in the test group. For comparative purpose, 11 individuals who tested negative were selected as the control group. Table 18 summarizes the demographic characteristics of the two groups. The mean age of participants in the control group was 34 years (range 22-53), whereas the test group had a mean age of 35.2 years (range 21-60). This difference was not statistically significant ($p=0.75$), indicating a high degree of age homogeneity between the two groups. Regarding gender distribution, the control group included 10 men (90.9%) and 1 women (9.1%), while the test group comprised 18 men (75%) and 6 women (25%). Overall, the demographic data indicates that the control and test groups were comparable in terms of age, with some variation in gender distribution.

Table 18. Characteristics of individuals included in the study of salivary lipidomic and metabolic profile variations in psychoactive substance dependence. Data are reported as median (min-max) or as n (%).

	Control group (n=11)	Test group (n=24)	
Characteristics			pvalue
Age	34 (22-53)	35.2 (21-60)	0.75
Gender			
Men	10 (90.9%)	18 (75%)	
Women	1 (9.1%)	6 (25%)	

Prior to omics analyses, oral fluid samples from the 24 positive individuals were also tested, using the same analytical techniques applied to hair, in order to assess their positivity or negativity at the time of collection, six of them tested positive. The results of this preliminary analysis are summarized

in Table 19 (Appendix E, Table O) enabled the definition of the two study groups subsequently subjected to lipidomic and metabolic analysis.

Table 19. Summary of preliminary analysis on hair and oral fluid taken in the two study groups

Positive samples (Test group, n=24)		
Substance	Hair	Oral fluid
Alcohol	1	-
Methadone	2	2
Cocaine	5	1
Cannabinoids	4	-
Ketamine	1	-
Methamphetamine/MDMA	2	-
Benzodiazepines	15	3
Negative samples (Control group, n=11)		
Substance	Hair	Oral fluid
All substances	-	-

Subsequently, oral fluid samples collected from the two groups, described above, were processed and analyzed to assess whether chronic substance use and abuse lead to alterations in the salivary lipidomic and metabolic profiles. In total, 2019 compounds were identified, 1641 of which were present in all analyzed samples. All compounds can be grouped into 106 subclasses and classes of lipids and metabolites, as reported in Table L (Appendix B). Among these, the most represented categories containing more 50% of compounds were lipids classes as: TG (279 species), OxTG (196 species), DG (132 species), EtherPC (121 species), SM (115 species), PC (105 species), EtherPE (100 species) and EtherPG (90 species). These subclasses could be grouped into three major lipid classes: glycerolipids, glycerophospholipids and sphingolipids. Conversely, the metabolic class containing most compounds was long-chain fatty acids (5 species).

Dataset was subsequently subject to statistical and data analyses using MetaboAnalyst 6.0. Prior to performing these dataset was filtered and normalized by applying a low variance filter (IRQ at 10%), followed by log transformation and autoscaling. Of the 2019 initially identified compounds (1956 lipids and 63 metabolites), 202 were removed during data filtering step as they did not meet the predefined selection criteria. The remaining features were subjected to statistical and data analyses to evaluate variations between the two groups considered in this study. The volcano plot, users vs CTRL (Figure 23.a), revealed 21 significantly downregulated compounds and 7 upregulated compounds in the oral fluid of substances users compared to controls (Table 20), while 1789 compounds did not show significant changes ($p\text{-value} < 0.05$ and $\text{fold change} > 2$). The 21

downregulated compounds (blue) were exclusively lipids, distributed across 14 subclasses. The majority belonged to glycerophospholipids (11 species), notably including several ether-linked species (PE, PG, EtherLPE, EtherPE, EtherPC and CL). This group was followed by glycerolipids (5 species across DG, OxTG and EtherDG), sphingolipids (3 species) and fatty acids (2 species). Conversely, the 7 upregulated compounds (red) did not cluster into broad classes, though they included three EtherPC species, One OxTG, one Hex2Cer, one dicarboxylic acid and one acylcarnitine (Appendix F, Table S).

The PLS-DA model (Figure 23.b) showed a clear separation between substance users (green) and controls (red) along the first principal component, indicating that the variables contributing to component 1 are key discriminants. The VIP score plot (Figure 23.c) identified the most influential features, primarily belonging to glycerophospholipids (PC O-31:1|PC O-16:1_15:0, PC O-29:1, LPE O-18:1, PE 28:0, LPE 14:0, PE O-34:2|PE O-16:1_17:1, LPC 22:1), glycerolipids (TG 24:0|TG 8:0_8:0_8:0, DG 48:12, TG 52:2;O|TG18:0_18:1_16:1;O, DG 52:10, DG O-34:2|DG O-16:1_18:1), fatty acids (FA 20:4;O4, Hexanoyl-L-Carnitine) and succinate. Several of these compounds were found to be downregulated, whereas others were upregulated in the test group relative to the control group. Finally, heatmap was generated: including the top 50 compound ranked by t-test (p-value <0.05) (Figure 23.d).

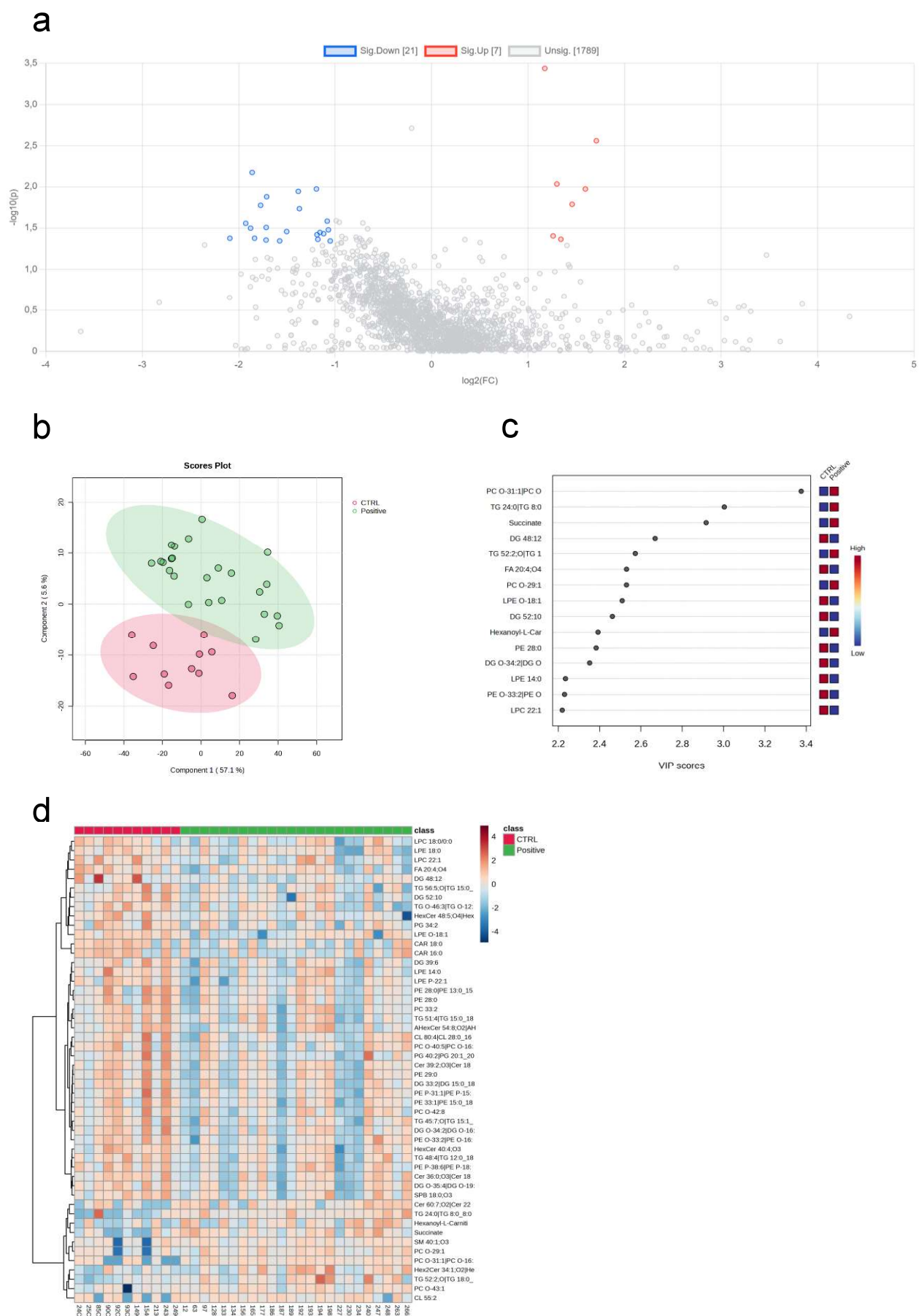


Figure 23. Statistical comparison of salivary lipidomic and metabolic profiles between substances users and controls. Shown are: (a) volcano plot (users vs CTRL), (b) PLS-DA score plot, (c) VIP scores plot, (d) heatmap of relative compounds abundances.

Table 20. Subclasses of salivary lipid and metabolite species found to be significantly up- or downregulated in drugs users compared with a control groups, as identified through volcano plot analysis.

Subclasses	N° of species
EtherPC	4
DG	3
PE	3
OxTG	2
EtherPE	2
PG	2
EtherLPE	2
EtherDG	1
HexCer_HS	1
HexCer_AP	1
Cer_HS	1
OxFA	1
Dicarboxylic acids and derivatives	1
CL	1
Hex2Cer	1
CAR	1
Acyl carnitines	1

Taken together, these findings reveal specific alterations in the salivary lipidomic and metabolomic profiles of individuals with a history of substance abuse, with glycerophospholipids emerging as particularly affected. While the heterogeneity of substances used and the limited cohort size constrain the strength of these observations, the results nonetheless highlighted the potential of saliva as a non-invasive biofluid for exploring molecular signatures of chronic substances use.

4. DISCUSSION

This chapter discusses the findings obtained from the characterization of the salivary metabolomic and lipidomic profiles, first examined in healthy individuals and compared with whole blood, which is considered an elite biofluid in both clinical and forensic contexts. The comparison aimed to assess the potential of oral fluid as a reliable alternative matrix for metabolic and lipidomic investigations. Subsequently, the study explored how salivary profiles vary under different physiological and pathological conditions, including aging, Alzheimer's disease and chronic substance dependence. The discussion will critically evaluate these results in light of current literature, highlighting their implications, limitations and perspective for future applications in clinical and forensic research.

4.1 Characterization of lipidomic and metabolic profiles of oral fluid

In the present study, the salivary metabolic and lipidomic profiles were characterized using high-performance liquid chromatography coupled with high-resolution time of flight mass spectrometry (HPLC-QTOF-HRMS). Specifically, the metabolic profile refers to the polar fraction of the metabolome, whereas the lipidomic profile focuses on its more apolar fraction. This dual-perspective approach offers a comprehensive overview of the molecular composition of saliva, reinforcing its value as a non-invasive matrix for probing both systemic and localized biochemical variations.

Concerning the metabolic profile (Section 3.1.1), 77 metabolites were identified, of which 58 were consistently present across all samples. These metabolites were classified into 25 distinct chemical classes, as reported in Table 13 along with the corresponding number of metabolites per class. This is not the first investigation to explore the salivary metabolome of healthy individuals. For instance, Meleti et al.²⁹⁸ examined the metabolic composition of whole (WS), parotid (PS) and submandibular/sublingual (SM/SL) oral fluid using ¹H-NMR. Their study revealed considerable heterogeneity in the metabolite composition among the three saliva types, identifying 54 metabolites in whole saliva, 49 in parotid saliva and 36 in SM/SL saliva, with 32 metabolites being common to all. In line with the current findings, amino acids were the most abundant class of metabolites in whole saliva, probably because free salivary amino acids are largely generated by endogenous and exogenous proteases originating from salivary glands, exfoliated cells and the oral microbiota. Proteolytic bacteria hydrolyze proteins and peptides into amino acids, subsequently converting them into short-chain fatty acids. Along with other bacterial species, these processes contribute to the organic acid content of saliva^{299,300}. It can therefore be hypothesized that the high abundance of amino acids and fatty acids in saliva reflects underlying bacterial metabolic pathways. Among these, taurine, a β -sulfonic amino acid, was detected in both studies cited before. Taurine is one of the most abundant

free amino acids in mammalian tissues and, as by Revenga-Parra et al.³⁰¹, its quantification may hold relevance for the early diagnosis of various diseases, including Alzheimer's disease, diabetes mellitus and epilepsy. In saliva, taurine has also been associated with physical stress³⁰². In our study as well, taurine was detected in all saliva samples analyzed. The carbohydrate class, by contrast, is strongly influenced by blood glucose levels, as these compounds enter oral fluid through the salivary glands in proportion to their systemic concentration. Consequently, fasting conditions, such as those applied in the present study, are expected to affect their salivary levels. Meleti et al.²⁹⁸ also reported the presence of several organic acids in whole saliva, which, in the current work, were instead detected in the lipid fraction. This discrepancy is likely attributable to differences in sample preparation and analytical methodology, as the present metabolomic analysis targeted the polar fraction of the metabolome, while the lipidomic workflow encompassed less polar compounds. Expanding on these earlier findings, Ciurli et al.³⁰³ examined the spatial and temporal salivary metabolic profile using a semi-targeted LC-MS platform rather than ¹H-NMR, thereby achieving broader metabolic coverage compared to Meleti et al.²⁹⁸. This extended analytical scope offers a clear advantage for deepening our understanding of oral physiology.

Recently, relatively few studies have provided a comprehensive characterization of the salivary lipidomic profile in healthy individuals. Early lipidomic research predominantly quantified the total lipid content, whereas predominantly quantified the detailed analysis of distinct lipid classes. Seminal work by Larsson et al.³⁰⁴ and Slomiany et al.³⁰⁵ demonstrated that approximately 99% of salivary lipids are non-polar, with neutral lipids such as: mono-, di-, triacylglycerols, cholesterol and its esters, free fatty acids and monoglycerides, constituting the predominant fraction. The remaining minor fraction comprises polar lipids, including glycerophospholipids, glycerolipids and sphingolipids, which despite their lower abundance, play critical roles in oral physiology. Glycerophospholipids contributes to the stabilization of the salivary pellicle, enhance lubrication and provide antimicrobial protection; while glycerolipids and sphingolipids are involved in cell-cell recognition and modulation of immune responses within the oral cavity. This compositional profile underscores the functional relevance of salivary lipids beyond their structural roles and supports their potential utility as biomarkers for both physiological variations and pathological alterations in the oral environment and systemic diseases^{306,307}. In the present study, we aimed to comprehensively characterize the salivary lipidomic profile of healthy young individuals using a high resolution mass spectrometry approach. This analysis was designed to establish a robust baseline reference for salivary lipid composition, which could serve as a foundation for identifying potential biomarkers of several conditions. Our investigation revealed 730 lipids spanning 77 diverse lipid-subclasses (Section 3.1.2) in all samples (n=16). The majority of identified species belonging to glycerophospholipids and their ether derivatives, triacylglycerols, sphingolipids and free fatty acids in agreement with previous literature. Several additional classes and subclasses, were also detected, highlighting their potential functional relevance in oral physiology.

4.2 Comparison of whole blood and salivary metabolic and lipidomic profiles

Recent studies increasingly employed metabolic and lipidomic approaches to compare blood (plasma and serum), chosen as the reference matrix due to its established use in numerous clinical and forensic studies, and oral fluid, with the aim of evaluating these matrices in the context of disease, exploring their relationship with various pathological conditions and identifying potential biomarkers for early diagnosis, disease progression monitoring or treatment assessment^{308–310}. While such comparisons have been extensively explored under pathological conditions, there is a striking scarcity of studies examining the lipid and metabolic profiles of blood and oral fluid collected under standard physiological conditions. To our knowledge, the only investigation addressing this gap was conducted by Ferrari et al.³¹¹, who employed quantitative ¹H-NMR spectroscopy to compare serum and saliva metabolic profiles. They reported that serum metabolites exhibited a more compact distribution compared to those in saliva, reflecting lower interindividual variability in serum. Although the overall chemical composition of the two matrices was broadly comparable, significant differences in the concentrations of shared metabolites were observed. Furthermore, VIP scores analysis from their PLS-DA model identified glucose, lactate and acetate as the most influential metabolites driving the separation between serum and oral fluid. To our knowledge no studies have yet directly compared the total lipid profile of blood and oral fluid; some research has, however, investigated specific lipid classes, such as cholesterol, triglycerides and lipoproteins between these two biological matrices³¹².

As outlined in the results (Section 3.1.3), this study analyzed whole blood and saliva collected from young and healthy individuals to characterize and compare their lipidomic and metabolic profiles under physiological conditions, with the aim of identifying potential salivary biomarkers for various diseases. Statistical analyses were conducted on lipids and metabolites common to both matrices. Our results indicate that most glycerophospholipids were downregulated in saliva compared to blood. Triglycerides and fatty acids showed upregulation in oral fluid compared to whole blood, which may also serve as potential biomarkers in saliva. Wang et al.³¹³ reported a similar pattern in serum, where glycerophospholipids and triglycerides together represented approximately 60% of the identified lipid species. Among the metabolite classes, purines and amino acids were the most abundant, with both upregulated and down regulated compounds observed. As discussed in section 4.1, the presence of amino acids and certain fatty acids in saliva could be linked to metabolic pathways associated with the activity of oral microbiota.

The PLS-DA and VIP scores analyses (Figure 20.b and 20.c) revealed distinct clustering of whole blood and oral fluid samples, with 15 features contributing most to the variance explained by component 1. Similar to the findings of Ferrari et al.³¹¹, blood samples displayed a tighter distribution

than saliva, indicating lower interindividual variability. The compounds with the highest VIP scores were primarily glycerophospholipids particularly: PE, EtherPE and PC along with 2-piperidone, niacinamide, ST 27:1;O;S and FA18:2. These molecules represent valuable candidates for further targeted biomarker research, although additional studies involving larger cohorts will be necessary to validate these observations. Finally, the heatmap (Figure 20.d) illustrating relative abundance patterns across the two matrices confirmed that the majority of lipids and metabolites were more abundant in whole blood than in oral fluid. Only a limited number of features, mainly fatty acids and certain metabolites, were found at higher concentrations in saliva, reinforcing the compositional differences between these two biofluids.

Taken together, these findings indicate that oral fluid should not be regarded merely as a surrogate for blood but rather as a complementary biofluid with unique biomarker potential. The distinct salivary profile, particularly in lipid classes relevant to cellular signaling and disease processes, highlights its promise for non-invasive diagnostic applications. Future investigations in larger cohorts will be required to validate these results and to assess the translational value of salivary lipids and metabolites in clinical contexts. Moreover, employing plasma or serum as the reference blood matrix, in line with most published studies, would allow more straightforward comparisons with the existing literature and facilitate the integration of salivary lipidomic into broader biomedical research.

4.3 How aging process impact on salivary lipid profile

The integrated application of lipidomic and metabolic analyses represents a promising approach to describe the biochemical transformations associated with aging. Metabolomics expands the analytical spectrum by revealing variations in amino acids, compounds involved in energy metabolism, redox pathways and nucleotide biosynthesis³¹⁴. In parallel, lipidomics enables the identification of specific lipid fractions that monitor different functions, including membrane stability, energy storage, cellular proliferation, inflammation, intercellular signaling and apoptosis. Lipids play a crucial role in aging processes and disruptions in major lipid pathways, lipid accumulation, peroxidation and impaired fatty acid utilization in organs have been linked to several age-related diseases. Lipid levels can therefore vary significantly with age, providing potential biomarkers of biological aging or “healthy aging”²³⁹. Several studies investigating age-related changes in metabolic and lipidomic profiles have primarily used plasma or serum as biological matrices. In many cases, sex-specific differences have also been evaluated, since metabolic pathways vary according to sex^{239,314,315}. Other works have employed alternative matrices such as oral fluid²⁴⁹, cerebrospinal fluid²⁴⁸ and muscle tissue³¹⁶.

Previous studies have reported heterogeneous results regarding lipid and metabolite class alterations with age. Almeida et al.³¹⁷ summarized age-related lipidomics changes in plasma and serum, highlighting substantial inconsistencies across studies. For glycerolipids, some studies reported an increase with age^{239,318}, while others observed both increases and decreases depending on the species of the analyzed triglycerides analyzed^{319,320}. In contrast, in the present study, all glycerolipids species (TG and OxTG) were found to be downregulated in adults, a trend that may reflect species-specific dynamics or, alternatively, the characteristics of the biological matrix analyzed. Indeed, as previously discussed, saliva exhibits a lipid profile that differs markedly from that of serum. Similarly, glycerophospholipids exhibit diverse patterns during aging, with certain species increasing while others decrease. For example, Pradas et al.³²¹ reported a general reduction of ether-like PC and PE species, accompanied by an increase in non-etherified PC and PE in plasma. Jove et al.³¹⁸ observed both decreases (LPC, LPE, LPG, PC, PE, PS) and increases in other phospholipid species in adults. Pan et al.³²² also reported reduced LPC and LPE levels in old individuals, suggesting that glycerophospholipids could serve as promising indicators of biological aging and potential targets for dietary or pharmacological interventions. These molecules are key precursors in PL, PC and PE biosynthesis, maintaining membrane structure and function; therefore, their reduction could affect membrane fluidity, protein interaction and transmembrane transport. The variability in the glycerophospholipid findings across studies may reflect differences in the specific species analyzed, as phospholipids are highly diverse and integrate multiple physiological processes that change with aging^{317,322}. In line with these studies, the volcano plot shows that all glycerophospholipids species identified in the present study were downregulated in adult subjects compared to young ones; in particular LPC 22:4 is the most downregulated compound in accordance with Pan et al.³²². This underlines that for this class of lipids what is observed in plasma and serum is aligned with what is observed in saliva. For fatty acids, the opposite trend was observed in this study, indeed, they were upregulated in adult individuals. The literature on this topic reports somewhat inconsistent findings. For instance, Collino et al.³²³ observed an increase in certain fatty acids but also a decrease in others in centenarians when compared with adults and the elderly group. In contrast, Jove et al.³²⁴ reported an increase in saturated fatty acids (SFA) together with a reduction in polyunsaturated fatty acids (PUFA), an association that appears to characterize individuals with exceptional longevity. In particular, FA C16:0 and FA C22:1n-9 have been proposed as potential promising biomarkers of extreme longevity.

Additionally, no significant changes in the overall salivary metabolomic profile were detected in this study, apart from a slight downregulation of palmitoyl-carnitine (acylcarnitine). This observation is partly consistent with previous reports: Sol et al.³¹⁴ reported age-associated increase in acylcarnitine and aromatic amino acids in plasma and that lipid and aromatic amino acid metabolism are the most strongly metabolite pathways affected by aging. While Slade et al.³²⁵ in a large cohort of 980 individuals aged 18-87, did not observe significant changes in acetyl-carnitine. In contrast, Teruya et

al.²⁴⁹ specifically investigated the salivary metabolome decline across age groups and identified 21 metabolites associated with aging, including three nucleotides, three nucleosides, five sugar phosphates, two vitamins, six amino acids and one antioxidant. All of these decreased with age, except for ATP.

In summary, while this study identified significant lipidomic alterations between adult and young individuals, several limitations must be acknowledged. The relatively small cohort size and the imbalance in sex distribution limited the possibility of assessing sex-specific metabolomic and lipidomic differences, which are increasingly recognized as important modulators of aging. Moreover, the different age ranges (other studies use higher age range or centenarians) and the wide age range within the adult group may have introduced additional variability, masking subtler age-associated changes. The use of oral fluid as a matrix, rather than serum and plasma, although minimally invasive and promising, also presents challenges due to its dynamic composition, potential influence of diet and oral health and the lower concentration of metabolites compared to plasma or serum. These factors, together with the discrepancies observed when compared with existing studies, indicate that caution is required in interpreting the results.

Despite the limitations of this part of the study, described above, oral fluid proved able to capture age-related lipidomic and metabolic changes, most notably the downregulation of glycerophospholipids and the strong reduction of LPC 22:4 in adult individuals. Triglycerides and other glycerolipids also contributed significantly to the separation between age groups, highlighting their potential as biomarkers. Overall, these findings support saliva as a minimally invasive matrix for aging research and reinforce the evidence that lipidomic profiling can provide valuable insights into the molecular mechanisms of aging. Future studies involving larger cohorts, longitudinal design and cross-matrix comparisons will be crucial to validate these findings and to advance the translational potential of salivary lipidomics and metabolomics in the development of biological aging clocks and personalized strategies for healthy aging.

4.4 Alzheimer's disease: pathological application

In the present work, we aimed to investigate alterations in salivary metabolic and lipidomic profiles associated with AD by comparing 17 patients diagnosed with the disease to 17 age- and sex-matched cognitively healthy controls (CTRL). The comparative oral fluid analysis between individuals with Alzheimer's disease and cognitive healthy controls provides novel insights into the molecular alterations associated with neurodegeneration. While most previous studies have primarily investigated plasma^{88,255}, urine²⁷⁵, cerebrospinal fluid⁸⁸, brain tissue²⁵⁶ (post-mortem analysis), oral fluid emerged as an accessible and non-invasive biofluid that holds considerable promise for

biomarker discovery. Much of the existing research has been focused on metabolic alteration across different biological matrices, whereas investigations on lipidomic changes in AD have only recently gained momentum, with the aim to identify biomarkers useful for early diagnosis, disease monitoring and progression assessment. Indeed, several studies have also examined mild cognitive impairment (MCI) or different stages of the disease, as mild AD^{254,326,327}, thereby capturing the dynamic nature of neurodegeneration. However, results show discrepancies across studies caused by differences in biological matrices analyzed and analytical platforms employed (e.g. ¹H-NMR, HPLC-QTOF-MS, HPLC-Orbitrap)²⁶⁸.

Liu et al.³²⁸ studied lipidomic alterations in plasma and observed that glycerophospholipids can be either up- or down-regulated depending on the specific subclass considered. PCs (PC 16:0_22:6, PC 18:2_18:2, PC 18:0_20:4, PC 36:2, PC 16:1_22:5), PEs (PE 18:0_18:1) and PIs (PI 18:0_18:3, PI 18:1_20:4) showed higher abundance in people affected by AD, whereas the majority of PEs (PE 16:0p_22:6, PE 18:0p_20:4, PE 16:0p_18:1, PE 18:p_22:4), as well as other PCs (PC 20:2_18:2, PC 38:7) were reduced. In contrast, Akyol et al.³²⁶ highlighted a consistent decrease of PIs, PEs and PCs in neuronal membranes of AD patients. The degradation of these lipids is known to be pro-inflammatory, responses by activating microglia and astrocytes, ultimately contributing to amyloid beta deposition. Moreover, this study emphasized that PEs levels decline progressively with disease stage, suggesting they are among the first glycerophospholipids affected during AD onset^{326,329}. Similar to Liu et al.³²⁸, we observed PEs, all of which were downregulated, consistent with the observations of Akyol et al.³²⁶. Importantly, several species (PG 36:3|PG 18:1_18:2, PG 33:0|PG 16:0_17:0, PE 36:4|PE 18:1_18:3, PC O-31:6, LPC 17:0, LPC O-20:2, LPC 18:3/0:0, LPC 20:3/0:0, LPC 18:0), belonging to glycerophospholipids class, were also identified as discriminant variables in the VIP score analysis, reinforcing their potential as salivary biomarkers of AD.

Sphingolipids are also crucial for synaptic transmission and stability, neuronal survival, signaling pathways by being a crucial component of the myelin sheath and tightly interconnected with ceramide in membrane phospholipids.³²⁶ Liu et al.³²⁸ reported bidirectional changes in sphingolipid species, with ceramides showing both increases and decreases in AD patients. In particular, dihydroxy ceramide species containing 18C fatty acyl chains with either no double bonds or two double bonds, as well as all dihydroxy ceramide species with 19C chains, were found to be significantly elevated in AD samples. Conversely, dihydroxy ceramide species containing 16C and 18C chains with a single double bond showed reduced levels in AD. In addition, most monohydroxy and trihydroxy ceramide species were significantly decreased in affected individuals. Liu et al. also observed marked reduction in several sphingomyelin (SM) species, including SM(d35:4), SM(d34:1), SM(d31:1), SM(d18:1_21:0), SM(t36:2), SM(d40:4), SM(d41:1) and SM(d18:1_24:3). Conversely, Chua et al.³³⁰, in a targeted study of plasma from AD and vascular dementia (VaD) patients, proposed several sphingolipids could serve as potential biomarkers for AD. They reported

five common alterations (downregulated: Cer d16:1/24:0, GM3 d16:1/22:0, SM d16:1/22:0; upregulated: Cer d18:1/16:0, HexCer d18:1/18:0) shared between the two pathologies when compared with the control group. Moreover, they found 14 sphingolipid species, including ceramides, SM and hexosyl-ceramides, upregulated in AD plasma compared with control. These included Cer d18:1/20:0, Cer d18:1/24:1, Cer d18:2/24:1, Hex2Cer d18:1/18:0, Hex2Cer d18:1/22:0, Hex2Cer d18:1/24:0, HexCer d18:1/16:0, HexCer d18:2/24:1, GM3 d18:1/16:0, GM3 d18:1/24:1, GM3 d18:2/16:0, GM3 d18:2/24:1, SM d18:1/16:0, SM d18:1/24:1. In our study, four salivary sphingolipid species displayed significant variation, being two upregulated (SM 43:2;2O|SM 18:1;2O/25:1, Cer 44:2;3O|Cer 18:1;2O/26:1;O) and two downregulated (HexCer 42:0;4O|HexCer 18:0;3O/24:0;(2OH), HexCer 42:0;3O). As can be observed, the individual sphingolipid species identified as statistically significant in the plasma of AD patients by Lyu et al.³²⁸ and Chua et al.³³⁰ differ considerably and, in some cases, the same species show opposite trends. Moreover, several discrepancies are also evident when comparing these findings with the results obtained in the present study on saliva samples. These variations may arise from differences in the biological matrix, the employed extraction methods and the analytical techniques used for lipid profiling.^[OBJ:OBJ] performed their analyses using HPLC-Orbitrap system,^[OBJ:OBJ] employed an LC-MS/MS triple quadrupole, while in this study an HPLC coupled to a time-of-flight (TOF) mass spectrometer was used.

Liu et al.³²⁸ described that approximately 30% of triglycerides (TG) were elevated and 18% decreased in AD plasma, alongside an increase in diacylglycerols (DG). Consistent with this, in oral fluid we observed both upregulated (DG 37:0|DG 15:0_22:0, TG 54:1;2O|TG 18:0_18:1_18:0;2O) and downregulated (DG 50:3|DG 16:1_34:2, TG 52:2;1O|TG 18:1_18:1_16:0;1O) glycerolipids species, with the two DG species highlighted as key discriminant in the VIP scores analysis. Fatty acids (FA 36:10, FA20:4;O, NAE 14:0, NAE 15:4, NAO_{rn} 15:0;O), on the other hand, were consistently upregulated in AD group compared to controls in our dataset, which aligns with the findings of Fonteh et al.³³¹, who reported elevated levels of total fatty acids in cerebrospinal fluid of AD patients. High levels of fatty acids and their intermediates (such as acyl carnitines and acyl-CoA) are known to be neurotoxic, contributing to mitochondrial uncoupling and bioenergetic dysfunction³³².

Most studies suggest that cholesterol levels are higher in patients with AD than in control subjects. However, some reports describe unchanged brain cholesterol concentrations, likely reflecting differences in the brain regions analyzed or in the disease stages considered. Notably, brain cholesterol levels have been shown to correlate positively with the severity of AD³³². Under physiological conditions, excess cellular cholesterol is converted into cholesterol esters (CE), a neutral lipid form stored within lipid droplets together with triacylglycerols. In the entorhinal cortex of human AD brains, total CE levels have been reported to increase by approximately 1.8 fold, a

finding that has also been confirmed in AD mouse models^{332,333}. Consistent with these observations, our study revealed an increase in CE 18:2, with a fold change of 3.20 and a p-value of 0.03.

Pantothenic acid (vitamin B5) could be a potential discriminatory biomarker in saliva as showed by its high VIP scores. Xu et al.³³⁴ reported decreased levels of this vitamin across seven post-mortem brain regions of AD patients, with greater depletion in the most affected areas. We also observed a significant downregulation of pantothenic acid in oral fluid of AD patients compared to the control group. Another discriminant metabolite, with a high VIP score, was 5-deoxy-5-methylthioadenosine (MTA), a polyamine-derived metabolite. While no direct association with AD have yet been established, MTA has been studied as a therapeutic agent in renal disease and multiple sclerosis and experimental models suggest it may cross the blood-brain barrier and exert neuroprotective effects in specific contexts³³⁵. Its downregulation in saliva of AD samples compared to controls might therefore be linked to disease onset and warrant further investigation as a possible biomarker. Interestingly, while we did not detect significant alterations in salivary metabolites (other than pantothenic acid and MTA), other studies have reported potential metabolites biomarkers. For example, Liang et al.³³⁶ identified sphinganine-1-phosphate, ornithine and phenyl lactic acid as potential biomarkers, all upregulated in oral fluid of AD patients. These metabolites are associated with alterations in sphingolipids metabolism, the urea cycle and phenylalanine metabolism, respectively. Pathways whose dysregulation can impair brain function and contribute to cognitive decline. In our study, however, these metabolites were not detected, most likely due to differences in the extraction method, instrumental conditions such as the mobile phase and chromatographic column used, as well as variations in the software employed for data acquisition, processing and compound identification libraries.

In summary, our results demonstrate that salivary lipidomic and metabolic profiles of patients with AD present significant alterations, partially consistent with findings in other biological matrices. The downregulation of PEs, together with changes in sphingolipids, glycerolipids, fatty acids and sterol lipids suggests the involvement of pathways linked to membrane composition, bioenergetics and neuroinflammation. Furthermore, the reduced levels of pantothenic acid and MTA highlight the potential role of metabolite (non-lipid) in AD-related metabolic reprogramming. Although further validation studies on larger cohorts are required, these findings support the use of oral fluid as a promising, non-invasive biofluid for the discovery of biomarkers in Alzheimer's disease, despite its peripheral origin and distance from the primary sites of pathology.

4.5 Addiction: forensic toxicology application

The comparison of salivary lipidomic and metabolic profiles between individuals with chronic substance abuse and a control group was undertaken to investigate the molecular alterations induced by prolonged drug intake. As for clinical studies, also in forensic context, oral fluid represents a particularly valuable biofluid due to its non-invasive collection and easy of storage and it is increasingly investigated in toxicological studies. By integrating metabolomic and lipidomic approaches, this study aimed to determine whether substance abuse produces detectable molecular signatures that could complement traditional toxicological markers, thereby providing additional insights into the physiological consequences of drug use. In forensic literature, several applications of metabolomics and lipidomics have been reported. Metabolomics, in particular, has been employed to investigate new psychoactive substances, substance dependence and acute intoxication, as well as in broader forensic medicine contexts, including post-mortem diagnosis, estimation of time of death and mortality risk prediction²⁹⁵. Lipidomics, on the other hand, has been applied to the study of substance addiction, the analysis of latent fingerprints, fire debris analysis and even in fields such as seafood authentications³³⁷.

To date, most metabolomics studies aimed at identifying biomarkers of substance dependence and intoxication have focused on drugs such as: MDMA³³⁸, cocaine³³⁹, crack²⁹³, heroin^{243,340} and cannabinoids²⁸⁹. Most of these investigations have been conducted on animal models (rats and monkeys)^{339,341}, where psychoactive substances were administered at known doses and after controlled exposure times, and biological matrices such as serum, urine, plasma and brain tissue were collected and analyzed using various analytical platforms, including GC-MS, IM-MS³³⁹, ¹H-NMR³⁴¹ and HPLC-MS²⁹². Other studies have instead been performed in human subjects to explore how drug intake alters the metabolome. For instance, Bijlsma et al.²⁸⁹ administered cannabis to volunteers and analyzed salivary and serum samples, while Nielsen et al.³³⁸ investigated MDMA in whole blood samples from drivers suspected of substance abuse. By contrast, lipidomics remains a relatively underexplored area in forensic toxicology, despite its recognized potential³³⁷. The few studies published so far have mainly been carried out in animal models, with a particular focus on brain tissue following exposure to specific drugs^{342,343}. Notably, Yang et al.³⁴⁴ investigated variations in fatty acid profiles and polymorphisms of the FADS gene in the whole blood of heroin-dependent subjects undergoing six months of methadone maintenance treatment. These findings highlight the potential of lipidomics in the forensic field, although further research is required to fully establish its applications in the study of substance abuse.

In this study, only limited variations in the salivary metabolic profile were observed in association with substance abuse. Specifically, alterations were detected in both directions for fatty acids (OxFA and acyl carnitines), while succinic acid was found to be upregulated in users compared to controls.

By contrast, the literature reports a broader range of metabolite variations associated with different substances, although results are often inconsistent across studies. Regarding opioids, several metabolic changes have been documented in animal tissues. Regarding morphine, some studies reported increased levels of lactic acid, uracil, proline and valine, while others identified variations in glutathione, taurine and creatinine. Several investigations specifically highlighted the disruption of amino acid metabolism, with a general decrease in amino acid concentrations²⁴³. Heroin, in turn, has been shown to affect energy metabolism, inducing bidirectional alterations in fatty acids and perturbing amino acid pathways, thereby modifying their levels in both blood and urine of rats. Additional studies observed changes in neurotransmitters such as dopamine, adrenaline, histamine and melatonin, while histidine levels have been reported to increase in some cases and decrease in others among chronic users²⁴³. Similarly, cocaine abuse has been investigated in various animal models. Chronic intake was associated with the upregulation of acetylcholine, valine, leucine, choline, carnitine, acetyl carnitine, creatine, creatinine and adenosine in different brain regions²⁴³. When cocaine was administered in combination with alcohol, distinct metabolomic effects emerged. Cocaine alone was found to increase methionine and decrease argininosuccinic acid, whereas in combination with alcohol, plasma levels of carnosine, spermidine and serotonin increased, alongside a reduction in methionine and argininosuccinic acid³⁴⁵. In a subsequent study, the same group examined different brain regions and reported an increase in inosine and xanthine with a concomitant decrease in hypoxanthine in mice treated with both cocaine and alcohol. Alterations in cytosine, cytidine and several fatty acids were also detected²⁹². Methamphetamine abuse has likewise been linked to significant metabolic changes. Various studies have reported alteration in fatty acids and amino acids, including reduced aspartate, alanine and glycine levels in mouse serum, as well as decrease phenylalanine, tyrosine and tryptophan in plasma²⁴³. In human studies, Nielsen et al.³³⁸ analyzed whole blood samples from MDMA users and identified significant increases in adenosine monophosphate, adenosine, inosine and acetyl carnitines alongside downregulation of tryptophan, thiomorpholine-3-carboxylate and LPCs. Finally, Bijlsma et al.²⁸⁹ investigated salivary metabolomic variations following cannabis consumption enriched with synthetic cannabinoids. They identified scopoletin and N,N-bis(2-hydroxyethyl)dodecylamine as potential biomarkers, capable of distinguishing between tobacco users and individuals consuming herb-tobacco mixture.

In forensic toxicology, lipidomics remains an underexplored yet highly promising field. Most studies to date have been conducted using animal models. For instance, Bodzon-Kulakowska et al.³⁴⁶ investigated some lipid alterations in the brains of three different groups of mice following administration of morphine, cocaine and amphetamine. Morphine intake was associated with upregulation of certain glycerophospholipids (PSs and PGs) and sulfatides, while other lipid species were downregulated. Amphetamine exposure produced bidirectional changes in glycerophospholipids (PSs, PGs and PEs) and sulfatides. Similarly, cocaine administration led to both increases and decreases in glycerophospholipids (PSs, PGs and PEs) and an upregulation of

selected sulfatides. In another study, Pati et al.³⁴³ demonstrated a widespread reduction in phospholipids abundance through the brain after cocaine exposure. Leishman et al.³⁴² explored the lipidomic consequences of THC and CBD administration, observing elevated levels of N-acylethanolamines (NAEs), likely linked to FAAH inhibition. In contrast, Wang et al.³⁴⁷ studied the effects of chronic alcohol abuse in different mouse brain regions, reporting significant alterations in glycerophospholipids, glycerolipids, fatty acids and sterol lipids. These findings suggest that alcohol abuse disrupts lipids metabolism in the central nervous system.

In the present study, several alterations were observed in glycerophospholipids, glycerolipids and sphingolipids. However, these changes could not be attributed to a single substance, as the test group included individuals with heterogeneous patterns of polysubstance use. Due to the limited number of participants testing positive for the same compound, all positive samples were therefore considered as a single group, regardless of the specific substance detected. This heterogeneity represents a major limitation, as it reduces the ability to identify reliable biomarkers for specific substances and may also explain why the heatmap (Figure 23.d) did not reveal substantial differences in the relative abundance of lipids. To obtain more consistent and substance-specific results, future investigations should include a larger number of participants addicted on a single drug. Expanding the study cohort would also provide greater statistical power and enable a more detailed stratification of subjects according to their substance use patterns. Another important consideration is the experimental design. Although both investigator- administered and self-administered drugs may induce similar neurochemical changes, significant differences remain between the two. Self-administration paradigms are widely regarded as valuable tools for investigating compulsive drug-seeking behavior; however, their methodological complexity often restricts their broader application. In contrast, investigator-administered approaches provide tighter experimental control and can improve the reproducibility and translational value of the results. When compared with animal models, studies on human drug users are inherently more time-consuming and complicated by numerous confounding variables. In real world settings, individuals with substance dependence frequently present with comorbid conditions, engage in polysubstance use, smoke tobacco or suffer from other health-related issues. For this reason, human studies must take into account a range of demographic and clinical factors, including age, sex, history of substance use, nutritional status and psychological conditions, all of which may influence metabolite and lipid profiles in biological samples. Although animal experiments can reduce environmental variability, they are unable to fully reproduce the neurobiological processes underlying human addiction. Bridging this gap and improving the translation of findings from animal models to the human context therefore remains a central challenge for future research²⁴⁴.

In summary, metabolomic and lipidomic analyses offer promising avenues for forensic toxicology, though their applications remain at an early stage. Metabolomic studies have revealed multiple

substance-related alterations, but findings are often inconsistent, while lipidomics research is still largely confined to animal models. The main limitation in human studies lies in polysubstance use and comorbidities, which hinder the identification of specific biomarkers. Future work should focus on larger and more homogeneous cohorts to improve reliability and translation of saliva value. Ultimately, combining metabolomic and lipidomic data with conventional toxicology could enhance substance abuse detection and deepen our understanding of its physiological impact.

5. CONCLUSION

This research aimed to evaluate the variation of salivary metabolic and lipidomic profiles under different physiological and pathological conditions, exploring the potential of oral fluid as non-invasive and informative biological matrix in omics studies. Oral fluid was selected for its recognized diagnostic potential and for the practical advantages it offers over traditional matrices such as blood and urine, including simple, non-invasive sampling procedures and minimal sample manipulation.

The findings of this study demonstrate that saliva represents a valuable and complementary biofluid in metabolomic and lipidomic research, capable of providing meaningful insights into systemic and neurological processes. In healthy individuals, comparative analyses between salivary and blood profiles revealed both shared and distinct molecular patterns, confirming that saliva can mirror systemic biochemical alterations. Moreover, the influence of aging was clearly observed: age-related variations in salivary lipidomic and metabolic signatures were detected, with triglycerides emerging as promising indicators for monitoring physiological changes and for supporting nutritional or pharmacological interventions. This observation is further supported by the identification of several triglyceride species contributing significantly to the separation observed in the VIP scores plots. In pathological contexts, particularly Alzheimer's disease, distinct alterations in both lipidomic and metabolic pathways were identified. Specifically, lipidomic analyses revealed a decrease in glycerophospholipids (particularly phosphatidylethanolamine (PE)) and sphingolipids, accompanied by an increase in fatty acids and sterol lipids in AD patients compared to cognitively healthy controls. These variations suggest a disruption of membrane composition, energy metabolism and neuroinflammatory balance, which are well-established hallmarks of neurodegeneration. Additionally, the observed reduction in pantothenic acid and 5-deoxy-5-methylthioadenosine (MTA) further highlights the potential involvement of these metabolites in AD-related metabolic reprogramming. Collectively, these findings emphasize the potential of oral fluid as a diagnostic and monitoring tool in neurodegenerative disorders, supporting its use as a source of accessible biomarkers for early detection and disease progression assessment. Furthermore, the application of metabolomic

and lipidomic approaches were extended to the field of drug addiction. To date, most studies in this area have been conducted using animal models, which offer certain advantages in terms of control and reproducibility. However, the analyses performed in the present study represent one of the first exploratory investigations on human saliva, demonstrating the promising potential of this matrix to capture metabolic and lipidomic alterations associated with chronic exposure to psychoactive substances. This approach opens new perspectives for identifying biomarkers of substance abuse and for elucidating the biological effects of drugs on the human body.

Future development should aim to validate and expand these preliminary findings through an increased sample size to enhance statistical robustness and confirm the observed trends. Further studies will include other neurodegenerative disorders for comparative analysis and substance-specific investigations in forensic applications, supported by larger and more homogeneous cohorts. In parallel, targeted mass spectrometry workflows will be developed to confirm and quantify potential biomarkers identified through untargeted approaches. Integrating omics data with clinical parameters such as age, gender, BMI and diet will enable more comprehensive biological interpretation and facilitate translational applications. Finally, the implementation of advanced computational tools, including machine learning algorithms, will allow the development of predictive models capable of improving diagnostic accuracy, enhancing disease monitoring and supporting personalized therapeutic and forensic strategies.

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7. APPENDICES

APPENDIX A

In Appendix A, the tables provide a detailed description of the demographic and clinical characteristics of all the volunteers included in this study. Specifically, Table A reports the general information of blood and saliva samples collected from healthy and young subjects; Table B presents the data from samples collected for the aging study; Table C and D contain the information related to the control group and to subjects diagnosed with Alzheimer's disease (AD), respectively; and finally, Table E summarizes the characteristics of the volunteers who participated in the part of the study focusing on addiction.

Table A. Healthy and young volunteers' information (first phase of the study)

Young and healthy individuals					
Samples Name	Oral Fluid	Whole Blood	Gender	Age	Pathology
TsBs_01	-	1	M	33	-
TsBs_02	1	1	F	24	-
TsBs_03	-	1	M	25	-
TsBs_04	1	1	M	25	-
TsBs_05	1	1	F	35	-
TsBs_06	1	1	F	27	-
TsBs_07	-	1	F	30	-
TsBs_08	-	1	M	28	-
TsBs_09	1	1	F	29	-
TsBs_10	-	1	M	35	-
TsBs_11	1	1	F	30	-
TsBs_12	1	1	F	23	-
TsBs_13	1	1	F	25	-
TsBs_14	1	1	F	24	-
TsBs_15	1	1	F	30	-
TsBs_16	1	1	F	33	-
TsBs_17	1	1	F	32	-
TsBs_18	1	1	F	34	-
TsBs_19	1	1	F	33	-
TsBs_20	1	1	F	34	-
TsBs_21	1	1	F	32	-

Table B. Volunteers' information who participated in aging study (second phase of the study)

Adult				Young			
Sample Name	Oral Fluid	Gender	Age	Sample Name	Oral Fluid	Gender	Age
1_O	1	F	55	1_Y	1	M	33
2_O	1	M	62	2_Y	1	F	24
3_O	1	F	59	3_Y	1	M	25
4_O	1	F	69	4_Y	1	M	25
5_O	1	F	51	5_Y	1	F	35
6_O	1	F	67	6_Y	1	F	27
7_O	1	F	61	7_Y	1	F	30
8_O	1	M	66	8_Y	1	M	28
9_O	1	F	52	9_Y	1	F	29
10_O	1	F	76	10_Y	1	M	35
11_O	1	F	56	11_Y	1	F	30
12_O	1	M	66	12_Y	1	F	23
13_O	1	M	61	13_Y	1	F	25
14_O	1	M	51	14_Y	1	F	24
15_O	1	M	87	15_Y	1	F	30
16_O	1	M	71	16_Y	1	F	33
17_O	1	M	60	17_Y	1	F	32
18_O	1	M	82	18_Y	1	F	34
19_O	1	M	80	19_Y	1	F	33
20_O	1	F	81	21_Y	1	F	32
21_O	1	M	77				
22_O	1	M	70				
23_O	1	F	52				
24_O	1	M	58				
25_O	1	M	66				
26_O	1	M	72				
27_O	1	F	57				

Table C. Volunteers' information who participated as control group in neurodegenerative diseases study (third phase of the study)

Control group				
Sample Name	Oral Fluid	Gender	Age	Co-morbidity
1_CTRL	1	F	55	NO
2_CTRL	1	M	62	NO
3_CTRL	1	F	59	NO
4_CTRL	1	F	69	NO
6_CTRL	1	F	67	NO
7_CTRL	1	F	61	NO
8_CTRL	1	M	66	Diabet II
9_CTRL	1	F	52	NO
10_CTRL	1	F	76	NO
11_CTRL	1	F	56	NO

Control group				
Sample Name	Oral Fluid	Gender	Age	Co-morbidity
12_CTRL	1	M	66	NO
13_CTRL	1	M	61	Hypertension
15_CTRL	1	M	87	NO
16_CTRL	1	M	71	NO
17_CTRL	1	M	60	NO
18_CTRL	1	M	77	NO
19_CTRL	1	M	70	NO

Table D. Volunteers' information who participated as test group in neurodegenerative diseases study (third phase of the study)

Alzheimer's samples									
Sample Name	Oral Fluid	Gender	Age	Beta Amiloide 42	Tau	Fosfo-Tau	Familiarità per demenza	Età MMSE	MMSE corretto
1_AD	1	M	59	456	642	126	sì	59	18.2
2_AD	1	F	74	467	444	79		74	19.7
3_AD	1	M	68	556	482	72	sì	67	26.2
4_AD	1	M	76						
5_AD	1	F	76	565	949	187	no	71	17.7
6_AD	1	F	74	529	548	96	sì	73	25.7
7_AD	1	M	69					65	22.9
8_AD	1	F	61	527	505	82	no	60	18.2
9_AD	1	M	75	413	259	49	sì		
10_AD	1	M	69	359	665	115		69	22.2
11_AD	1	M	78	1798	517	77.2			
12_AD	1	F	72	423	385	39	sì	72	18
13_AD	1	M	50	358	476	97	sì	45	24.2
14_AD	1	F	68	496	588	93	no	68	26.2
15_AD	1	F	78	596	1097	154	sì	78	13
16_AD	1	F	78	359	494	74		77	19.3
17_AD	1	M	64	464	613	95		64	19

Table U. Volunteers' information who participated in drug addiction study (last phase of the study)

Control group			
Sample Name	Oral Fluid	Gender	Age
24	1	M	42
25	1	M	39
85	1	F	42
90	1	M	28
92	1	M	26
93	1	M	30
149	1	M	32
154	1	M	22
213	1	M	25

Test group			
Sample Name	Oral Fluid	Gender	Age
12	1	M	42
63	1	M	57
97	1	M	29
128	1	M	35
133	1	M	26
134	1	M	29
156	1	F	42
165	1	F	33
177	1	F	26

Control group			
Sample Name	Oral Fluid	Gender	Age
243	1	M	35
249	1	M	53

Test group			
Sample Name	Oral Fluid	Gender	Age
186	1	F	26
187	1	F	35
189	1	M	39
192	1	F	38
193	1	M	55
194	1	M	60
198	1	M	32
227	1	M	25
230	1	M	36
234	1	M	30
240	1	M	30
247	1	M	21
248	1	M	53
263	1	M	22
266	1	M	25

APPENDIX B

In Appendix B, all the lipids and metabolites identified in the different samples analyzed in this study are reported. Specifically, Tables F, G, H and I present the metabolites and lipids detected in saliva and blood, respectively. Table J lists the lipids and metabolites found to be common between saliva and blood samples. Table K provides the lipids and metabolites identified in saliva samples used both for the physiological studies and for those related to Alzheimer's disease. Finally, Table L reports the lipids and metabolites detected in the saliva of subjects with drug use disorders and in the corresponding control group.

Table F. List of metabolites and their corresponding classes identified in oral fluid taken from young and healthy people

Metabolite Name	class
1-Methylguanine	Purines and derivatives
2-Piperidinone	Piperidinones
3-Indolepropionic acid	Indoles and derivatives
4-Ethylbenzoic acid	Benzoic acids and derivatives
5-Aminopentanoic acid	Amino acids and derivatives
5'-Methylthioadenosine	Purines and derivatives
6-Hydroxypurine	Purines and derivatives
7-Methylguanine	Purines and derivatives
7-Methylxanthine	Purines and derivatives
Adenine	Purines and derivatives
Adenosine	Purine nucleotides
Alpha-ketoisovaleric acid	Keto acids and derivatives
Betaine	Amino acids and derivatives
Capric acid	Fatty acids and conjugates

Metabolite Name	class
Cholesterol sulfate	Steroids
Choline	Bile acids
Cinnamic acid	Cinnamic acid
Cotinine	Pyridines and derivatives
Creatine	Amino acids and derivatives
Creatinine	Amino acids and derivatives
Desaminotyrosine	Phenylpropanoic acids
Hesperidin?	Flavonoids
Hydroxyphenyllactic acid	Phenylpropanoic acids
Indoleacetic acid	Indoles and derivatives
Inosine	Purines and derivatives
L-Acetylcarnitine	Fatty acid esters
Lactic acid	Hydroxy acids
L-Carnitine	Organonitrogen compounds
Leucinic acid	Fatty acids and conjugates
L-Glutamic acid	Amino acids and derivatives
L-Isoleucine	Amino acids and derivatives
L-Leucine	Amino acids and derivatives
L-Phenylalanine	Amino acids and derivatives
L-Proline	Amino acids and derivatives
L-Tryptophan	Amino acids and derivatives
L-Tyrosine	Amino acids and derivatives
L-Valine	Amino acids and derivatives
Mannitol	Carbohydrates and carbohydrate conjugates
Monosaccharide - C ₆ H ₁₂ O ₆	Carbohydrates and carbohydrate conjugates
N-Acetyl-L-phenylalanine	Amino acids and derivatives
N-Acetylputrescine	Carboximide acids
Niacinamide	Pyridines and derivatives
Nicotinic acid	Pyridines and derivatives
N-Methylnicotinamide	Pyridines and derivatives
PC(16:0/16:0)	Organonitrogen compounds
Phthalic acid	Benzoic acids and derivatives
Pyrrolidonecarboxylic acid	Amino acids and derivatives
Riboflavin	Pteridines and derivatives
Senecioic acid	Fatty acids and conjugates
Sphinganine	Organonitrogen compounds
Taurine	Sulfate and sulfonates
Theophylline	Purines and derivatives
Thymidine	Pyrimidine nucleotides
Thymine	Pyrimidines and derivatives
Trigonelline	Alkaloids and derivatives
Uracil	Pyrimidines and derivatives
Urea	Ureas
Uridine	Pyrimidine nucleotides

Table G. List of lipids and their corresponding classes identified in oral fluid taken from young and healthy people

Lipid Name	Class		Lipid Name	Class
ADGGA 50:2 ADGGA 16:0 16:0 18:2	ADGGA		PE 28:0 PE 14:0 14:0	PE
ADGGA 52:4 ADGGA 16:0 18:2 18:2	ADGGA		PE 29:0 PE 14:0 15:0	PE
AHexCer 60:9;3O AHexCer (O-18:2)42:7;3O	AHexCer		PE 30:0 PE 14:0 16:0	PE
AHexCer 62:11;3O AHexCer (O-20:3)42:8;3O	AHexCer		PE 30:0 PE 15:0 15:0	PE
ASG 27:1;O;Hex;FA 16:0	AHexCS		PE 30:1 PE 14:0 16:1	PE
ASG 27:1;O;Hex;FA 18:2	AHexCS		PE 31:0 PE 15:0 16:0	PE
ASG 27:1;O;Hex;FA 20:0	AHexCS		PE 31:1 PE 15:0 16:1	PE
ASG 28:1;O;Hex;FA 16:0	AHexCAS		PE 32:0 PE 15:0 17:0	PE
ASG 28:1;O;Hex;FA 18:2	AHexCAS		PE 32:0 PE 16:0 16:0	PE
ASG 29:1;O;Hex;FA 18:1	AHexSIS		PE 32:1 PE 16:0 16:1	PE
ASG 29:1;O;Hex;FA 18:2	AHexSIS		PE 32:2 PE 16:1 16:1	PE
ASG 29:2;O;Hex;FA 26:6	AHexSTS		PE 33:0 PE 16:0 17:0	PE
BA 24:1;O4;G;S	BASulfate		PE 33:1 PE 15:0 18:1	PE
CAR 11:0	CAR		PE 33:2 PE 15:0 18:2	PE
CAR 15:1	CAR		PE 34:0 PE 16:0 18:0	PE
CAR 16:0	CAR		PE 34:1 PE 16:0 18:1	PE
CAR 5:0	CAR		PE 34:2 PE 16:0 18:2	PE
CE 18:2	CE		PE 34:3 PE 16:0 18:3	PE
CE 18:3	CE		PE 34:3 PE 16:1 18:2	PE
CE 20:3	CE		PE 35:1 PE 17:0 18:1	PE
CE 20:4	CE		PE 35:2 PE 17:1 18:1	PE
CE 20:5	CE		PE 36:0;O PE 18:0 18:0;O	OxPE
CE 22:6	CE		PE 36:1;2O PE 18:1 18:0;2O	OxPE
Cer 29:1;4O	Cer_AP		PE 36:1;O PE 18:1 18:0;O	OxPE
Cer 31:1;4O	Cer_AP		PE 36:1 PE 18:0 18:1	PE
Cer 34:0;2O Cer 18:0;2O/16:0	Cer_NDS		PE 36:2 PE 18:1 18:1	PE
Cer 34:0;3O Cer 18:0;2O/16:0;(2OH)	Cer_ADS		PE 36:3 PE 18:1 18:2	PE
Cer 34:0;3O Cer 21:0;2O/13:0;O	Cer_HDS		PE 36:4 PE 16:0 20:4	PE
Cer 34:1;2O Cer 18:1;2O/16:0	Cer_NS		PE 36:4 PE 18:2 18:2	PE
Cer 34:1;3O Cer 18:1;2O/16:0;(2OH)	Cer_AS		PE 37:2 PE 18:1 19:1	PE
Cer 34:5;4O	Cer_AP		PE 37:4;O PE 20:3 17:1;O	OxPE
Cer 35:1;4O Cer 18:0;3O/17:1;(2OH)	Cer_AP		PE 37:5;O PE 20:3 17:2;O	OxPE
Cer 36:1;3O Cer 18:0;2O/18:1;O	Cer_ADS		PE 38:1 PE 18:0 20:1	PE
Cer 37:1;4O Cer 20:0;3O/17:1;(2OH)	Cer_AP		PE 38:1 PE 20:0 18:1	PE
Cer 39:1;4O Cer 22:0;3O/17:1;(2OH)	Cer_AP		PE 38:2 PE 18:1 20:1	PE
Cer 40:0;4O Cer 18:0;3O/22:0;(2OH)	Cer_AP		PE 38:3 PE 18:0 20:3	PE
Cer 41:1;4O Cer 22:0;3O/19:1;(2OH)	Cer_AP		PE 38:4	PE
Cer 41:7;4O Cer 25:3;3O/16:4;(2OH)	Cer_AP		PE 38:4 PE 18:0 20:4	PE
Cer 42:1;2O Cer 18:1;2O/24:0	Cer_NS		PE 38:4 PE 18:1 20:3	PE
Cer 42:1;3O Cer 18:1;2O/24:0;(2OH)	Cer_AS		PE 38:5;O PE 18:2 20:3;O	OxPE

Lipid Name	Class		Lipid Name	Class
Cer 42:2;2O Cer 18:1;2O/24:1	Cer_NS		PE 38:5 PE 18:1_20:4	PE
Cer 42:3;2O Cer 18:1;2O/24:2	Cer_NS		PE 38:6;O PE 18:2_20:4;O	OxPE
Cer 43:1;3O Cer 18:1;2O/25:0;(2OH)	Cer_AS		PE 38:6 PE 16:0_22:6	PE
Cer 43:1;4O Cer 27:0;3O(FA 16:0)	Cer_EODS		PE 38:6 PE 20:1_18:5	PE
Cer 43:2;4O Cer 26:1;3O/17:1;(2OH)	Cer_AP		PE 39:3 PE 19:1_20:2	PE
Cer 43:8;4O	Cer_AP		PE 39:5;O PE 17:0_22:5;O	OxPE
Cer 45:2;4O Cer 28:1;3O/17:1;(2OH)	Cer_AP		PE 39:5;O PE 22:4_17:1;O	OxPE
Cer 45:3;4O Cer 18:2;2O/27:1;2O	Cer_EOS		PE 40:0 PE 20:0_20:0	PE
Cer 45:8;2O Cer 17:2;2O/28:6	Cer_NS		PE 40:1 PE 22:0_18:1	PE
Cer 48:10;4O Cer 26:3;3O(FA 22:6)	Cer_EOS		PE 40:2 PE 18:1_22:1	PE
Cer 48:9;3O	Cer_NP		PE 40:4 PE 18:0_22:4	PE
Cer 53:9;4O Cer 21:3;3O/32:6;(2OH)	Cer_AP		PE 40:5 PE 18:1_22:4	PE
Cer 55:9;4O Cer 21:3;3O/34:6;(2OH)	Cer_AP		PE 40:6	PE
Cer 56:11;4O Cer 38:9;3O(FA 18:1)	Cer_EOS		PE 40:6;O PE 18:2_22:4;O	OxPE
Cer 57:5;4O Cer 17:2;2O/40:3;2O	Cer_EOS		PE 40:6 PE 18:1_22:5	PE
Cer 57:9;4O Cer 21:3;3O/36:6;(2OH)	Cer_AP		PE 40:7;O PE 20:4_20:3;O	OxPE
Cer 61:8;4O Cer 17:3;2O/44:5;2O	Cer_EOS		PE 42:1 PE 24:0_18:1	PE
Cer 66:5;4O Cer 18:2;2O/48:3;2O	Cer_EOS		PE 42:8;O PE 20:4_22:4;O	OxPE
Cer 75:5;4O Cer 18:1;2O/57:4;2O	Cer_EOS		PE O-29:1 PE O-15:1_14:0	EtherPE
CL 68:1 CL 16:0_16:0_18:0_18:1	CL		PE O-30:1 PE O-16:1_14:0	EtherPE
CL 68:2 CL 34:1_34:1	CL		PE O-30:2 PE O-16:2_14:0	EtherPE
CL 70:4 CL 16:0_18:1_18:1_18:2	CL		PE O-31:1 PE O-16:1_15:0	EtherPE
CL 72:0 CL 16:0_16:0_16:0_24:0	CL		PE O-31:2 PE O-15:1_16:1	EtherPE
CL 72:3 CL 24:0_16:1_16:1_16:1	CL		PE O-32:0 PE O-16:0_16:0	EtherPE
CL 73:1 CL 16:0_17:0_22:0_18:1	CL		PE O-32:1 PE O-16:1_16:0	EtherPE
CL 74:6 CL 16:0_18:1_18:1_22:4	CL		PE O-32:2 PE O-16:1_16:1	EtherPE
CL 76:7 CL 18:1_18:1_18:2_22:3	CL		PE O-32:3 PE O-16:2_16:1	EtherPE
CL 76:8 CL 18:1_18:1_20:3_20:3	CL		PE O-33:1 PE O-16:1_17:0	EtherPE
CL 76:9 CL 18:1_18:2_18:2_22:4	CL		PE O-33:2 PE O-15:1_18:1	EtherPE
CL 77:4 CL 16:0_17:0_24:0_20:4	CL		PE O-33:3 PE O-16:2_17:1	EtherPE
CL 78:1 CL 16:0_18:0_26:0_18:1	CL		PE O-34:0;2O PE O-18:0_16:0;2O	EtherOxPE
CL 79:6 CL 24:0_17:1_18:1_20:4	CL		PE O-34:0 PE O-18:0_16:0	EtherPE
CL 80:0 CL 16:0_18:0_18:0_28:0	CL		PE O-34:1 PE O-18:1_16:0	EtherPE
CL 80:10 CL 18:1_20:3_20:3_22:3	CL		PE O-34:2 PE O-16:1_18:1	EtherPE
CL 80:2 CL 16:0_28:0_18:1_18:1	CL		PE O-34:3 PE O-16:1_18:2	EtherPE
CL 81:6 CL 28:0_17:2_18:2_18:2	CL		PE O-35:2 PE O-17:1_18:1	EtherPE

Lipid Name	Class		Lipid Name	Class
CL 83:9 CL 26:0_17:1_18:2_22:6	CL		PE O-35:3 PE O-17:1_18:2	EtherPE
CL 84:13 CL 18:0_22:3_22:5_22:5	CL		PE O-36:1 PE O-18:0_18:1	EtherPE
CL 86:12 CL 26:0_20:4_20:4_20:4	CL		PE O-36:2 PE O-18:1_18:1	EtherPE
CL 90:1 CL 24:0_24:0_24:0_18:1	CL		PE O-36:3 PE O-16:0_20:3	EtherPE
CL 94:1 CL 26:0_26:0_26:0_16:1	CL		PE O-36:3 PE O-18:2_18:1	EtherPE
Daidzein	Others		PE O-36:4 PE O-16:1_20:3	EtherPE
DG 34:1 DG 16:0_18:1	DG		PE O-36:5 PE O-16:1_20:4	EtherPE
DG 34:2 DG 16:0_18:2	DG		PE O-36:6 PE O-16:1_20:5	EtherPE
DG 36:4 DG 18:2_18:2	DG		PE O-37:2 PE O-19:1_18:1	EtherPE
DG 37:0 DG 16:0_21:0	DG		PE O-37:3 PE O-19:1_18:2	EtherPE
DG 38:4 DG 18:0_20:4	DG		PE O-37:4 PE O-17:0_20:4	EtherPE
DGDG 34:1 DGDG 16:0_18:1	DGDG		PE O-37:4 PE O-17:1_20:3	EtherPE
DGDG 34:2 DGDG 16:0_18:2	DGDG		PE O-37:5 PE O-17:1_20:4	EtherPE
DGDG 34:3 DGDG 16:0_18:3	DGDG		PE O-38:2 PE O-20:1_18:1	EtherPE
DGDG 36:1 DGDG 18:0_18:1	DGDG		PE O-38:3 PE O-20:2_18:1	EtherPE
DGDG 36:2 DGDG 18:0_18:2	DGDG		PE O-38:4 PE O-18:1_20:3	EtherPE
DGDG 36:3 DGDG 18:1_18:2	DGDG		PE O-38:5 PE O-16:1_22:4	EtherPE
DGDG 36:4 DGDG 18:2_18:2	DGDG		PE O-38:5 PE O-18:1_20:4	EtherPE
DGDG 36:5 DGDG 18:2_18:3	DGDG		PE O-38:5 PE O-22:5_16:0	EtherPE
DGGA 29:2 DGGA 14:1_15:1	DGGA		PE O-38:6 PE O-18:2_20:4	EtherPE
DGGA 33:0 DGGA 15:0_18:0	DGGA		PE O-38:7 PE O-16:1_22:6	EtherPE
DGGA 36:2 DGGA 18:1_18:1	DGGA		PE O-38:7 PE O-18:2_20:5	EtherPE
FA 18:0;2O	OxFA		PE O-39:7 PE O-17:1_22:6	EtherPE
FA 18:1;3O	OxFA		PE O-40:2 PE O-22:1_18:1	EtherPE
FA 18:1;O	OxFA		PE O-40:3 PE O-22:2_18:1	EtherPE
FA 18:2	FA		PE O-40:4 PE O-22:2_18:2	EtherPE
FA 18:2;3O	OxFA		PE O-40:5 PE O-18:1_22:4	EtherPE
FA 18:2;O	OxFA		PE O-40:5 PE O-20:1_20:4	EtherPE
FA 18:3	FA		PE O-40:6 PE O-20:2_20:4	EtherPE
FA 18:3;O	OxFA		PE O-40:7 PE O-18:1_22:6	EtherPE
FA 19:2	FA		PE O-40:7 PE O-20:3_20:4	EtherPE
FA 20:0	FA		PE O-40:8 PE O-18:2_22:6	EtherPE
FA 20:0;2O	OxFA		PE O-42:2 PE O-24:1_18:1	EtherPE

Lipid Name	Class		Lipid Name	Class
FA 20:2;3O	OxFA		PE O-42:3 PE O-24:2_18:1	EtherPE
FA 20:2;O	OxFA		PE O-42:4 PE O-24:2_18:2	EtherPE
FA 20:3	FA		PE O-42:5 PE O-22:1_20:4	EtherPE
FA 20:3;2O	OxFA		PE O-42:5 PE O-24:3_18:2	EtherPE
FA 20:3;3O	OxFA		PE O-42:6 PE O-22:2_20:4	EtherPE
FA 20:3;4O	OxFA		PE O-42:7 PE O-20:1_22:6	EtherPE
FA 20:3;O	OxFA		PE O-42:7 PE O-22:3_20:4	EtherPE
FA 20:4	FA		PE O-42:8 PE O-20:2_22:6	EtherPE
FA 20:4;2O	OxFA		PE O-44:4 PE O-26:3_18:1	EtherPE
FA 20:4;4O	OxFA		PE O-44:5 PE O-24:1_20:4	EtherPE
FA 20:4;O	OxFA		PE O-44:6 PE O-24:2_20:4	EtherPE
FA 20:5	FA		PE O-44:7 PE O-24:3_20:4	EtherPE
FA 20:5;2O	OxFA		PE O-44:8 PE O-22:2_22:6	EtherPE
FA 20:5;O	OxFA		PE O-46:8 PE O-24:2_22:6	EtherPE
FA 22:4	FA		PE P-34:1 PE P-16:0_18:1	EtherPE
FA 22:5	FA		PE P-34:2 PE P-16:0_18:2	EtherPE
FA 22:5;(2OH)	OxFA		PE P-35:2 PE P-17:0_18:2	EtherPE
FA 22:5;O	OxFA		PE P-36:1 PE P-18:0_18:1	EtherPE
FA 22:6	FA		PE P-36:2 PE P-18:0_18:2	EtherPE
FA 32:0	FA		PE P-36:3 PE P-18:1_18:2	EtherPE
FA 34:0	FA		PE P-36:4 PE P-16:0_20:4	EtherPE
FA 36:0	FA		PE P-38:2 PE P-20:1_18:1	EtherPE
FA 42:11	FA		PE P-38:3 PE P-18:0_20:3	EtherPE
FA 44:11	FA		PE P-38:4 PE P-16:0_22:4	EtherPE
FAHFA 40:0;O FAHFA 16:0/24:0;O	FAHFA		PE P-38:4 PE P-16:1_22:3	EtherPE
FAHFA 42:0;O FAHFA 16:0/26:0;O	FAHFA		PE P-38:4 PE P-18:0_20:4	EtherPE
FAHFA 42:1;O FAHFA 18:1/24:0;O	FAHFA		PE P-38:4 PE P-20:3_18:1	EtherPE
FAHFA 44:0;O FAHFA 16:0/28:0;O	FAHFA		PE P-38:5 PE P-18:1_20:4	EtherPE
HBMP 50:2 HBMP 16:0/16:0_18:2	HBMP		PE P-38:6 PE P-16:0_22:6	EtherPE
HBMP 52:0 HBMP 16:0_18:0_18:0	HBMP		PE P-40:2 PE P-22:1_18:1	EtherPE
HBMP 52:2 HBMP 16:0_18:0_18:2	HBMP		PE P-40:3 PE P-22:1_18:2	EtherPE
HBMP 52:4 HBMP 18:2/16:0_18:2	HBMP		PE P-40:4 PE P-18:0_22:4	EtherPE
HBMP 54:2 HBMP 18:0_18:0_18:2	HBMP		PE P-40:4 PE P-20:0_20:4	EtherPE
HBMP 54:6 HBMP 18:2/18:2_18:2	HBMP		PE P-40:4 PE P-22:2_18:2	EtherPE
HBMP 56:5 HBMP 19:1_19:1_18:3	HBMP		PE P-40:5 PE P-18:0_22:5	EtherPE
Hex2Cer 32:1;2O Hex2Cer 18:1;2O/14:0	Hex2Cer		PE P-40:6 PE P-18:0_22:6	EtherPE
Hex2Cer 33:1;2O Hex2Cer 17:1;2O/16:0	Hex2Cer		PE P-40:6 PE P-18:1_22:5	EtherPE
Hex2Cer 34:1;2O	Hex2Cer		PE P-40:7 PE P-18:1_22:6	EtherPE
Hex2Cer 34:1;2O Hex2Cer 18:1;2O/16:0	Hex2Cer		PE P-42:3 PE P-24:1_18:2	EtherPE
Hex2Cer 40:1;2O Hex2Cer 18:1;2O/22:0	Hex2Cer		PE P-42:4 PE P-22:0_20:4	EtherPE
Hex2Cer 40:2;2O Hex2Cer 16:1;2O/24:1	Hex2Cer		PE P-42:4 PE P-24:2_18:2	EtherPE

Lipid Name	Class		Lipid Name	Class
Hex2Cer 41:1;2O Hex2Cer 18:1;2O/23:0	Hex2Cer		PE P-42:5 PE P-22:1_20:4	EtherPE
Hex2Cer 42:1;2O Hex2Cer 18:1;2O/24:0	Hex2Cer		PE P-44:4 PE P-16:1_28:3	EtherPE
Hex2Cer 42:2;2O	Hex2Cer		PE P-44:5 PE P-24:1_20:4	EtherPE
Hex2Cer 42:2;2O Hex2Cer 18:1;2O/24:1	Hex2Cer		PE P-44:6 PE P-24:2_20:4	EtherPE
Hex2Cer 42:3;2O Hex2Cer 18:1;2O/24:2	Hex2Cer		PE-Cer 34:0;2O PE-Cer 18:0;2O/16:0	PE_Cer
Hex2Cer 43:5;2O Hex2Cer 17:0;2O/26:5	Hex2Cer		PE-Cer 34:0;3O PE-Cer 18:0;2O/16:0;O	PE_Cer
Hex2Cer 44:2;2O Hex2Cer 18:1;2O/26:1	Hex2Cer		PE-Cer 34:1;3O PE-Cer 18:0;2O/16:1;O	PE_Cer
HexCer 34:0;2O HexCer 18:0;2O/16:0	HexCer_NDS		PE-Cer 35:0;3O PE-Cer 18:0;2O/17:0;O	PE_Cer
HexCer 34:1;3O HexCer 17:0;2O/17:1;O	HexCer_HDS		PE-Cer 35:1;3O PE-Cer 18:0;2O/17:1;O	PE_Cer
HexCer 38:1;3O HexCer 21:1;2O/17:0;O	HexCer_HS		PE-Cer 36:0;2O PE-Cer 19:0;2O/17:0	PE_Cer
HexCer 41:2;4O HexCer 17:2;3O/24:0;(2OH)	HexCer_AP		PE-Cer 36:0;3O PE-Cer 19:0;2O/17:0;O	PE_Cer
HexCer 42:0;2O	HexCer_NDS		PE-Cer 36:1;3O PE-Cer 19:0;2O/17:1;O	PE_Cer
HexCer 42:0;2O HexCer 18:0;2O/24:0	HexCer_NDS		PE-Cer 36:6;2O	PE_Cer
HexCer 42:0;3O	HexCer_HDS		PE-Cer 37:0;3O PE-Cer 19:0;2O/18:0;O	PE_Cer
HexCer 42:0;3O HexCer 16:0;2O/26:0;O	HexCer_HDS		PG 32:0 PG 16:0_16:0	PG
HexCer 42:0;4O HexCer 18:0;3O/24:0;(2OH)	HexCer_AP		PG 32:1 PG 16:0_16:1	PG
HexCer 42:1;3O HexCer 16:1;2O/26:0;O	HexCer_HS		PG 33:0 PG 16:0_17:0	PG
HexCer 42:1;3O HexCer 18:1;2O/24:0;O	HexCer_HS		PG 33:1 PG 15:0_18:1	PG
HexCer 42:6;3O	HexCer_HS		PG 34:1 PG 16:0_18:1	PG
HexCer 43:2;4O	HexCer_AP		PG 34:2 PG 16:0_18:2	PG
HexCer 43:8;4O HexCer 17:2;3O/26:6;(2OH)	HexCer_AP		PG 36:1 PG 18:0_18:1	PG
HexCer 44:0;2O	HexCer_NDS		PG 36:2 PG 18:1_18:1	PG
HexCer 44:0;4O HexCer 18:0;3O/26:0;(2OH)	HexCer_AP		PG 36:3 PG 18:1_18:2	PG
HexCer 44:1;3O HexCer 16:1;2O/28:0;O	HexCer_HS		PG 38:2 PG 19:0_19:2	PG
HexCer 44:1;3O HexCer 18:1;2O/26:0;O	HexCer_HS		PG 40:2 PG 20:1_20:1	PG
HexCer 44:1;4O HexCer 18:0;3O/26:1;(2OH)	HexCer_AP		PG O-34:2 PG O-16:1_18:1	EtherPG
HexCer 44:6;4O HexCer 28:5;3O(FA 16:0)	HexCer_EOS		PG O-36:2 PG O-18:1_18:1	EtherPG
HexCer 50:5;4O	HexCer_EOS		PG O-36:4 PG O-18:2_18:2	EtherPG
HexCer 50:6;4O	HexCer_EOS		PG O-36:5 PG O-18:3_18:2	EtherPG
HexCer 52:7;4O	HexCer_AP		PG O-38:5 PG O-20:3_18:2	EtherPG
HexCer 52:7;4O HexCer 16:1;3O/36:6;(2OH)	HexCer_AP		PG O-38:6 PG O-20:4_18:2	EtherPG
HexCer 52:8;4O	HexCer_AP		PG O-38:6 PG O-20:5_18:1	EtherPG
HexCer 54:10;4O HexCer 21:2;2O/33:8;2O	HexCer_EOS		PI 34:2	PI
HexCer 57:9;4O	HexCer_EOS		PI 36:1 PI 18:0_18:1	PI
HexCer 58:9;4O	HexCer_EOS		PI 36:2	PI
HexCer 68:5;4O HexCer 18:3;2O/50:2;2O	HexCer_EOS		PI 36:2 PI 18:0_18:2	PI
HexCer 68:6;4O HexCer 18:2;2O/50:4;2O	HexCer_EOS		PI 38:3 PI 18:0_20:3	PI
HexCer 70:6;4O	HexCer_EOS		PI 38:4	PI
Inosine	Others		PI 38:4 PI 18:0_20:4	PI

Lipid Name	Class		Lipid Name	Class
LDGCC 18:3	LDGCC		PI 40:4	PI
LPA 20:1	LPA		PI-Cer 40:1;2O	PI_Cer
LPC 15:1/0:0	LPC		PI-Cer 40:1;2O PI-Cer 21:1;2O/19:0	PI_Cer
LPC 16:0	LPC		PS 34:1 PS 16:0_18:1	PS
LPC 16:0/0:0	LPC		PS 34:2;2O PS 18:1_16:1;2O	OxPS
LPC 16:1	LPC		PS 34:3	PS
LPC 16:1/0:0	LPC		PS 36:1 PS 18:0_18:1	PS
LPC 17:0/0:0	LPC		PS 36:2 PS 18:0_18:2	PS
LPC 18:0	LPC		PS 36:2 PS 18:1_18:1	PS
LPC 18:0/0:0	LPC		PS 38:3 PS 12:0_26:3	PS
LPC 18:1	LPC		PS 38:3 PS 18:0_20:3	PS
LPC 18:1/0:0	LPC		PS 38:4;2O PS 16:0_22:4;2O	OxPS
LPC 18:2	LPC		PS 38:4 PS 12:0_26:4	PS
LPC 18:2/0:0	LPC		PS 40:6 PS 18:0_22:6	PS
LPC 18:3/0:0	LPC		PS O-35:1 PS O-17:0_18:1	EtherPS
LPC 20:1	LPC		PS O-37:1 PS O-19:0_18:1	EtherPS
LPC 20:1/0:0	LPC		PS O-37:2 PS O-19:0_18:2	EtherPS
LPC 20:2/0:0	LPC		PS O-39:3 PS O-19:0_20:3	EtherPS
LPC 20:4	LPC		PS O-41:4 PS O-19:0_22:4	EtherPS
LPC 20:4/0:0	LPC		SE 28:1/10:0	CASE
LPC 22:6	LPC		SE 29:1/18:3	SISE
LPC O-16:0	EtherLPC		SHexCer 32:6;2O	SHexCer
LPC O-16:1	EtherLPC		SHexCer 38:3;3O	SHexCer
LPC O-18:0	EtherLPC		SHexCer 39:2;2O	SHexCer
LPC O-18:1	EtherLPC		SHexCer 40:0;2O	SHexCer
LPC O-20:0	EtherLPC		SHexCer 42:5;3O	SHexCer
LPC O-20:1	EtherLPC		SHexCer 48:2;2O	SHexCer
LPC O-22:1	EtherLPC		SHexCer 50:2;2O	SHexCer
LPC O-22:2	EtherLPC		SHexCer 53:6;2O	SHexCer
LPE 15:0	LPE		SHexCer 54:9;2O	SHexCer
LPE 16:0	LPE		SL 32:0;O SL 17:0;O/15:0	SL
LPE 16:1	LPE		SM 31:1;2O SM 17:1;2O/14:0	SM
LPE 17:0	LPE		SM 32:0;2O SM 17:0;2O/15:0	SM
LPE 18:0	LPE		SM 32:1;2O SM 16:1;2O/16:0	SM
LPE 18:1	LPE		SM 32:1;3O	SM
LPE 18:2	LPE		SM 33:0;2O SM 19:0;2O/14:0	SM
LPE 20:4	LPE		SM 33:0;3O	SM
LPE 22:6	LPE		SM 33:1;2O SM 17:1;2O/16:0	SM
LPE O-16:0	EtherLPE		SM 33:1;3O	SM
LPE O-16:1	EtherLPE		SM 34:0;2O SM 20:0;2O/14:0	SM
LPE O-17:1	EtherLPE		SM 34:0;3O	SM

Lipid Name	Class		Lipid Name	Class
LPE O-18:0	EtherLPE		SM 34:1;2O SM 17:1;2O/17:0	SM
LPE O-18:1	EtherLPE		SM 34:1;2O SM 18:1;2O/16:0	SM
LPE O-18:2	EtherLPE		SM 34:1;3O	SM
LPE O-20:1	EtherLPE		SM 34:2;2O SM 18:2;2O/16:0	SM
LPE O-20:2	EtherLPE		SM 35:0;2O	SM
LPE O-20:3	EtherLPE		SM 35:0;3O	SM
LPE O-22:1	EtherLPE		SM 35:1;2O SM 19:1;2O/16:0	SM
LPE O-22:2	EtherLPE		SM 35:3;3O	SM
LPE O-24:2	EtherLPE		SM 36:0;2O SM 18:0;2O/18:0	SM
LPE-N (FA)34:1 LPE-N (FA 18:1)16:0	LNAPE		SM 36:1;2O SM 18:1;2O/18:0	SM
LPE-N (FA)34:2 LPE-N (FA 18:2)16:0	LNAPE		SM 36:1;3O	SM
LPE-N (FA)36:1 LPE-N (FA 18:0)18:1	LNAPE		SM 36:2;2O SM 18:1;2O/18:1	SM
LPE-N (FA)36:4 LPE-N (FA 18:2)18:2	LNAPE		SM 38:0;2O SM 20:0;2O/18:0	SM
LPG 16:0	LPG		SM 38:1;2O SM 28:1;2O/10:0	SM
LPG 18:0	LPG		SM 38:2;2O SM 19:1;2O/19:1	SM
LPG 18:1	LPG		SM 39:0;2O SM 19:0;2O/20:0	SM
LPG 18:2	LPG		SM 39:1;2O SM 16:0;2O/23:1	SM
LPI 18:0	LPI		SM 39:1;3O	SM
LPS 18:0	LPS		SM 39:2;2O SM 18:2;2O/21:0	SM
LPS 18:1	LPS		SM 39:7;2O	SM
MG 15:3	MG		SM 40:0;2O	SM
MGDG 28:0	MGDG		SM 40:0;3O	SM
MGDG 32:1 MGDG 15:0 17:1	MGDG		SM 40:1;2O SM 18:1;2O/22:0	SM
MGDG 36:4 MGDG 18:2 18:2	MGDG		SM 40:1;3O	SM
MGDG 44:10 MGDG 22:5 22:5	MGDG		SM 40:2;2O SM 16:1;2O/24:1	SM
MGDG O-30:1 MGDG O-15:1 15:0	EtherMGDG		SM 41:0;2O	SM
MGDG O-36:4 MGDG O-18:3 18:1	EtherMGDG		SM 41:0;3O	SM
NAE 16:1	NAE		SM 41:1;2O	SM
NAE 16:2	NAE		SM 41:2;2O SM 17:1;2O/24:1	SM
NAE 16:3	NAE		SM 41:3;2O	SM
NAE 16:4	NAE		SM 42:0;2O	SM
NAE 17:0	NAE		SM 42:0;3O	SM
NAE 18:2	NAE		SM 42:1;2O SM 18:1;2O/24:0	SM
NAE 18:4	NAE		SM 42:1;3O	SM
NAE 18:5	NAE		SM 42:2;2O SM 18:1;2O/24:1	SM
NAE 20:0	NAE		SM 42:3;2O SM 18:1;2O/24:2	SM
NAGly 13:1;O	NAGly		SM 43:0;2O	SM
NAGly 16:0;O	NAGly		SM 43:1;2O SM 18:1;2O/25:0	SM

Lipid Name	Class		Lipid Name	Class
NAGly 32:1;2O NAGly 17:0;O(FA 15:0)	NAGly		SM 43:2;2O SM 18:1;2O/25:1	SM
NAGlySer 20:5;O	NAGlySer		SM 43:4;3O	SM
NAGlySer 31:1;2O NAGlySer 16:0;O(FA 15:0)	NAGlySer		SM 44:0;2O	SM
NAGlySer 32:1;2O NAGlySer 17:0;O(FA 15:0)	NAGlySer		SM 44:1;2O SM 19:1;2O/25:0	SM
NAGlySer 33:1;2O NAGlySer 17:0;O(FA 16:0)	NAGlySer		SM 44:1;3O	SM
NAGlySer 34:1;2O NAGlySer 17:0;O(FA 17:0)	NAGlySer		SM 44:2;2O SM 22:0;2O/22:2	SM
NAOrn 18:3;O	NAOrn		SM 48:1;3O	SM
NAOrn 22:6;O	NAOrn		SM 48:2;3O	SM
NAOrn 25:1;O	NAOrn		SM 50:1;3O	SM
NAOrn 30:1;2O NAOrn 14:0;O(FA 16:0)	NAOrn		Soyasaponin Bb	Others
NAOrn 31:1;2O NAOrn 16:0;O(FA 15:0)	NAOrn		SPB 18:0;2O	DHSph
NAOrn 32:1;2O NAOrn 16:0;O(FA 16:0)	NAOrn		ST 27:1;O	ST
NAOrn 32:1;2O NAOrn 17:0;O(FA 15:0)	NAOrn		ST 27:1;O;S	SSulfate
NAOrn 33:1;2O NAOrn 17:0;O(FA 16:0)	NAOrn		ST 28:1;O	ST
PC 21:4	PC		TG 26:0 TG 8:0 8:0 10:0	TG
PC 28:0 PC 14:0 14:0	PC		TG 32:0;2O TG 9:0 13:0 10:0;2O	OxTG
PC 29:0	PC		TG 36:0 TG 12:0 12:0 12:0	TG
PC 30:0 PC 15:0 15:0	PC		TG 38:0 TG 12:0 12:0 14:0	TG
PC 31:0 PC 15:0 16:0	PC		TG 38:1 TG 10:0 10:0 18:1	TG
PC 32:0 PC 16:0 16:0	PC		TG 38:1 TG 8:0 12:0 18:1	TG
PC 32:1 PC 16:0 16:1	PC		TG 38:2 TG 8:0 14:1 16:1	TG
PC 32:2	PC		TG 40:0 TG 12:0 12:0 16:0	TG
PC 33:0 PC 16:0 17:0	PC		TG 40:2 TG 8:0 14:1 18:1	TG
PC 33:1 PC 16:0 17:1	PC		TG 40:3 TG 8:0 14:1 18:2	TG
PC 33:2 PC 15:0 18:2	PC		TG 44:1 TG 10:0 16:0 18:1	TG
PC 34:0 PC 16:0 18:0	PC		TG 46:4;1O TG 13:1 16:1 17:2;1O	OxTG
PC 34:1 PC 16:0 18:1	PC		TG 48:3 TG 10:0 18:1 20:2	TG
PC 34:2 PC 16:0 18:2	PC		TG 52:1 TG 16:0 18:0 18:1	TG
PC 34:3 PC 16:0 18:3	PC		TG 52:2;1O TG 16:0 18:1 18:1;1O	OxTG
PC 34:3 PC 16:1 18:2	PC		TG 52:3;1O TG 16:0 18:1 18:2;1O	OxTG
PC 35:1 PC 17:0 18:1	PC		TG 52:3 TG 16:0 18:1 18:2	TG
PC 35:2 PC 17:0 18:2	PC		TG 52:4 TG 16:0 18:2 18:2	TG
PC 35:3	PC		TG 54:0 TG 18:0 18:0 18:0	TG
PC 35:5 PC 15:1 20:4	PC		TG 54:1 TG 18:0 18:0 18:1	TG
PC 36:0 PC 18:0 18:0	PC		TG 54:3;2O TG 18:1 18:1 18:1;2O	OxTG
PC 36:1 PC 18:0 18:1	PC		TG 54:4;1O TG 18:2 18:2 18:0;1O	OxTG

Lipid Name	Class		Lipid Name	Class
PC 36:2	PC		TG 54:4;2O TG 18:2 18:2 18:0;2O	OxTG
PC 36:2 PC 18:1 18:1	PC		TG 54:4 TG 18:1 18:1 18:2	TG
PC 36:3 PC 18:1 18:2	PC		TG 54:5;1O TG 18:1 18:1 18:3;1O	OxTG
PC 36:4	PC		TG 54:5;1O TG 18:2 18:2 18:1;1O	OxTG
PC 36:4 PC 16:0 20:4	PC		TG 54:5;2O TG 18:2 18:2 18:1;2O	OxTG
PC 36:4 PC 18:2 18:2	PC		TG 54:5;3O TG 18:2 18:2 18:1;3O	OxTG
PC 36:5	PC		TG 54:5 TG 18:1 18:2 18:2	TG
PC 36:5 PC 16:0 20:5	PC		TG 54:6;1O TG 18:2 18:2 18:2;1O	OxTG
PC 36:5 PC 18:2 18:3	PC		TG 54:6 TG 18:2 18:2 18:2	TG
PC 38:1	PC		TG 54:7 TG 18:2 18:2 18:3	TG
PC 38:3	PC		TG 54:8 TG 18:2 18:3 18:3	TG
PC 38:4 PC 18:0 20:4	PC		TG 54:9 TG 18:3 18:3 18:3	TG
PC 38:4 PC 18:1 20:3	PC		TG 55:7 TG 18:2 18:2 19:3	TG
PC 38:5	PC		TG 56:3;2O TG 20:1 18:2 18:0;2O	OxTG
PC 38:5 PC 18:1 20:4	PC		TG 56:3;3O TG 18:1 18:1 20:1;3O	OxTG
PC 38:6 PC 16:0 22:6	PC		TG 56:4;1O TG 18:2 18:2 20:0;1O	OxTG
PC 38:6 PC 18:2 20:4	PC		TG 56:6 TG 20:1 18:2 18:3	TG
PC 40:5	PC		TG 56:7 TG 18:1 18:2 20:4	TG
PC 40:6	PC		TG 56:8 TG 18:1 18:2 20:5	TG
PC 40:8	PC		TG 57:8;1O TG 18:2 18:2 21:4;1O	OxTG
PC 50:9	PC		TG 57:9;1O TG 22:4 21:5 14:0;1O	OxTG
PC O-30:0	EtherPC		TG 58:10 TG 18:2 18:2 22:6	TG
PC O-30:1	EtherPC		TG 58:5;4O TG 18:2 18:2 22:1;4O	OxTG
PC O-31:0	EtherPC		TG 58:6;1O TG 19:0 22:3 17:3;1O	OxTG
PC O-31:1	EtherPC		TG 58:8;1O TG 19:0 22:5 17:3;1O	OxTG
PC O-32:0	EtherPC		TG 58:8 TG 18:1 18:1 22:6	TG
PC O-32:1	EtherPC		TG 58:9 TG 18:1 18:2 22:6	TG
PC O-33:0	EtherPC		TG 59:7;4O TG 15:0 22:3 22:4;4O	OxTG
PC O-33:1	EtherPC		TG 59:8;1O TG 22:3 21:5 16:0;1O	OxTG
PC O-34:0	EtherPC		TG 60:8 TG 18:1 20:1 22:6	TG
PC O-34:1	EtherPC		TG 62:8 TG 18:1 22:1 22:6	TG
PC O-34:2	EtherPC		TG 62:9 TG 18:1 22:4 22:4	TG
PC O-34:3	EtherPC		TG 63:4 TG 27:0 18:2 18:2	TG

Lipid Name	Class		Lipid Name	Class
PC O-36:0	EtherPC		TG 64:9;O2 TG 18:2_18:2_8:0;O(FA 20:4)	TG_EST
PC O-36:1	EtherPC		TG 65:0 TG 16:0_16:0_33:0	TG
PC O-36:2	EtherPC		TG 65:4 TG 15:0_16:1_34:3	TG
PC O-36:3	EtherPC		TG 67:0 TG 16:0_16:0_35:0	TG
PC O-36:4	EtherPC		TG 70:7 TG 16:1_18:1_36:5	TG
PC O-36:5	EtherPC		TG 76:9;O2 TG 18:2_18:2_18:1;O(FA 22:3)	TG_EST
PC O-37:10	EtherPC		TG 78:11;O2 TG 16:0_18:2_22:3;O(FA 22:5)	TG_EST
PC O-37:8	EtherPC		TG O-34:1 TG O-14:1_10:0_10:0	EtherTG
PC O-38:0	EtherPC		TG O-34:1 TG O-8:0_8:0_18:1	EtherTG
PC O-38:1	EtherPC		TG O-38:2 TG O-12:0_13:1_13:1	EtherTG
PC O-38:2	EtherPC		TG O-47:6 TG O-17:4_15:1_15:1	EtherTG
PC O-38:3	EtherPC		TG O-51:0 TG O-17:0_17:0_17:0	EtherTG
PC O-38:4	EtherPC		TG O-52:3 TG O-18:1_16:1_18:1	EtherTG
PC O-38:5	EtherPC		TG O-52:4 TG O-16:1_17:1_19:2	EtherTG
PC O-38:6	EtherPC		TG O-52:5 TG O-13:0_17:3_22:2	EtherTG
PC O-39:10	EtherPC		TG O-52:6 TG O-22:6_15:0_15:0	EtherTG
PC O-40:1	EtherPC		TG O-53:3 TG O-19:2_16:0_18:1	EtherTG
PC O-40:10	EtherPC		TG O-55:10 TG O-19:0_18:5_18:5	EtherTG
PC O-40:3	EtherPC		TG O-56:5 TG O-15:1_20:0_21:4	EtherTG
PC O-40:5	EtherPC		TG O-57:12 TG O-21:4_15:3_21:5	EtherTG
PC O-40:6	EtherPC		TG O-57:13 TG O-15:3_21:5_21:5	EtherTG
PC O-40:7	EtherPC		TG O-57:5 TG O-21:4_17:1_19:0	EtherTG
PC O-42:3	EtherPC		TG O-58:7 TG O-16:0_21:3_21:4	EtherTG
PC O-42:4	EtherPC		TG O-59:9 TG O-16:0_21:5_22:4	EtherTG
PC O-42:5	EtherPC		TG O-60:4 TG O-22:1_18:2_20:1	EtherTG
PC O-42:6	EtherPC		TG O-61:12 TG O-17:4_22:4_22:4	EtherTG
PC O-44:5	EtherPC		VAE 25:1	VAE
PC O-44:6	EtherPC		VAE 26:6	VAE

Table H. List of metabolites and their corresponding classes identified in whole blood taken from young and healthy people

Metabolite Name	Class
1,3,7-Trimethyluric acid	Purines and derivatives

Metabolite Name	Class
1-Methyladenosine	Purines and derivatives
1-Methylguanine	Purines and derivatives
2,3-Dihydroxybenzoic acid	Benzoic acids and derivatives
2-Ethyl-2-Hydroxybutyric acid	Fatty acids and conjugates
2-Hydroxy-2-methylbutyric acid	Fatty acids and conjugates
2-Methyl-3-ketovaleric acid	Keto acids and derivatives
2-Phenylbutyric acid	Benzene and derivatives
2-Piperidinone	Piperidinones
3-Indolepropionic acid	indoles and derivatives
3-Pyridylacetic acid	Pyridines and derivatives
4-Ethylbenzoic acid	Benzoic acids and derivatives
4-Hydroxybenzoic acid	Benzoic acids and derivatives
4-Methylcatechol	Phenols
5-Methoxysalicylic acid	Benzoic acids and derivatives
5"-Methylthioadenosine	Purines and derivatives
6-Hydroxypurine	Purines and derivatives
7-Methylxanthine	Purines and derivatives
Adenine	Purines and derivatives
Adenosine	Purine nucleotides
Alpha-ketoisovaleric acid	Keto acids and derivatives
Arachidic acid	Fatty acids and conjugates
Argininosuccinic acid	Amino acids and derivatives
Betaine	Amino acids and derivatives
Bilirubin	Bilirubins
Biocytin	Amino acids and derivatives
Butyrylcarnitine (C4)	Fatty acid esters
Capric acid	Fatty acids and conjugates
Caprylic acid	Fatty acids and conjugates
Cholesterol sulfate	Steroids
Choline, M+	Bile acids
Cotinine	Pyridines and derivatives
Creatine	Amino acids and derivatives
Creatinine	Amino acids and derivatives
Cytosine	Pyridines and derivatives
Decanoylcarnitine (C10)	Fatty acids and conjugates
Decenoylcarnitine (C10:1)	Fatty acids and conjugates
Diethanolamine	Organonitrogen compounds
Dodecanoic acid	Fatty acids and conjugates
Dodecanoylcarnitine (C12)	Fatty acid esters
Erucic acid	Fatty acids and conjugates
Heptadecanoic acid	Fatty acids and conjugates
Hexadecanoylcarnitine - Palmitoylcarnitine (C16)	Fatty acid esters
Hippuric acid	Benzoic acids and derivatives
Hydrocinnamic acid	phenylpropanoic acids

Metabolite Name	Class
Hydroxybutyrylcarnitine (C4- OH (C3-DC))	Fatty acid esters
Hydroxyhexanoylcarnitine (C6-OH)	Fatty acid esters
Hydroxyisobutyric acid	Hydroxy acids
Hydroxyphenyllactic acid	phenylpropanoic acids
Hydroxyvalerylcarnitine (C5-OH (C3-DC-M))	Fatty acid esters
Indoleacrylic acid	indoles and derivatives
Indolelactic acid	indoles and derivatives
Inosine	Purines and derivatives
Isovanillin	phenols
L-3-Phenyllactic acid	phenylpropanoic acids
L-Acetylcarnitine	Fatty acid esters
L-Carnitine	Organonitrogen compounds
Leucinic acid	Fatty acids and conjugates
Linoleic acid	Fatty acid esters
Linolenic acid	Fatty acids and conjugates
L-Isoleucine	Amino acids and derivatives
L-Leucine	Amino acids and derivatives
L-Methionine	Amino acids and derivatives
L-Phenylalanine	Amino acids and derivatives
L-Proline	Amino acids and derivatives
L-Tryptophan	Amino acids and derivatives
L-Tyrosine	Amino acids and derivatives
L-Valine	Amino acids and derivatives
Mannitol/Sorbitol	Carbohydrates and carbohydrate conjugates
Mesaconic acid	Fatty acids and conjugates
Myristic acid	Fatty acids and conjugates
N-Acetyl-D-glucosamine	Carbohydrates and carbohydrate conjugates
N-Acetyl-L-methionine	Amino acids and derivatives
N-Acetyl-L-phenylalanine	Amino acids and derivatives
Nervonic acid	Fatty acids and conjugates
Niacinamide	Pyridines and derivatives
N-Methylnicotinamide	Pyridines and derivatives
Nonadecanoic acid	Fatty acids and conjugates
Nonacylcarnitine (C9)	Fatty acid esters
Octadecadienylcarnitine (C18:2)	Eicosanoid
Octadecanoylcarnitine - Acylcarnitine (C18)	Fatty acid esters
Octadecenoylcarnitine (C18:1)	Fatty acid esters
Octanoylcarnitine (C8)	Fatty acid esters
Oleic acid	Fatty acids and conjugates
PC(16:0 16:0)	Organonitrogen compounds
Pentadecanoic acid	Fatty acids and conjugates
Pregnenolone sulfate	Steroids
Propionylcarnitine (C3)	Fatty acid esters
Pyrrolidonecarboxylic acid	Amino acids and derivatives

Metabolite Name	Class
Rhamnose	Carbohydrates and carbohydrate conjugates
Sphinganine	Organonitrogen compounds
Stearic acid	Fatty acids and conjugates
Succinylacetone	Keto acids and derivatives
Taurine	Sulfate and sulfonates
Taurodeoxycholic acid	Bile acids
Tetradecanoylcarnitine (C14)	Fatty acid esters
Theophylline	Purines and derivatives
Traumatic acid	Fatty acids and conjugates
Tridecanoic acid	Fatty acids and conjugates
Trigonelline	Alkaloids and derivatives
Trimethylamine	Organonitrogen compounds
Undecanoic acid	Fatty acids and conjugates
Urea	ureas
Uridine	Pyrimidine nucleotides
Ursodeoxycholic acid	Bile acids
Valerylcarnitine - Methylbutyrylcarnitine (C5)	Fatty acid esters

Table I. List of lipids and their corresponding classes identified in whole blood taken from young and healthy people

Lipid Name	Class		Lipid Name	Class
ASG 27:1;O;Hex;FA 10:0	AHexCS		PE 39:4;O PE 22:3_17:1;O	OxPE
ASG 27:1;O;Hex;FA 20:0	AHexCS		PE 39:5	PE
BA 24:1;O4;G;S	BASulfate		PE 39:5;O PE 22:4_17:1;O	OxPE
BA 24:1;O4;T;S	BASulfate		PE 39:6 PE 13:0_26:6	PE
CAR 11:0	CAR		PE 39:7;O PE 22:5_17:2;O	OxPE
CAR 14:0	CAR		PE 40:4	PE
CAR 16:0	CAR		PE 40:4 PE 18:0_22:4	PE
CAR 16:1	CAR		PE 40:5 PE 18:0_22:5	PE
CAR 17:4	CAR		PE 40:5 PE 18:1_22:4	PE
CAR 18:0	CAR		PE 40:6;2O PE 22:6_18:0;2O	OxPE
CAR 18:1	CAR		PE 40:6;O PE 18:1_22:5;O	OxPE
CAR 18:2	CAR		PE 40:6 PE 18:0_22:6	PE
CAR 20:1	CAR		PE 40:6 PE 18:1_22:5	PE
CE 16:0	CE		PE 40:7	PE
CE 16:1	CE		PE 40:7 PE 18:1_22:6	PE
CE 18:1	CE		PE 40:7 PE 20:3_20:4	PE
CE 18:2	CE		PE 40:8 PE 18:2_22:6	PE
CE 18:3	CE		PE 40:8 PE 20:4_20:4	PE
CE 20:3	CE		PE 42:1 PE 9:0_33:1	PE
CE 20:4	CE		PE 42:10 PE 20:4_22:6	PE
CE 20:5	CE		PE 42:5 PE 20:1_22:4	PE
CE 22:5	CE		PE 42:6 PE 20:1_22:5	PE
CE 22:6	CE		PE 42:7	PE
Cer 34:1;2O Cer 18:1;2O/16:0	Cer_NS		PE 42:8 PE 20:3_22:5	PE
Cer 35:1;4O Cer 18:0;3O/17:1;(2OH)	Cer_AP		PE 42:8 PE 20:4_22:4	PE

Lipid Name	Class		Lipid Name	Class
Cer 37:1;40 Cer 20:0;30/17:1;(2OH)	Cer_AP		PE 42:9	PE
Cer 38:1;20 Cer 18:1;20/20:0	Cer_NS		PE 42:9 PE 20:3 22:6	PE
Cer 39:1;40 Cer 18:0;30/21:1;(2OH)	Cer_AP		PE 44:11 PE 22:5 22:6	PE
Cer 40:1;20 Cer 18:1;20/22:0	Cer_NS		PE 44:12 PE 22:6 22:6	PE
Cer 40:2;20 Cer 18:2;20/22:0	Cer_NS		PE O-32:1 PE O-16:1 16:0	EtherPE
Cer 41:1;20 Cer 18:1;20/23:0	Cer_NS		PE O-34:1 PE O-18:1 16:0	EtherPE
Cer 41:1;40 Cer 18:0;30/23:1;(2OH)	Cer_AP		PE O-34:2 PE O-16:0 18:2	EtherPE
Cer 41:2;20 Cer 17:1;20/24:1	Cer_NS		PE O-34:2 PE O-16:1 18:1	EtherPE
Cer 42:0;20 Cer 18:0;20/24:0	Cer_NDS		PE O-34:3 PE O-16:1 18:2	EtherPE
Cer 42:1;20 Cer 18:0;20/24:1	Cer_NDS		PE O-34:5 PE O-14:1 20:4	EtherPE
Cer 42:1;20 Cer 18:1;20/24:0	Cer_NS		PE O-35:1	EtherPE
Cer 42:2;20 Cer 18:1;20/24:1	Cer_NS		PE O-35:2 PE O-17:1 18:1	EtherPE
Cer 42:3;20 Cer 18:1;20/24:2	Cer_NS		PE O-36:2 PE O-18:1 18:1	EtherPE
Cer 42:3;20 Cer 18:2;20/24:1	Cer_NS		PE O-36:3 PE O-18:2 18:1	EtherPE
Cer 42:3;30 Cer 18:1;20/24:2;O	Cer_HS		PE O-36:4 PE O-16:0 20:4	EtherPE
Cer 42:4;30 Cer 18:2;20/24:2;O	Cer_HS		PE O-36:4 PE O-16:1 20:3	EtherPE
Cer 43:1;40 Cer 18:0;30/25:1;(2OH)	Cer_AP		PE O-36:5 PE O-16:0 20:5	EtherPE
Cer 43:3;30 Cer 19:0;20/24:3;O	Cer_HDS		PE O-36:5 PE O-16:1 20:4	EtherPE
Cer 43:3;40 Cer 17:3;30/26:0;(2OH)	Cer_AP		PE O-36:6 PE O-16:1 20:5	EtherPE
Cer 43:3;40 Cer 26:1;30/17:2;(2OH)	Cer_AP		PE O-36:7 PE O-14:1 22:6	EtherPE
Cer 43:4;30	Cer_BS		PE O-37:5 PE O-17:1 20:4	EtherPE
Cer 43:4;40 Cer 19:3;30/24:1;(2OH)	Cer_AP		PE O-37:6 PE O-17:1 20:5	EtherPE
Cer 45:1;40 Cer 28:0;30/17:1;(2OH)	Cer_AP		PE O-38:2 PE O-18:1 20:1	EtherPE
Cer 45:1;40 Cer 28:1;30/17:0;(2OH)	Cer_AP		PE O-38:3 PE O-20:1 18:2	EtherPE
Cer 45:2;30 Cer 17:1;20/28:1;O	Cer_HS		PE O-38:4 PE O-18:0 20:4	EtherPE
Cer 45:2;40 Cer 28:1;30/17:1;(2OH)	Cer_AP		PE O-38:5 PE O-16:1 22:4	EtherPE
Cer 45:4;30 Cer 19:3;20/26:1;O	Cer_HS		PE O-38:5 PE O-18:1 20:4	EtherPE
Cer 45:4;40 Cer 18:3;20/27:1;2O	Cer_EOS		PE O-38:6 PE O-18:2 20:4	EtherPE
Cer 45:5;30 Cer 21:1;20/24:4;O	Cer_HS		PE O-38:7 PE O-16:1 22:6	EtherPE
Cer 46:3;30 Cer 24:0;20/22:3;O	Cer_HDS		PE O-38:7 PE O-18:2 20:5	EtherPE
Cer 46:4;30 Cer 18:1;20/28:3;O	Cer_HS		PE O-38:7 PE O-18:3 20:4	EtherPE
Cer 46:9;30	Cer_NP		PE O-38:8 PE O-18:3 20:5	EtherPE
Cer 47:8;40	Cer_AP		PE O-39:5 PE O-17:1 22:4	EtherPE
Cer 49:12;40 Cer 27:6;30(FA 22:5)	Cer_EOS		PE O-39:5 PE O-19:0 20:5	EtherPE
Cer 50:9;30	Cer_NP		PE O-39:6 PE O-17:1 22:5	EtherPE
Cer 52:4;40 Cer 14:1;20/38:3;2O	Cer_EOS		PE O-39:7 PE O-17:1 22:6	EtherPE
Cer 53:12;40 Cer 14:1;20/39:11;2O	Cer_EOS		PE O-40:2 PE O-22:1 18:1	EtherPE
Cer 54:10;40 Cer 38:9;30(FA 16:0)	Cer_EOS		PE O-40:3 PE O-18:1 22:2	EtherPE
Cer 56:10;40 Cer 40:9;30(FA 16:0)	Cer_EOS		PE O-40:4 PE O-18:1 22:3	EtherPE
Cer 58:10;40 Cer 42:9;30(FA 16:0)	Cer_EOS		PE O-40:4 PE O-22:2 18:2	EtherPE
Cer 58:11;40 Cer 40:9;30(FA 18:1)	Cer_EOS		PE O-40:5	EtherPE
Cer 60:13;40 Cer 40:8;30(FA 20:4)	Cer_EOS		PE O-40:5 PE O-18:1 22:4	EtherPE
CL 58:5 CL 12:0 12:0 22:5	CL		PE O-40:6 PE O-18:1 22:5	EtherPE
CL 67:3	CL		PE O-40:7 PE O-18:1 22:6	EtherPE
CL 69:5	CL		PE O-40:7 PE O-18:2 22:5	EtherPE
CL 70:1 CL 37:0 33:1	CL		PE O-40:8 PE O-18:2 22:6	EtherPE
CL 74:7 CL 39:3 35:4	CL		PE O-40:9 PE O-18:3 22:6	EtherPE

Lipid Name	Class		Lipid Name	Class
CL 75:4 CL 36:1_39:3	CL		PE O-41:3 PE O-21:0_20:3	EtherPE
CL 75:5 CL 36:2_39:3	CL		PE O-41:7	EtherPE
CL 85:1 CL 18:0_18:0_26:0_23:1	CL		PE O-41:7 PE O-21:4_20:3	EtherPE
CL 85:10 CL 15:0_28:0_20:4_22:6	CL		PE O-42:3 PE O-24:2_18:1	EtherPE
CL 85:7 CL 17:0_26:0_20:3_22:4	CL		PE O-42:4 PE O-24:2_18:2	EtherPE
CL 85:8 CL 15:0_28:0_20:4_22:4	CL		PE O-42:5 PE O-18:1_24:4	EtherPE
CL 86:14 CL 26:0_20:4_20:5_20:5	CL		PE O-42:6 PE O-22:2_20:4	EtherPE
CL 86:7 CL 24:0_18:1_22:3_22:3	CL		PE O-42:7 PE O-20:1_22:6	EtherPE
CL 86:8 CL 16:0_26:0_22:4_22:4	CL		PE O-42:7 PE O-22:3_20:4	EtherPE
CL 94:18 CL 28:0_22:6_22:6_22:6	CL		PE O-42:8 PE O-20:2_22:6	EtherPE
DG 38:4 DG 18:0_20:4	DG		PE O-42:9 PE O-20:3_22:6	EtherPE
DG 41:2 DG 20:0_21:2	DG		PE O-44:6 PE O-24:2_20:4	EtherPE
DG 42:5 DG 16:0_26:5	DG		PE O-44:8 PE O-22:2_22:6	EtherPE
DGGA 34:1 DGGA 16:0_18:1	DGGA		PE O-46:8 PE O-24:2_22:6	EtherPE
DGGA 36:2 DGGA 18:1_18:1	DGGA		PE P-32:0 PE P-16:0_16:0	EtherPE
DGGA 36:4 DGGA 16:0_20:4	DGGA		PE P-34:0 PE P-18:0_16:0	EtherPE
DGGA 36:4 DGGA 18:2_18:2	DGGA		PE P-34:1 PE P-16:0_18:1	EtherPE
DGGA 38:4 DGGA 18:0_20:4	DGGA		PE P-34:2 PE P-16:0_18:2	EtherPE
DGGA 40:6 DGGA 20:3_20:3	DGGA		PE P-36:1 PE P-18:0_18:1	EtherPE
FA 15:3	FA		PE P-36:2 PE P-18:1_18:1	EtherPE
FA 18:1	FA		PE P-36:3 PE P-18:1_18:2	EtherPE
FA 18:2	FA		PE P-36:4 PE P-16:0_20:4	EtherPE
FA 18:3	FA		PE P-36:4 PE P-18:2_18:2	EtherPE
FA 19:1;2O	OxFA		PE P-36:5 PE P-16:0_20:5	EtherPE
FA 20:3	FA		PE P-37:4 PE P-17:0_20:4	EtherPE
FA 20:4	FA		PE P-38:2 PE P-20:1_18:1	EtherPE
FA 20:5	FA		PE P-38:3 PE P-16:1_22:2	EtherPE
FA 22:4	FA		PE P-38:4 PE P-16:0_22:4	EtherPE
FA 22:5	FA		PE P-38:4 PE P-16:1_22:3	EtherPE
FA 22:6	FA		PE P-38:5 PE P-18:1_20:4	EtherPE
FA 25:0;O	OxFA		PE P-38:6 PE P-16:0_22:6	EtherPE
FA 26:0;O	OxFA		PE P-38:6 PE P-18:2_20:4	EtherPE
FA 26:5	FA		PE P-39:4 PE P-17:0_22:4	EtherPE
GM3 34:1;2O	GM3		PE P-39:6 PE P-17:0_22:6	EtherPE
HBMP 42:0 HBMP 14:0_14:0_14:0	HBMP		PE P-40:3 PE P-18:0_22:3	EtherPE
HBMP 42:3 HBMP 14:1_14:1_14:1	HBMP		PE P-40:4 PE P-18:0_22:4	EtherPE
HBMP 46:1 HBMP 14:0_14:0_18:1	HBMP		PE P-40:5 PE P-18:0_22:5	EtherPE
HBMP 46:4 HBMP 13:0_13:0_20:4	HBMP		PE P-40:5 PE P-18:1_22:4	EtherPE
HBMP 48:2 HBMP 16:0_16:1_16:1	HBMP		PE P-40:6 PE P-18:0_22:6	EtherPE
HBMP 48:4 HBMP 14:0_14:0_20:4	HBMP		PE P-40:6 PE P-18:1_22:5	EtherPE
HBMP 48:5 HBMP 13:0_13:0_22:5	HBMP		PE P-40:7 PE P-18:1_22:6	EtherPE
HBMP 48:6 HBMP 14:1_14:1_20:4	HBMP		PE P-40:8 PE P-18:2_22:6	EtherPE
HBMP 52:6 HBMP 18:1_18:1_16:4	HBMP		PE P-42:3 PE P-24:1_18:2	EtherPE
Hex2Cer 33:1;2O Hex2Cer 17:1;2O/16:0	Hex2Cer		PE P-42:4 PE P-18:0_24:4	EtherPE
Hex2Cer 34:1;2O	Hex2Cer		PE P-42:4 PE P-22:0_20:4	EtherPE
Hex2Cer 34:1;2O Hex2Cer 18:1;2O/16:0	Hex2Cer		PE P-42:5 PE P-22:1_20:4	EtherPE
Hex2Cer 40:1;2O Hex2Cer 18:1;2O/22:0	Hex2Cer		PE P-42:6 PE P-20:0_22:6	EtherPE

Lipid Name	Class		Lipid Name	Class
Hex2Cer 42:1;2O Hex2Cer 18:1;2O/24:0	Hex2Cer		PE P-42:7 PE P-20:1_22:6	EtherPE
Hex2Cer 42:2;2O Hex2Cer 18:1;2O/24:1	Hex2Cer		PE P-42:7 PE P-20:2_22:5	EtherPE
Hex2Cer 42:3;2O Hex2Cer 18:1;2O/24:2	Hex2Cer		PE P-42:8 PE P-20:2_22:6	EtherPE
Hex2Cer 44:2;2O Hex2Cer 18:1;2O/26:1	Hex2Cer		PE P-43:7 PE P-21:3_22:4	EtherPE
Hex3Cer 34:1;2O Hex3Cer 18:1;2O/16:0	Hex3Cer		PE P-44:5 PE P-24:1_20:4	EtherPE
Hex3Cer 42:1;2O Hex3Cer 18:1;2O/24:0	Hex3Cer		PE P-44:6 PE P-24:2_20:4	EtherPE
Hex3Cer 42:2;2O Hex3Cer 18:1;2O/24:1	Hex3Cer		PE P-44:7 PE P-22:1_22:6	EtherPE
HexCer 34:1;2O HexCer 18:1;2O/16:0	HexCer_NS		PE-Cer 34:1;2O PE-Cer 18:1;2O/16:0	PE_Cer
HexCer 43:2;4O	HexCer_AP		PE-Cer 42:2;2O PE-Cer 18:1;2O/24:1	PE_Cer
HexCer 48:11;4O	HexCer_EOS		PE-Cer 42:3;2O PE-Cer 18:0;2O/24:3	PE_Cer
HexCer 52:7;4O	HexCer_AP		PEtOH 34:1 PEtOH 16:0_18:1	PEtOH
HexCer 55:12;4O HexCer 33:5;3O(FA 22:6)	HexCer_EOS		PEtOH 40:5 PEtOH 18:1_22:4	PEtOH
Inosine	Others		PG O-36:1 PG O-18:1_18:0	EtherPG
LPC 13:0	LPC		PI 34:2	PI
LPC 14:0/0:0	LPC		PI 36:0	PI
LPC 16:0	LPC		PI 36:1 PI 18:0_18:1	PI
LPC 16:0/0:0	LPC		PI 36:2 PI 18:0_18:2	PI
LPC 16:1/0:0	LPC		PI 36:4	PI
LPC 17:0/0:0	LPC		PI 36:4 PI 16:0_20:4	PI
LPC 18:0	LPC		PI 38:3 PI 18:0_20:3	PI
LPC 18:0/0:0	LPC		PI 38:4	PI
LPC 18:1	LPC		PI 38:4 PI 18:0_20:4	PI
LPC 18:1/0:0	LPC		PI 40:4 PI 18:0_22:4	PI
LPC 18:2	LPC		PI 40:6	PI
LPC 20:0	LPC		PI 40:6 PI 18:0_22:6	PI
LPC 20:1	LPC		PI-Cer 36:1;3O	PI_Cer
LPC 20:1/0:0	LPC		PI-Cer 36:3;2O	PI_Cer
LPC 20:3/0:0	LPC		PI-Cer 40:1;2O	PI_Cer
LPC 20:4	LPC		PI-Cer 40:5;3O	PI_Cer
LPC 22:6/0:0	LPC		PI-Cer 41:5;3O	PI_Cer
LPC 28:0	LPC		PI-Cer 43:6;3O	PI_Cer
LPC O-16:0	EtherLPC		PI-Cer 44:2;2O	PI_Cer
LPC O-16:1	EtherLPC		PI-Cer 44:2;3O	PI_Cer
LPC O-18:0	EtherLPC		PI-Cer 51:8;3O	PI_Cer
LPC O-18:1	EtherLPC		PMeOH 27:2	PMeOH
LPE 16:0	LPE		PMeOH 34:8	PMeOH
LPE 18:0	LPE		PMeOH 50:8	PMeOH
LPE 18:1	LPE		PS 34:0	PS
LPE 18:2	LPE		PS 34:0 PS 16:0_18:0	PS
LPE 20:4	LPE		PS 34:1	PS
LPE 22:4	LPE		PS 34:1;3O PS 18:1_16:0;3O	OxPS
LPE 22:6	LPE		PS 34:1 PS 16:0_18:1	PS
LPE O-16:1	EtherLPE		PS 36:0;2O PS 18:0_18:0;2O	OxPS
LPE O-18:1	EtherLPE		PS 36:1 PS 18:0_18:1	PS
LPE O-18:2	EtherLPE		PS 36:2	PS
LPE-N (FA)34:0 LPE-N (FA 18:0)16:0	LNAPE		PS 36:2 PS 18:1_18:1	PS
LPE-N (FA)36:1 LPE-N (FA 18:0)18:1	LNAPE		PS 36:3;3O PS 18:1_18:2;3O	OxPS

Lipid Name	Class		Lipid Name	Class
LPE-N (FA)36:2 LPE-N (FA 18:0)18:2	LNAPE		PS 36:4;2O PS 18:1_18:3;2O	OxPS
LPE-N (FA)38:4 LPE-N (FA 18:0)20:4	LNAPE		PS 36:4 PS 15:2_21:2	PS
LPE-N (FA)38:6 LPE-N (FA 16:0)22:6	LNAPE		PS 36:4 PS 16:0_20:4	PS
LPS 18:0	LPS		PS 38:3	PS
MG 18:3	MG		PS 38:4 PS 18:0_20:4	PS
MG 27:0	MG		PS 38:5	PS
MG 35:0	MG		PS 38:5 PS 18:1_20:4	PS
MG 35:1	MG		PS 38:6	PS
MGDG 36:0 MGDG 18:0_18:0	MGDG		PS 40:4 PS 18:0_22:4	PS
NAE 21:3	NAE		PS 40:5 PS 18:0_22:5	PS
NAE 22:4	NAE		PS 40:6 PS 18:0_22:6	PS
NAGly 15:0;O	NAGly		PS 40:7 PS 18:1_22:6	PS
NAGly 24:3;O	NAGly		PS 40:7 PS 20:3_20:4	PS
NAGly 30:3;2O NAGly 9:0;O(FA 21:2)	NAGly		PS 40:8 PS 20:4_20:4	PS
NAOrn 10:0;O	NAOrn		PS 42:10 PS 20:4_22:6	PS
PC 28:0 PC 14:0_14:0	PC		PS 42:8 PS 20:2_22:6	PS
PC 29:0	PC		PS 42:9	PS
PC 30:0 PC 14:0_16:0	PC		PS O-35:0 PS O-19:0_16:0	EtherPS
PC 30:1 PC 14:0_16:1	PC		PS O-37:1 PS O-19:0_18:1	EtherPS
PC 31:0 PC 15:0_16:0	PC		PS O-37:2 PS O-19:0_18:2	EtherPS
PC 31:1	PC		PS O-39:4 PS O-19:0_20:4	EtherPS
PC 32:0 PC 16:0_16:0	PC		PS O-39:5 PS O-19:1_20:4	EtherPS
PC 32:1	PC		PS O-40:6 PS O-18:0_22:6	EtherPS
PC 32:1 PC 16:0_16:1	PC		PS O-41:4 PS O-19:0_22:4	EtherPS
PC 32:2 PC 14:0_18:2	PC		PS O-41:5 PS O-19:0_22:5	EtherPS
PC 33:0 PC 16:0_17:0	PC		SE 28:1/14:0	CASE
PC 33:1	PC		SE 28:1/18:2	CASE
PC 33:1 PC 15:0_18:1	PC		SHexCer 24:2;2O	SHexCer
PC 33:2 PC 15:0_18:2	PC		SHexCer 34:1;2O	SHexCer
PC 33:3;O PC 18:2_15:1;O	OxPC		SHexCer 34:1;3O	SHexCer
PC 34:0 PC 16:0_18:0	PC		SHexCer 37:1;2O	SHexCer
PC 34:1 PC 16:0_18:1	PC		SHexCer 37:2;2O	SHexCer
PC 34:2	PC		SHexCer 37:3;2O	SHexCer
PC 34:2 PC 16:0_18:2	PC		SHexCer 38:1;3O	SHexCer
PC 34:3 PC 16:0_18:3	PC		SHexCer 38:3;3O	SHexCer
PC 34:3 PC 16:1_18:2	PC		SHexCer 38:4;3O	SHexCer
PC 34:4	PC		SHexCer 39:1;2O	SHexCer
PC 34:4 PC 14:0_20:4	PC		SHexCer 39:1;3O	SHexCer
PC 35:0	PC		SHexCer 39:2;2O	SHexCer
PC 35:1 PC 17:0_18:1	PC		SHexCer 39:4;2O	SHexCer
PC 35:2 PC 17:0_18:2	PC		SHexCer 39:5;2O	SHexCer
PC 35:3	PC		SHexCer 39:5;3O	SHexCer
PC 35:4 PC 15:0_20:4	PC		SHexCer 40:0;2O	SHexCer
PC 35:5;O PC 20:4_15:1;O	OxPC		SHexCer 40:0;3O	SHexCer
PC 36:0 PC 18:0_18:0	PC		SHexCer 40:1;2O	SHexCer
PC 36:1 PC 18:0_18:1	PC		SHexCer 40:1;3O	SHexCer
PC 36:2 PC 18:0_18:2	PC		SHexCer 40:2;2O	SHexCer

Lipid Name	Class		Lipid Name	Class
PC 36:2 PC 18:1_18:1	PC		SHexCer 40:3;3O	SHexCer
PC 36:3 PC 16:0_20:3	PC		SHexCer 40:4;3O	SHexCer
PC 36:3 PC 18:1_18:2	PC		SHexCer 40:5;3O	SHexCer
PC 36:4 PC 16:0_20:4	PC		SHexCer 41:5;3O	SHexCer
PC 36:4 PC 18:2_18:2	PC		SHexCer 42:1;3O	SHexCer
PC 36:5 PC 16:0_20:5	PC		SHexCer 42:4;3O	SHexCer
PC 36:5 PC 16:1_20:4	PC		SHexCer 42:5;3O	SHexCer
PC 36:5 PC 18:2_18:3	PC		SHexCer 42:6;3O	SHexCer
PC 36:6 PC 14:0_22:6	PC		SHexCer 42:7;3O	SHexCer
PC 37:1	PC		SHexCer 42:8;3O	SHexCer
PC 37:2	PC		SHexCer 43:5;3O	SHexCer
PC 37:3 PC 17:0_20:3	PC		SHexCer 43:6;3O	SHexCer
PC 37:4 PC 17:0_20:4	PC		SHexCer 44:0;2O	SHexCer
PC 37:5	PC		SHexCer 44:6;3O	SHexCer
PC 37:5 PC 17:1_20:4	PC		SHexCer 44:8;3O	SHexCer
PC 37:6	PC		SHexCer 44:9;3O	SHexCer
PC 37:6 PC 15:0_22:6	PC		SHexCer 45:0;2O	SHexCer
PC 37:6 PC 15:1_22:5	PC		SHexCer 45:1;2O	SHexCer
PC 37:8	PC		SHexCer 45:7;3O	SHexCer
PC 37:9	PC		SHexCer 46:2;3O	SHexCer
PC 38:0	PC		SHexCer 46:3;3O	SHexCer
PC 38:1	PC		SHexCer 47:0;2O	SHexCer
PC 38:2	PC		SHexCer 47:0;3O	SHexCer
PC 38:2 PC 18:0_20:2	PC		SHexCer 47:1;3O	SHexCer
PC 38:3 PC 18:0_20:3	PC		SHexCer 48:3;2O	SHexCer
PC 38:4	PC		SHexCer 49:0;3O	SHexCer
PC 38:4 PC 16:0_22:4	PC		SHexCer 49:1;3O	SHexCer
PC 38:4 PC 18:0_20:4	PC		SHexCer 49:3;2O	SHexCer
PC 38:5 PC 16:0_22:5	PC		SHexCer 49:4;2O	SHexCer
PC 38:5 PC 18:0_20:5	PC		SHexCer 49:5;2O	SHexCer
PC 38:5 PC 18:1_20:4	PC		SHexCer 50:2;3O	SHexCer
PC 38:5 PC 21:1_17:4	PC		SHexCer 51:2;2O	SHexCer
PC 38:6	PC		SHexCer 53:9;2O	SHexCer
PC 38:6 PC 16:0_22:6	PC		SHexCer 55:9;2O	SHexCer
PC 38:6 PC 18:2_20:4	PC		SL 31:3;O	SL
PC 38:7 PC 16:1_22:6	PC		SL 32:7;O	SL
PC 38:7 PC 18:2_20:5	PC		SL 49:7;2O	SL
PC 39:4	PC		SL 51:8;2O	SL
PC 39:6 PC 17:0_22:6	PC		SL 53:6;O SL 19:2;O/34:4	SL
PC 39:8	PC		SL 53:9;2O	SL
PC 40:0	PC		SL 55:9;2O	SL
PC 40:1	PC		SL 57:7;2O	SL
PC 40:2 PC 20:1_20:1	PC		SL 57:9;2O	SL
PC 40:3	PC		SM 30:1;2O SM 18:1;2O/12:0	SM
PC 40:4 PC 18:0_22:4	PC		SM 31:1;2O SM 17:1;2O/14:0	SM
PC 40:5 PC 18:0_22:5	PC		SM 32:0;2O	SM
PC 40:6 PC 18:0_22:6	PC		SM 32:1;2O SM 16:1;2O/16:0	SM

Lipid Name	Class		Lipid Name	Class
PC 40:6 PC 20:3_20:3	PC		SM 32:1;2O SM 18:1;2O/14:0	SM
PC 40:7	PC		SM 32:1;3O	SM
PC 40:7 PC 18:1_22:6	PC		SM 32:2;2O SM 18:2;2O/14:0	SM
PC 40:8	PC		SM 33:0;2O	SM
PC 40:8 PC 20:4_20:4	PC		SM 33:0;2O SM 19:0;2O/14:0	SM
PC 40:9	PC		SM 33:1;2O SM 17:1;2O/16:0	SM
PC 42:0	PC		SM 34:0;2O	SM
PC 42:1	PC		SM 34:0;3O	SM
PC 42:10 PC 20:4_22:6	PC		SM 34:1;2O	SM
PC 42:10 PC 21:5_21:5	PC		SM 34:1;2O SM 18:1;2O/16:0	SM
PC 42:2	PC		SM 34:1;3O	SM
PC 42:3 PC 16:0_26:3	PC		SM 34:2;2O	SM
PC 42:4 PC 16:0_26:4	PC		SM 34:2;2O SM 16:1;2O/18:1	SM
PC 42:5	PC		SM 34:2;2O SM 18:2;2O/16:0	SM
PC 42:6	PC		SM 35:0;3O	SM
PC 42:7 PC 20:1_22:6	PC		SM 35:1;2O SM 17:1;2O/18:0	SM
PC 42:8 PC 20:4_22:4	PC		SM 35:2;2O SM 18:2;2O/17:0	SM
PC 42:9	PC		SM 35:2;3O	SM
PC 44:0	PC		SM 35:3;3O	SM
PC 44:1	PC		SM 36:0;2O SM 14:0;2O/22:0	SM
PC 44:1 PC 26:0_18:1	PC		SM 36:1;2O	SM
PC 44:11	PC		SM 36:1;2O SM 18:1;2O/18:0	SM
PC 44:2	PC		SM 36:1;3O	SM
PC 44:3	PC		SM 36:2;2O	SM
PC 44:4	PC		SM 36:2;2O SM 18:2;2O/18:0	SM
PC 46:3	PC		SM 36:3;2O	SM
PC 46:5	PC		SM 36:3;2O SM 18:2;2O/18:1	SM
PC 48:9	PC		SM 37:0;3O	SM
PC 49:10	PC		SM 37:1;3O	SM
PC O-22:5	EtherOxPC		SM 37:4;3O	SM
PC O-30:0	EtherPC		SM 38:0;2O	SM
PC O-30:1	EtherPC		SM 38:1;2O SM 18:1;2O/20:0	SM
PC O-31:0	EtherPC		SM 38:2;2O	SM
PC O-31:1	EtherPC		SM 38:3;2O SM 14:1;2O/24:2	SM
PC O-32:0	EtherPC		SM 38:3;3O	SM
PC O-32:1	EtherPC		SM 38:5;3O	SM
PC O-32:2	EtherPC		SM 38:6;2O SM 20:1;2O/18:5	SM
PC O-33:0	EtherPC		SM 38:7;2O	SM
PC O-33:3	EtherPC		SM 38:7;3O	SM
PC O-34:0	EtherPC		SM 39:0;2O	SM
PC O-34:1	EtherPC		SM 39:1;2O SM 16:1;2O/23:0	SM
PC O-34:2	EtherPC		SM 39:2;2O SM 20:1;2O/19:1	SM
PC O-34:3	EtherPC		SM 39:4;3O	SM
PC O-35:1	EtherPC		SM 39:9;3O	SM
PC O-35:2	EtherPC		SM 40:0;2O	SM
PC O-35:3	EtherPC		SM 40:0;3O	SM
PC O-35:6	EtherPC		SM 40:1;2O	SM

Lipid Name	Class		Lipid Name	Class
PC O-35:8	EtherPC		SM 40:1;2O SM 16:1;2O/24:0	SM
PC O-36:0	EtherPC		SM 40:1;3O	SM
PC O-36:1	EtherPC		SM 40:2;2O SM 16:1;2O/24:1	SM
PC O-36:2	EtherPC		SM 40:2;3O	SM
PC O-36:3	EtherPC		SM 40:3;2O SM 16:1;2O/24:2	SM
PC O-36:4	EtherPC		SM 40:3;3O	SM
PC O-36:5	EtherPC		SM 40:6;3O	SM
PC O-36:6	EtherPC		SM 40:7;3O	SM
PC O-36:8 PC O-16:4_20:4	EtherPC		SM 40:8;2O	SM
PC O-37:0	EtherPC		SM 40:8;3O	SM
PC O-37:1	EtherPC		SM 40:9;2O	SM
PC O-37:10	EtherPC		SM 40:9;3O	SM
PC O-37:2	EtherPC		SM 41:1;2O SM 18:1;2O/23:0	SM
PC O-37:8	EtherPC		SM 41:1;3O	SM
PC O-37:9	EtherPC		SM 41:2;2O SM 17:1;2O/24:1	SM
PC O-38:0	EtherPC		SM 41:2;3O	SM
PC O-38:1	EtherPC		SM 41:3;2O SM 15:2;2O/26:1	SM
PC O-38:2	EtherPC		SM 41:3;3O	SM
PC O-38:3	EtherPC		SM 41:4;3O	SM
PC O-38:4	EtherPC		SM 41:7;3O	SM
PC O-38:5	EtherPC		SM 41:9;2O	SM
PC O-38:6	EtherPC		SM 41:9;2O SM 15:3;2O/26:6	SM
PC O-38:7	EtherPC		SM 42:0;2O	SM
PC O-38:8	EtherPC		SM 42:0;3O	SM
PC O-38:9	EtherPC		SM 42:1;2O SM 18:1;2O/24:0	SM
PC O-39:1	EtherPC		SM 42:1;3O	SM
PC O-39:10	EtherPC		SM 42:2;2O SM 18:1;2O/24:1	SM
PC O-39:3	EtherPC		SM 42:2;2O SM 25:1;2O/17:1	SM
PC O-39:4	EtherPC		SM 42:2;3O	SM
PC O-39:7	EtherPC		SM 42:3;2O SM 16:2;2O/26:1	SM
PC O-39:8	EtherPC		SM 42:3;2O SM 18:2;2O/24:1	SM
PC O-39:9	EtherPC		SM 42:3;3O	SM
PC O-40:1	EtherPC		SM 42:4;2O SM 18:2;2O/24:2	SM
PC O-40:11	EtherPC		SM 42:4;3O	SM
PC O-40:2	EtherPC		SM 42:5;2O SM 26:3;2O/16:2	SM
PC O-40:3	EtherPC		SM 42:6;3O	SM
PC O-40:4	EtherPC		SM 42:7;2O	SM
PC O-40:5	EtherPC		SM 42:8;3O	SM
PC O-40:6	EtherPC		SM 42:9;3O	SM
PC O-40:7	EtherPC		SM 43:0;2O	SM
PC O-40:8	EtherPC		SM 43:1;2O SM 18:1;2O/25:0	SM
PC O-40:9	EtherPC		SM 43:2;2O SM 19:1;2O/24:1	SM
PC O-41:10	EtherPC		SM 43:4;3O	SM
PC O-41:3	EtherPC		SM 43:5;3O	SM
PC O-41:4	EtherPC		SM 43:7;2O	SM
PC O-41:5	EtherPC		SM 44:1;2O	SM
PC O-41:8	EtherPC		SM 44:1;2O SM 18:1;2O/26:0	SM

Lipid Name	Class		Lipid Name	Class
PC O-41:9	EtherPC		SM 44:1;3O	SM
PC O-42:1	EtherPC		SM 44:2;2O SM 18:1;2O/26:1	SM
PC O-42:2	EtherPC		SM 44:3;2O SM 18:2;2O/26:1	SM
PC O-42:3	EtherPC		SM 44:3;3O	SM
PC O-42:4	EtherPC		SM 44:4;3O	SM
PC O-42:5	EtherPC		SM 45:2;3O	SM
PC O-42:6	EtherPC		SM 45:3;3O	SM
PC O-42:7	EtherPC		SM 45:4;3O	SM
PC O-43:10	EtherPC		SM 45:6;2O	SM
PC O-44:2	EtherPC		SM 46:3;2O	SM
PC O-44:3	EtherPC		SM 46:4;3O	SM
PC O-44:4	EtherPC		SM 46:8;3O	SM
PC O-44:5	EtherPC		SM 46:9;3O	SM
PC O-44:6	EtherPC		SM 47:1;3O	SM
PC O-44:7	EtherPC		SM 47:2;3O	SM
PC O-44:8	EtherPC		SM 47:4;2O	SM
PC O-46:10	EtherPC		SM 48:8;2O	SM
PC O-46:5	EtherPC		SM 48:8;3O	SM
PC O-46:6	EtherPC		SM 49:9;2O	SM
PC O-46:7	EtherPC		SM 50:9;3O	SM
PC O-46:8	EtherPC		SM 51:9;3O	SM
PC O-46:9	EtherPC		SM 58:3;3O	SM
PC O-48:10	EtherPC		SM 60:3;3O	SM
PC O-48:9	EtherPC		ST 27:0;O	ST
PC O-50:9	EtherPC		ST 27:1;O	ST
PE 19:1	PE		ST 27:1;O;S	SSulfate
PE 23:4	PE		ST 28:1;O;S	SSulfate
PE 30:0 PE 14:0 16:0	PE		TG 38:0;1O TG 9:0 19:0 10:0;1O	OxTG
PE 32:0 PE 16:0 16:0	PE		TG 38:1;1O TG 10:0 19:1 9:0;1O	OxTG
PE 32:1 PE 16:0 16:1	PE		TG 49:3;3O TG 15:0 18:2 16:1;3O	OxTG
PE 32:2 PE 14:0 18:2	PE		TG 50:3 TG 16:0 16:1 18:2	TG
PE 33:1 PE 15:0 18:1	PE		TG 50:4 TG 16:1 16:1 18:2	TG
PE 34:0 PE 16:0 18:0	PE		TG 52:2;1O TG 16:0 18:1 18:1;1O	OxTG
PE 34:1 PE 16:0 18:1	PE		TG 52:2 TG 16:0 18:1 18:1	TG
PE 34:2 PE 16:0 18:2	PE		TG 52:3;1O TG 16:0 18:1 18:2;1O	OxTG
PE 34:3 PE 16:0 18:3	PE		TG 52:3 TG 16:0 18:1 18:2	TG
PE 34:3 PE 16:1 18:2	PE		TG 52:4;1O TG 16:0 18:2 18:2;1O	OxTG
PE 34:4 PE 14:0 20:4	PE		TG 52:4;2O TG 16:0 18:3 18:1;2O	OxTG
PE 35:1 PE 17:0 18:1	PE		TG 52:4 TG 16:0 18:2 18:2	TG
PE 35:2 PE 17:0 18:2	PE		TG 52:5 TG 16:1 18:2 18:2	TG
PE 35:4 PE 15:0 20:4	PE		TG 52:6 TG 14:0 16:0 22:6	TG
PE 36:0 PE 18:0 18:0	PE		TG 52:6 TG 16:1 18:2 18:3	TG
PE 36:1;2O PE 18:1 18:0;2O	OxPE		TG 54:4 TG 18:1 18:1 18:2	TG
PE 36:1;3O PE 18:1 18:0;3O	OxPE		TG 54:5 TG 18:1 18:2 18:2	TG
PE 36:1 PE 18:0 18:1	PE		TG 54:6 TG 18:2 18:2 18:2	TG
PE 36:2;2O PE 18:2 18:0;2O	OxPE		TG 54:7 TG 18:2 18:2 18:3	TG
PE 36:2;O PE 18:1 18:1;O	OxPE		TG 54:8 TG 14:0 18:2 22:6	TG

Lipid Name	Class		Lipid Name	Class
PE 36:2 PE 18:1_18:1	PE		TG 56:4 TG 18:1_20:1_18:2	TG
PE 36:3 PE 18:1_18:2	PE		TG 56:5 TG 18:0_18:1_20:4	TG
PE 36:4 PE 16:0_20:4	PE		TG 56:6 TG 18:1_18:1_20:4	TG
PE 36:4 PE 18:2_18:2	PE		TG 56:7;1O TG 16:0_18:1_22:6;1O	OxTG
PE 36:5 PE 16:0_20:5	PE		TG 56:7 TG 16:0_18:1_22:6	TG
PE 36:5 PE 16:1_20:4	PE		TG 56:8;1O TG 16:0_18:2_22:6;1O	OxTG
PE 36:5 PE 18:2_18:3	PE		TG 56:8 TG 16:0_18:2_22:6	TG
PE 37:4 PE 17:0_20:4	PE		TG 56:9 TG 16:1_18:2_22:6	TG
PE 37:5;2O PE 20:4_17:1;2O	OxPE		TG 58:10 TG 18:2_20:4_20:4	TG
PE 38:1 PE 18:0_20:1	PE		TG 58:11 TG 18:2_18:3_22:6	TG
PE 38:2 PE 18:0_20:2	PE		TG 58:11 TG 18:2_20:4_20:5	TG
PE 38:2 PE 18:1_20:1	PE		TG 58:6 TG 16:0_18:1_24:5	TG
PE 38:3	PE		TG 58:7 TG 16:0_18:1_24:6	TG
PE 38:3;2O PE 20:3_18:0;2O	OxPE		TG 58:7 TG 18:1_18:1_22:5	TG
PE 38:3 PE 18:0_20:3	PE		TG 58:8 TG 18:1_18:1_22:6	TG
PE 38:3 PE 18:1_20:2	PE		TG 58:9;1O TG 18:1_18:2_22:6;1O	OxTG
PE 38:4	PE		TG 58:9 TG 18:1_18:2_22:6	TG
PE 38:4;2O PE 20:4_18:0;2O	OxPE		TG 60:10;4O TG 19:2_19:2_22:6;4O	OxTG
PE 38:4 PE 16:0_22:4	PE		TG 60:10 TG 18:0_20:4_22:6	TG
PE 38:4 PE 18:0_20:4	PE		TG 60:11 TG 18:1_20:4_22:6	TG
PE 38:4 PE 18:1_20:3	PE		TG 60:12 TG 16:0_22:6_22:6	TG
PE 38:5	PE		TG 60:13 TG 18:2_20:5_22:6	TG
PE 38:5;O PE 20:4_18:1;O	OxPE		TG 60:8 TG 18:1_20:3_22:4	TG
PE 38:5 PE 18:1_20:4	PE		TG 60:9 TG 18:0_20:4_22:5	TG
PE 38:6	PE		TG 62:11 TG 18:1_22:4_22:6	TG
PE 38:6 PE 16:0_22:6	PE		TG 62:12 TG 18:1_22:5_22:6	TG
PE 38:6 PE 18:2_20:4	PE		TG 62:13 TG 18:1_22:6_22:6	TG
PE 38:7	PE		VAE 25:1	VAE
PE 38:7 PE 16:1_22:6	PE			

Table J. Metabolites and lipids identified in both oral fluid and whole blood.

Metabolite and Lipid Name	Class		Metabolite and Lipid Name	Class
1-Methylguanine	Purines and derivatives		PC O-38:2	EtherPC
2-Piperidinone	Piperidinones		PC O-38:3	EtherPC
3-Indolepropionic acid	Indoles and derivatives		PC O-38:4	EtherPC
4-Hydroxybenzoic acid	Benzoic acids and derivatives		PC O-38:5	EtherPC
6-Hydroxypurine	Purines and derivatives		PC O-38:6	EtherPC
7-Methylxanthine	Purines and derivatives		PC O-39:10	EtherPC
Adenine	Purines and derivatives		PC O-40:1	EtherPC
Adenosine	Purine nucleotides		PC O-40:3	EtherPC
Alpha-ketoisovaleric acid	Keto acids and derivatives		PC O-40:5	EtherPC
Capric acid	Fatty acids and conjugates		PC O-40:6	EtherPC
Cholesterol sulfate	Steroids		PC O-40:7	EtherPC
Creatine	Amino acids and derivatives		PC O-42:3	EtherPC
Creatinine	Amino acids and derivatives		PC O-42:4	EtherPC
Inosine	Purines and derivatives		PC O-42:5	EtherPC

Metabolite and Lipid Name	Class	Metabolite and Lipid Name	Class
L-Acetylcarnitine	Fatty acid esters	PC O-42:6	EtherPC
L-Carnitine	Organonitrogen compounds	PC O-44:5	EtherPC
Leucinic acid	Fatty acids and conjugates	PC O-44:6	EtherPC
L-Isoleucine	Amino acids and derivatives	PE 30:0 PE 14:0_16:0	PE
L-Leucine	Amino acids and derivatives	PE 32:0 PE 16:0_16:0	PE
L-Methionine	Amino acids and derivatives	PE 32:1 PE 16:0_16:1	PE
L-Phenylalanine	Amino acids and derivatives	PE 33:1 PE 15:0_18:1	PE
L-Proline	Amino acids and derivatives	PE 34:0 PE 16:0_18:0	PE
L-Tryptophan	Amino acids and derivatives	PE 34:1 PE 16:0_18:1	PE
L-Tyrosine	Amino acids and derivatives	PE 34:2 PE 16:0_18:2	PE
L-Valine	Amino acids and derivatives	PE 34:3 PE 16:0_18:3	PE
N-Acetyl-L-phenylalanine	Amino acids and derivatives	PE 34:3 PE 16:1_18:2	PE
Niacinamide	Pyridines and derivatives	PE 35:1 PE 17:0_18:1	PE
N-Methylnicotinamide	Pyridines and derivatives	PE 36:1;2O PE 18:1_18:0;2O	OxPE
Pyrrolidonecarboxylic acid	Amino acids and derivatives	PE 36:1 PE 18:0_18:1	PE
Sphinganine	Organonitrogen compounds	PE 36:2 PE 18:1_18:1	PE
Succinylacetone	Keto acids and derivatives	PE 36:3 PE 18:1_18:2	PE
Taurine	Sulfate and sulfonates	PE 36:4 PE 16:0_20:4	PE
Trigonelline	Alkaloids and derivatives	PE 36:4 PE 18:2_18:2	PE
Uridine	Pyrimidine nucleotides	PE 38:1 PE 18:0_20:1	PE
Urea	Ureas	PE 38:2 PE 18:1_20:1	PE
BA 24:1;O4;G;S	BASulfate	PE 38:3 PE 18:0_20:3	PE
CAR 11:0	CAR	PE 38:4	PE
CAR 16:0	CAR	PE 38:4 PE 18:0_20:4	PE
CE 18:2	CE	PE 38:4 PE 18:1_20:3	PE
CE 18:3	CE	PE 38:5 PE 18:1_20:4	PE
CE 20:3	CE	PE 38:6 PE 16:0_22:6	PE
CE 20:4	CE	PE 39:5;O PE 22:4_17:1;O	OxPE
CE 20:5	CE	PE 40:4 PE 18:0_22:4	PE
CE 22:6	CE	PE 40:5 PE 18:1_22:4	PE
Cer 34:1;2O Cer 18:1;2O/16:0	Cer_NS	PE 40:6 PE 18:1_22:5	PE
Cer 35:1;4O Cer 18:0;3O/17:1;(2OH)	Cer_AP	PE O-32:1 PE O-16:1_16:0	EtherPE
Cer 37:1;4O Cer 20:0;3O/17:1;(2OH)	Cer_AP	PE O-34:1 PE O-18:1_16:0	EtherPE
Cer 42:1;2O Cer 18:1;2O/24:0	Cer_NS	PE O-34:2 PE O-16:1_18:1	EtherPE
Cer 42:2;2O Cer 18:1;2O/24:1	Cer_NS	PE O-34:3 PE O-16:1_18:2	EtherPE
Cer 42:3;2O Cer 18:1;2O/24:2	Cer_NS	PE O-35:2 PE O-17:1_18:1	EtherPE
DG 38:4 DG 18:0_20:4	DG	PE O-36:2 PE O-18:1_18:1	EtherPE
DGGA 36:2 DGGA 18:1_18:1	DGGA	PE O-36:3 PE O-18:2_18:1	EtherPE
FA 18:2	FA	PE O-36:4 PE O-16:1_20:3	EtherPE
FA 18:3	FA	PE O-36:5 PE O-16:1_20:4	EtherPE
FA 20:3	FA	PE O-36:6 PE O-16:1_20:5	EtherPE
FA 20:4	FA	PE O-37:5 PE O-17:1_20:4	EtherPE
FA 20:5	FA	PE O-38:5 PE O-16:1_22:4	EtherPE
FA 22:4	FA	PE O-38:5 PE O-18:1_20:4	EtherPE
FA 22:5	FA	PE O-38:6 PE O-18:2_20:4	EtherPE
FA 22:6	FA	PE O-38:7 PE O-16:1_22:6	EtherPE
Hex2Cer 33:1;2O Hex2Cer 17:1;2O/16:0	Hex2Cer	PE O-38:7 PE O-18:2_20:5	EtherPE

Metabolite and Lipid Name	Class	Metabolite and Lipid Name	Class
Hex2Cer 34:1;2O	Hex2Cer	PE O-39:7 PE O-17:1_22:6	EtherPE
Hex2Cer 34:1;2O Hex2Cer 18:1;2O/16:0	Hex2Cer	PE O-40:2 PE O-22:1_18:1	EtherPE
Hex2Cer 40:1;2O Hex2Cer 18:1;2O/22:0	Hex2Cer	PE O-40:4 PE O-22:2_18:2	EtherPE
Hex2Cer 42:1;2O Hex2Cer 18:1;2O/24:0	Hex2Cer	PE O-40:5 PE O-18:1_22:4	EtherPE
Hex2Cer 42:2;2O Hex2Cer 18:1;2O/24:1	Hex2Cer	PE O-40:7 PE O-18:1_22:6	EtherPE
Hex2Cer 42:3;2O Hex2Cer 18:1;2O/24:2	Hex2Cer	PE O-40:8 PE O-18:2_22:6	EtherPE
Hex2Cer 44:2;2O Hex2Cer 18:1;2O/26:1	Hex2Cer	PE O-42:3 PE O-24:2_18:1	EtherPE
HexCer 43:2;4O	HexCer_AP	PE O-42:4 PE O-24:2_18:2	EtherPE
LPC 16:0	LPC	PE O-42:6 PE O-22:2_20:4	EtherPE
LPC 16:0/0:0	LPC	PE O-42:7 PE O-20:1_22:6	EtherPE
LPC 16:1/0:0	LPC	PE O-42:7 PE O-22:3_20:4	EtherPE
LPC 17:0/0:0	LPC	PE O-42:8 PE O-20:2_22:6	EtherPE
LPC 18:0	LPC	PE O-44:6 PE O-24:2_20:4	EtherPE
LPC 18:0/0:0	LPC	PE O-44:8 PE O-22:2_22:6	EtherPE
LPC 18:1	LPC	PE O-46:8 PE O-24:2_22:6	EtherPE
LPC 18:1/0:0	LPC	PE P-34:1 PE P-16:0_18:1	EtherPE
LPC 18:2	LPC	PE P-34:2 PE P-16:0_18:2	EtherPE
LPC 20:1	LPC	PE P-36:1 PE P-18:0_18:1	EtherPE
LPC 20:1/0:0	LPC	PE P-36:3 PE P-18:1_18:2	EtherPE
LPC 20:4	LPC	PE P-36:4 PE P-16:0_20:4	EtherPE
LPC O-16:0	EtherLPC	PE P-38:2 PE P-20:1_18:1	EtherPE
LPC O-16:1	EtherLPC	PE P-38:4 PE P-16:0_22:4	EtherPE
LPC O-18:0	EtherLPC	PE P-38:4 PE P-16:1_22:3	EtherPE
LPC O-18:1	EtherLPC	PE P-38:5 PE P-18:1_20:4	EtherPE
LPE 16:0	LPE	PE P-38:6 PE P-16:0_22:6	EtherPE
LPE 18:0	LPE	PE P-40:4 PE P-18:0_22:4	EtherPE
LPE 18:1	LPE	PE P-40:5 PE P-18:0_22:5	EtherPE
LPE 18:2	LPE	PE P-40:6 PE P-18:0_22:6	EtherPE
LPE 20:4	LPE	PE P-40:6 PE P-18:1_22:5	EtherPE
LPE 22:6	LPE	PE P-40:7 PE P-18:1_22:6	EtherPE
LPE O-16:1	EtherLPE	PE P-42:3 PE P-24:1_18:2	EtherPE
LPE O-18:1	EtherLPE	PE P-42:4 PE P-22:0_20:4	EtherPE
LPE O-18:2	EtherLPE	PE P-42:5 PE P-22:1_20:4	EtherPE
LPE-N (FA)36:1 LPE-N (FA 18:0)18:1	LNAPE	PE P-44:5 PE P-24:1_20:4	EtherPE
LPS 18:0	LPS	PE P-44:6 PE P-24:2_20:4	EtherPE
PC 28:0 PC 14:0_14:0	PC	PI 34:2	PI
PC 29:0	PC	PI 36:1 PI 18:0_18:1	PI
PC 31:0 PC 15:0_16:0	PC	PI 36:2 PI 18:0_18:2	PI
PC 32:0 PC 16:0_16:0	PC	PI 38:3 PI 18:0_20:3	PI
PC 32:1 PC 16:0_16:1	PC	PI 38:4	PI
PC 33:0 PC 16:0_17:0	PC	PI 38:4 PI 18:0_20:4	PI
PC 33:2 PC 15:0_18:2	PC	PI-Cer 40:1;2O	PI_Cer
PC 34:0 PC 16:0_18:0	PC	PS 34:1 PS 16:0_18:1	PS
PC 34:1 PC 16:0_18:1	PC	PS 36:1 PS 18:0_18:1	PS
PC 34:2 PC 16:0_18:2	PC	PS 36:2 PS 18:1_18:1	PS
PC 34:3 PC 16:0_18:3	PC	PS 40:6 PS 18:0_22:6	PS
PC 34:3 PC 16:1_18:2	PC	PS O-37:1 PS O-19:0_18:1	EtherPS

Metabolite and Lipid Name	Class	Metabolite and Lipid Name	Class
PC 35:1 PC 17:0_18:1	PC	PS O-37:2 PS O-19:0_18:2	EtherPS
PC 35:2 PC 17:0_18:2	PC	PS O-41:4 PS O-19:0_22:4	EtherPS
PC 35:3	PC	SHexCer 38:3;3O	SHexCer
PC 36:0 PC 18:0_18:0	PC	SHexCer 40:0;2O	SHexCer
PC 36:1 PC 18:0_18:1	PC	SM 32:1;3O	SM
PC 36:2 PC 18:1_18:1	PC	SM 33:0;2O SM 19:0;2O/14:0	SM
PC 36:3 PC 18:1_18:2	PC	SM 34:0;3O	SM
PC 36:4 PC 16:0_20:4	PC	SM 34:1;2O SM 18:1;2O/16:0	SM
PC 36:4 PC 18:2_18:2	PC	SM 34:1;3O	SM
PC 36:5 PC 16:0_20:5	PC	SM 34:2;2O SM 18:2;2O/16:0	SM
PC 36:5 PC 18:2_18:3	PC	SM 35:3;3O	SM
PC 38:1	PC	SM 36:1;2O SM 18:1;2O/18:0	SM
PC 38:4 PC 18:0_20:4	PC	SM 36:1;3O	SM
PC 38:5 PC 18:1_20:4	PC	SM 40:0;2O	SM
PC 38:6 PC 16:0_22:6	PC	SM 40:0;3O	SM
PC 38:6 PC 18:2_20:4	PC	SM 40:1;3O	SM
PC 40:8	PC	SM 42:0;2O	SM
PC O-30:0	EtherPC	SM 42:0;3O	SM
PC O-30:1	EtherPC	SM 42:1;2O SM 18:1;2O/24:0	SM
PC O-31:0	EtherPC	SM 42:1;3O	SM
PC O-31:1	EtherPC	SM 42:2;2O SM 18:1;2O/24:1	SM
PC O-32:0	EtherPC	SM 43:0;2O	SM
PC O-32:1	EtherPC	SM 43:1;2O SM 18:1;2O/25:0	SM
PC O-33:0	EtherPC	SM 43:4;3O	SM
PC O-34:0	EtherPC	SM 44:1;3O	SM
PC O-34:1	EtherPC	ST 27:1;O	ST
PC O-34:2	EtherPC	ST 27:1;O;S	SSulfate
PC O-34:3	EtherPC	TG 52:2;1O TG 16:0_18:1_18:1;1O	OxTG
PC O-36:0	EtherPC	TG 52:3;1O TG 16:0_18:1_18:2;1O	OxTG
PC O-36:1	EtherPC	TG 52:3 TG 16:0_18:1_18:2	TG
PC O-36:2	EtherPC	TG 52:4 TG 16:0_18:2_18:2	TG
PC O-36:3	EtherPC	TG 54:4 TG 18:1_18:1_18:2	TG
PC O-36:4	EtherPC	TG 54:5 TG 18:1_18:2_18:2	TG
PC O-36:5	EtherPC	TG 54:6 TG 18:2_18:2_18:2	TG
PC O-37:10	EtherPC	TG 54:7 TG 18:2_18:2_18:3	TG
PC O-37:8	EtherPC	TG 58:8 TG 18:1_18:1_22:6	TG
PC O-38:0	EtherPC	TG 58:9 TG 18:1_18:2_22:6	TG
PC O-38:1	EtherPC	VAE 25:1	VAE

Table K. Salivary metabolites and lipids identified in samples used for physiological and pathological phase of the study.

Metabolite and Lipid name	Class	Metabolite and Lipid Name	Class
9-Trans-Palmitelaidic acid	Long-chain fatty acids	PC 40:6 PC 20:3_20:3	PC
Adenosine	Purine nucleosides	PC 42:0	PC
Ala-Leu	Peptides	PC 42:0 PC 15:0_27:0	PC
cyclo(tyrosyl-prolyl)	Alpha amino acids	PC 42:5	PC
PC 36:2	PC	PC 43:9	PC

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
PC 36:3	PC		PC 44:2	PC
PC 36:4	PC		PC O-29:1	EtherPC
2'-O-Methyladenosine	Purine nucleosides		PC O-31:0	EtherPC
5-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanoic acid	Biotin and derivatives		PC O-31:1	EtherPC
5'-Deoxy-5'-Methylthioadenosine	5'-deoxy-5'-thionucleosides		PC O-31:6	EtherPC
CORTISOL	21-hydroxysteroids		PC O-33:2	EtherPC
Decaethylene glycol	Polyethylene glycols		PC O-33:3	EtherPC
Isopentenyladenine	6-alkylaminopurines		PC O-34:2;1O PC O-17:0_17:2;1O	EtherOxPC
LPC 18:1	LPC		PC O-35:3	EtherPC
LPC 18:2	LPC		PC O-36:7	EtherPC
LysoPC(0:0/18:0)	LPC		PC O-37:1 PC O-19:0_18:1	EtherPC
N-ACETYLGLUCOSAMINE	N-acyl-alpha-hexosamines		PC O-37:10	EtherPC
Palmitoylcarnitine cation	Acyl carnitines		PC O-37:3	EtherPC
Stearoyl-L-Carnitine	Acyl carnitines		PC O-38:8	EtherPC
Thymidine	Pyrimidine 2'-deoxyribonucleosides		PC O-40:7	EtherPC
AAHFA 18:0;O AAHFA 7:0/11:0;O	FAHFA		PC O-40:8	EtherPC
AAHFA 20:0;O AAHFA 11:0/9:0;O	FAHFA		PC O-42:4	EtherPC
BMP 36:2 BMP 18:1_18:1	BMP		PC O-42:5	EtherPC
CAR 20:0	CAR		PC O-44:6	EtherPC
CE 18:2	CE		PE 14:0 PE 7:0_7:0	PE
Cer 24:2;4O Cer 15:2;3O/9:0;(2OH)	Cer_AP		PE 28:0 PE 13:0_15:0	PE
Cer 27:2;2O Cer 13:2;2O/14:0	Cer_NS		PE 29:0 PE 13:0_16:0	PE
Cer 31:4;4O	Cer_AP		PE 30:0 PE 14:0_16:0	PE
Cer 32:1;2O Cer 18:1;2O/14:0	Cer_NS		PE 30:0 PE 15:0_15:0	PE
Cer 32:7;4O Cer 12:2;3O/20:5;(2OH)	Cer_AP		PE 31:0 PE 15:0_16:0	PE
Cer 32:7;4O Cer 14:2;3O/18:5;(2OH)	Cer_AP		PE 31:1 PE 15:0_16:1	PE
Cer 33:1;4O Cer 18:0;3O/15:1;(2OH)	Cer_AP		PE 31:2 PE 13:0_18:2	PE
Cer 34:0;3O Cer 17:0;2O/17:0;O	Cer_HDS		PE 32:0 PE 15:0_17:0	PE
Cer 34:0;4O Cer 18:0;3O/16:0;(2OH)	Cer_AP		PE 32:1 PE 16:0_16:1	PE
Cer 34:1;2O Cer 18:1;2O/16:0	Cer_NS		PE 32:2 PE 16:1_16:1	PE
Cer 34:2;2O Cer 18:2;2O/16:0	Cer_NS		PE 33:1 PE 15:0_18:1	PE
Cer 34:2;3O Cer 18:2;2O/16:0;O	Cer_HS		PE 33:2 PE 15:0_18:2	PE
Cer 35:1;2O Cer 18:1;2O/17:0	Cer_NS		PE 34:0;2O PE 16:0_18:0;2O	OxPE
Cer 35:1;4O Cer 20:0;3O/15:1;(2OH)	Cer_AP		PE 34:0 PE 16:0_18:0	PE
Cer 36:0;4O Cer 18:0;3O/18:0;(2OH)	Cer_AP		PE 34:1 PE 16:0_18:1	PE
Cer 36:1;2O Cer 18:1;2O/18:0	Cer_NS		PE 34:2;O PE 16:1_18:1;O	OxPE
Cer 36:5;4O	Cer_AP		PE 34:2 PE 16:0_18:2	PE
Cer 36:5;4O Cer 18:0;3O/18:5;(2OH)	Cer_AP		PE 34:2 PE 16:1_18:1	PE
Cer 37:1;4O Cer 20:0;3O/17:1;(2OH)	Cer_AP		PE 34:3 PE 16:0_18:3	PE
Cer 38:0;2O Cer 18:0;2O/20:0	Cer_NDS		PE 34:3 PE 16:1_18:2	PE
Cer 38:0;4O	Cer_AP		PE 35:1 PE 17:0_18:1	PE
Cer 38:1;2O Cer 18:1;2O/20:0	Cer_NS		PE 35:2 PE 17:0_18:2	PE
Cer 39:1;4O Cer 22:0;3O/17:1;(2OH)	Cer_AP		PE 35:2 PE 17:1_18:1	PE
Cer 40:0;2O Cer 18:0;2O/22:0	Cer_NDS		PE 35:3 PE 15:0_20:3	PE
Cer 40:1;3O Cer 19:0;2O/21:1;O	Cer_HDS		PE 35:4 PE 15:0_20:4	PE

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
Cer 40:1;4O Cer 18:1;3O/22:0;(2OH)	Cer_AP		PE 36:0;O PE 18:0_18:0;O	OxPE
Cer 41:0;2O Cer 18:0;2O/23:0	Cer_NDS		PE 36:1;2O PE 18:1_18:0;2O	OxPE
Cer 41:1;4O Cer 22:0;3O/19:1;(2OH)	Cer_AP		PE 36:1;O PE 18:1_18:0;O	OxPE
Cer 42:0;2O Cer 18:0;2O/24:0	Cer_NDS		PE 36:1 PE 18:0_18:1	PE
Cer 42:1;2O Cer 18:1;2O/24:0	Cer_NS		PE 36:2 PE 18:1_18:1	PE
Cer 42:1;3O Cer 18:1;2O/24:0;O	Cer_HS		PE 36:3	PE
Cer 42:1;4O Cer 18:0;3O/24:1;(2OH)	Cer_AP		PE 36:3 PE 18:1_18:2	PE
Cer 42:1;4O Cer 18:1;3O/24:0;(2OH)	Cer_AP		PE 36:4 PE 16:0_20:4	PE
Cer 42:2;2O Cer 18:1;2O/24:1	Cer_NS		PE 36:4 PE 18:1_18:3	PE
Cer 42:8;3O Cer 18:2;2O/24:6;O	Cer_HS		PE 36:4 PE 18:2_18:2	PE
Cer 43:0;3O Cer 18:0;2O/25:0;O	Cer_HDS		PE 36:5 PE 16:0_20:5	PE
Cer 43:0;4O Cer 18:0;3O/25:0;(2OH)	Cer_AP		PE 37:4;O PE 20:3_17:1;O	OxPE
Cer 43:1;4O Cer 18:0;3O/25:1;(2OH)	Cer_AP		PE 37:4 PE 17:0_20:4	PE
Cer 43:1;4O Cer 26:1;3O/17:0;(2OH)	Cer_AP		PE 38:1 PE 18:0_20:1	PE
Cer 43:2;4O Cer 26:1;3O/17:1;(2OH)	Cer_AP		PE 38:2	PE
Cer 43:3;4O Cer 23:3;3O/20:0;(2OH)	Cer_AP		PE 38:3;2O PE 20:3_18:0;2O	OxPE
Cer 43:5;4O	Cer_AP		PE 38:3 PE 18:0_20:3	PE
Cer 44:0;4O Cer 18:0;3O/26:0;(2OH)	Cer_AP		PE 38:4 PE 18:0_20:4	PE
Cer 44:0;4O Cer 20:0;3O/24:0;(2OH)	Cer_AP		PE 38:5;O PE 18:2_20:3;O	OxPE
Cer 44:1;4O Cer 18:0;3O/26:1;(2OH)	Cer_AP		PE 38:5 PE 18:1_20:4	PE
Cer 44:2;3O Cer 18:1;2O/26:1;O	Cer_HS		PE 38:6 PE 18:2_20:4	PE
Cer 44:2;4O Cer 27:1;3O/17:1;(2OH)	Cer_AP		PE 39:5;O PE 22:4_17:1;O	OxPE
Cer 45:0;4O Cer 21:0;3O/24:0;(2OH)	Cer_AP		PE 39:7;O PE 22:6_17:1;O	OxPE
Cer 45:1;3O Cer 21:0;2O/24:1;O	Cer_HDS		PE 40:0 PE 20:0_20:0	PE
Cer 45:2;4O Cer 28:1;3O/17:1;(2OH)	Cer_AP		PE 40:1 PE 22:0_18:1	PE
Cer 46:0;4O Cer 18:0;3O/28:0;(2OH)	Cer_AP		PE 40:4	PE
Cer 46:1;4O Cer 18:1;3O/28:0;(2OH)	Cer_AP		PE 40:4 PE 18:0_22:4	PE
Cer 46:3;2O Cer 18:1;2O/28:2	Cer_NS		PE 40:5 PE 18:1_22:4	PE
Cer 47:9;4O Cer 21:3;3O/26:6;(2OH)	Cer_AP		PE 40:6;O PE 20:3_20:3;O	OxPE
Cer 48:1;4O Cer 18:0;3O/30:1;(2OH)	Cer_AP		PE 40:6 PE 18:0_22:6	PE
Cer 49:2;3O Cer 18:1;2O/31:1;O	Cer_HS		PE 40:6 PE 18:1_22:5	PE
Cer 50:0;4O Cer 20:0;3O/30:0;(2OH)	Cer_AP		PE 40:7 PE 18:1_22:6	PE
Cer 50:1;3O Cer 18:0;2O/32:1;O	Cer_HDS		PE 42:0 PE 20:0_22:0	PE
Cer 50:1;3O Cer 18:1;2O/32:0;O	Cer_HS		PE 42:1	PE
Cer 50:1;4O Cer 18:0;3O/32:1;(2OH)	Cer_AP		PE 42:2 PE 18:1_24:1	PE
Cer 52:1;4O Cer 18:0;3O/34:1;(2OH)	Cer_AP		PE 42:7 PE 20:3_22:4	PE
Cer 65:7;4O	Cer_AP		PE 44:0 PE 22:0_22:0	PE
CL 54:0 CL 12:0_14:0_14:0_14:0	CL		PE 44:2 PE 20:1_24:1	PE
CL 66:5 CL 14:0_14:0_19:0_19:5	CL		PE 46:2;O PE 18:2_28:0;O	OxPE
CL 68:2 CL 34:1_34:1	CL		PE 52:2 PE 18:1_34:1	PE
CL 68:3 CL 17:0_17:0_16:1_18:2	CL		PE O-29:1 PE O-15:1_14:0	EtherPE
CL 68:5 CL 15:0_15:0_18:0_20:5	CL		PE O-30:1 PE O-15:1_15:0	EtherPE
CL 72:0 CL 15:0_16:0_16:0_25:0	CL		PE O-31:1 PE O-15:1_16:0	EtherPE
CL 72:1 CL 18:0_18:0_18:0_18:1	CL		PE O-31:3 PE O-16:2_15:1	EtherPE
CL 72:8 CL 36:4_36:4	CL		PE O-32:1 PE O-16:1_16:0	EtherPE
CL 73:2 CL 17:0_24:0_16:1_16:1	CL		PE O-32:2 PE O-16:1_16:1	EtherPE
CL 74:1 CL 16:0_16:0_26:0_16:1	CL		PE O-33:1 PE O-16:1_17:0	EtherPE

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
CL 74:8 CL 18:1_18:1_18:1_20:5	CL		PE O-33:2 PE O-17:1_16:1	EtherPE
CL 76:7 CL 18:1_18:1_18:1_22:4	CL		PE O-33:3 PE O-16:2_17:1	EtherPE
CL 76:8 CL 16:0_18:1_22:3_20:4	CL		PE O-34:1 PE O-16:0_18:1	EtherPE
CL 77:2 CL 15:0_26:0_18:1_18:1	CL		PE O-34:1 PE O-18:1_16:0	EtherPE
CL 77:4 CL 16:0_24:0_18:1_19:3	CL		PE O-34:2 PE O-16:1_18:1	EtherPE
CL 77:5 CL 15:0_28:0_16:1_18:4	CL		PE O-34:3 PE O-16:1_18:2	EtherPE
CL 78:0 CL 16:0_18:0_18:0_26:0	CL		PE O-35:2 PE O-17:1_18:1	EtherPE
CL 78:3 CL 24:0_18:1_18:1_18:1	CL		PE O-35:3 PE O-17:1_18:2	EtherPE
CL 78:5 CL 24:0_18:1_18:2_18:2	CL		PE O-35:4 PE O-17:2_18:2	EtherPE
CL 80:1 CL 18:0_18:0_26:0_18:1	CL		PE O-36:1 PE O-18:0_18:1	EtherPE
CL 80:2 CL 16:0_28:0_18:1_18:1	CL		PE O-36:2 PE O-18:0_18:2	EtherPE
CL 80:4 CL 28:0_16:1_18:1_18:2	CL		PE O-36:2 PE O-18:1_18:1	EtherPE
CL 82:12 CL 20:3_20:3_20:3_22:3	CL		PE O-36:3 PE O-18:0_18:3	EtherPE
CL 84:12 CL 24:0_20:4_20:4_20:4	CL		PE O-36:3 PE O-18:2_18:1	EtherPE
CL 84:4 CL 18:0_28:0_18:1_20:3	CL		PE O-36:4 PE O-16:1_20:3	EtherPE
CL 85:10 CL 28:0_17:2_20:4_20:4	CL		PE O-36:5 PE O-16:1_20:4	EtherPE
CL 85:4 CL 17:0_18:0_28:0_22:4	CL		PE O-37:2 PE O-19:1_18:1	EtherPE
CL 86:12 CL 26:0_20:4_20:4_20:4	CL		PE O-37:5 PE O-17:1_20:4	EtherPE
CL 90:1 CL 24:0_24:0_24:0_18:1	CL		PE O-38:2 PE O-20:1_18:1	EtherPE
CL 90:14 CL 28:0_18:2_22:6_22:6	CL		PE O-38:3 PE O-18:0_20:3	EtherPE
CL 93:2 CL 24:0_24:0_27:0_18:2	CL		PE O-38:3 PE O-20:2_18:1	EtherPE
CL 94:1 CL 26:0_26:0_26:0_16:1	CL		PE O-38:4 PE O-18:1_20:3	EtherPE
CL 98:1 CL 28:0_28:0_28:0_14:1	CL		PE O-38:5 PE O-18:1_20:4	EtherPE
DG 24:0 DG 12:0_12:0	DG		PE O-38:6 PE O-18:2_20:4	EtherPE
DG 32:0 DG 15:0_17:0	DG		PE O-38:7 PE O-16:1_22:6	EtherPE
DG 32:1 DG 14:0_18:1	DG		PE O-39:5 PE O-19:1_20:4	EtherPE
DG 33:1 DG 15:0_18:1	DG		PE O-39:6 PE O-21:4_18:2	EtherPE
DG 37:0 DG 15:0_22:0	DG		PE O-39:7 PE O-17:1_22:6	EtherPE
DG 43:2 DG 18:1_25:1	DG		PE O-40:2 PE O-22:0_18:2	EtherPE
DG 50:1 DG 32:0_18:1	DG		PE O-40:3 PE O-22:2_18:1	EtherPE
DG 50:3 DG 16:1_34:2	DG		PE O-40:4 PE O-22:2_18:2	EtherPE
DG 52:2 DG 16:1_36:1	DG		PE O-40:5 PE O-18:1_22:4	EtherPE
FA 15:2	FA		PE O-40:5 PE O-20:1_20:4	EtherPE
FA 15:3	FA		PE O-40:6 PE O-20:2_20:4	EtherPE
FA 16:0;3O	OxFA		PE O-40:7 PE O-18:1_22:6	EtherPE
FA 16:2;3O	OxFA		PE O-40:7 PE O-18:2_22:5	EtherPE
FA 17:0;(2OH)	OxFA		PE O-40:8 PE O-18:2_22:6	EtherPE
FA 18:0;2O	OxFA		PE O-42:3 PE O-24:2_18:1	EtherPE
FA 18:0;3O	OxFA		PE O-42:4 PE O-24:2_18:2	EtherPE
FA 18:1	FA		PE O-42:5 PE O-24:3_18:2	EtherPE
FA 18:1;3O	OxFA		PE O-42:6 PE O-22:2_20:4	EtherPE
FA 18:1;O	OxFA		PE O-44:6 PE O-24:2_20:4	EtherPE
FA 18:2	FA		PE O-46:6 PE O-24:2_22:4	EtherPE
FA 18:2;3O	OxFA		PE P-31:0 PE P-16:0_15:0	EtherPE
FA 18:2;O	OxFA		PE P-34:0 PE P-18:0_16:0	EtherPE
FA 18:3	FA		PE P-38:4 PE P-16:0_22:4	EtherPE
FA 18:3;O	OxFA		PE P-39:4 PE P-17:0_22:4	EtherPE

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
FA 19:1;2O	OxFA		PE P-42:6 PE P-20:1_22:5	EtherPE
FA 19:2	FA		PE P-42:7 PE P-20:1_22:6	EtherPE
FA 19:3;O	OxFA		PG 30:1 PG 14:0_16:1	PG
FA 20:0;2O	OxFA		PG 31:0 PG 15:0_16:0	PG
FA 20:1	FA		PG 32:0 PG 16:0_16:0	PG
FA 20:2	FA		PG 32:1 PG 16:0_16:1	PG
FA 20:2;3O	OxFA		PG 33:0 PG 16:0_17:0	PG
FA 20:2;4O	OxFA		PG 33:2 PG 15:0_18:2	PG
FA 20:3	FA		PG 34:0 PG 16:0_18:0	PG
FA 20:3;2O	OxFA		PG 34:1 PG 16:0_18:1	PG
FA 20:3;3O	OxFA		PG 34:2 PG 16:0_18:2	PG
FA 20:3;O	OxFA		PG 34:2 PG 16:1_18:1	PG
FA 20:4	FA		PG 34:3 PG 16:1_18:2	PG
FA 20:4;2O	OxFA		PG 35:2 PG 17:0_18:2	PG
FA 20:4;3O	OxFA		PG 36:0 PG 18:0_18:0	PG
FA 20:4;4O	OxFA		PG 36:1 PG 18:0_18:1	PG
FA 20:4;O	OxFA		PG 36:2 PG 18:1_18:1	PG
FA 20:5	FA		PG 36:3 PG 18:1_18:2	PG
FA 20:5;2O	OxFA		PG 36:4 PG 16:0_20:4	PG
FA 20:5;3O	OxFA		PG 36:4 PG 18:2_18:2	PG
FA 20:5;O	OxFA		PG 38:2 PG 18:1_20:1	PG
FA 21:2	FA		PG 38:3 PG 18:1_20:2	PG
FA 21:4	FA		PG 40:3 PG 20:1_20:2	PG
FA 22:1	FA		PG O-30:1 PG O-14:1_16:0	EtherPG
FA 22:2	FA		PG O-32:1 PG O-16:1_16:0	EtherPG
FA 22:3;2O	OxFA		PG O-34:2 PG O-16:1_18:1	EtherPG
FA 22:4	FA		PG O-34:3 PG O-16:1_18:2	EtherPG
FA 22:4;2O	OxFA		PG O-35:2 PG O-18:2_17:0	EtherPG
FA 22:4;O	OxFA		PG O-36:3 PG O-18:2_18:1	EtherPG
FA 22:5;(2OH)	OxFA		PG O-38:5 PG O-18:2_20:3	EtherPG
FA 22:5;2O	OxFA		PI 20:0	PI
FA 22:5;3O	OxFA		PI 36:1 PI 18:0_18:1	PI
FA 22:5;O	OxFA		PI 36:2	PI
FA 22:6;(2OH)	OxFA		PI 36:2 PI 18:1_18:1	PI
FA 22:6;3O	OxFA		PI 38:3 PI 18:0_20:3	PI
FA 23:1	FA		PI 38:4 PI 18:0_20:4	PI
FA 24:1	FA		PI 40:4	PI
FA 24:3;O	OxFA		PI 40:4 PI 18:0_22:4	PI
FA 24:5	FA		PI 40:6	PI
FA 26:1	FA		PI 47:11	PI
FA 26:5	FA		PI 50:0 PI 16:0_34:0	PI
FA 36:10	FA		PI-Cer 25:3;3O	PI_Cer
FAHFA 12:0;O FAHFA 2:0/10:0;O	FAHFA		PI-Cer 51:0;3O	PI_Cer
FAHFA 20:0;O FAHFA 2:0/18:0;O	FAHFA		PI-Cer 53:6;2O	PI_Cer
FAHFA 32:2;O FAHFA 17:0/15:2;O	FAHFA		PMeOH 38:4 PMeOH 18:2_20:2	PMeOH
GM3 49:5;2O	GM3		PS 36:1	PS

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
Hex2Cer 32:1;2O Hex2Cer 18:1;2O/14:0	Hex2Cer		PS 36:1 PS 18:0_18:1	PS
Hex2Cer 35:1;2O Hex2Cer 18:1;2O/17:0	Hex2Cer		PS 36:4 PS 18:2_18:2	PS
Hex2Cer 42:2;2O	Hex2Cer		PS 38:4 PS 12:0_26:4	PS
HexCer 34:1;2O	HexCer_NS		PS 38:4 PS 18:0_20:4	PS
HexCer 34:1;3O HexCer 17:0;2O/17:1;O	HexCer_HDS		PS O-37:1 PS O-19:0_18:1	EtherPS
HexCer 34:1;3O HexCer 18:1;2O/16:0;O	HexCer_HS		SE 24:1;O4/17:4;O	DCAE
HexCer 35:0;2O HexCer 18:0;2O/17:0	HexCer_NDS		SE 24:1;O4/18:4;O	DCAE
HexCer 36:0;4O HexCer 18:0;3O/18:0;(2OH)	HexCer_AP		SL 51:6;O SL 15:0;O/36:6	SL
HexCer 36:1;2O HexCer 18:1;2O/18:0	HexCer_NS		SM 31:1;2O SM 17:1;2O/14:0	SM
HexCer 38:1;3O HexCer 21:1;2O/17:0;O	HexCer_HS		SM 33:6;3O	SM
HexCer 39:1;4O HexCer 18:0;3O/21:1;(2OH)	HexCer_AP		SM 34:1;2O	SM
HexCer 40:0;2O	HexCer_NDS		SM 34:1;2O SM 18:1;2O/16:0	SM
HexCer 40:0;2O HexCer 18:0;2O/22:0	HexCer_NDS		SM 34:1;2O SM 19:0;2O/15:1	SM
HexCer 40:1;2O HexCer 18:1;2O/22:0	HexCer_NS		SM 34:2;3O	SM
HexCer 42:0;2O	HexCer_NDS		SM 34:3;3O	SM
HexCer 42:0;3O	HexCer_HDS		SM 35:2;3O	SM
HexCer 42:0;3O HexCer 16:0;2O/26:0;O	HexCer_HDS		SM 36:4;3O	SM
HexCer 42:0;4O HexCer 18:0;3O/24:0;(2OH)	HexCer_AP		SM 37:0;3O	SM
HexCer 42:1;4O HexCer 18:0;3O/24:1;(2OH)	HexCer_AP		SM 37:1;3O	SM
HexCer 42:2;2O HexCer 21:0;2O/21:2	HexCer_NDS		SM 37:2;3O	SM
HexCer 42:2;3O HexCer 18:1;2O/24:1;O	HexCer_HS		SM 37:8;3O	SM
HexCer 42:2;4O HexCer 18:1;3O/24:1;(2OH)	HexCer_AP		SM 38:1;3O	SM
HexCer 43:0;4O	HexCer_AP		SM 38:3;2O	SM
HexCer 43:1;3O HexCer 18:1;2O/25:0;O	HexCer_HS		SM 39:1;3O	SM
HexCer 43:1;4O	HexCer_AP		SM 40:3;2O	SM
HexCer 44:0;2O	HexCer_NDS		SM 41:1;3O	SM
HexCer 44:0;3O	HexCer_HDS		SM 42:0;3O	SM
HexCer 44:1;3O HexCer 18:1;2O/26:0;O	HexCer_HS		SM 43:0;3O	SM
HexCer 44:1;4O	HexCer_AP		SM 43:2;2O SM 18:1;2O/25:1	SM
HexCer 44:1;4O HexCer 18:0;3O/26:1;(2OH)	HexCer_AP		SM 44:2;3O	SM
HexCer 44:2;3O HexCer 16:1;2O/28:1;O	HexCer_HS		ST 24:1;O3;S	BASulfate
HexCer 44:6;4O	HexCer_AP		ST 27:1;O	ST
HexCer 45:1;3O	HexCer_HDS		ST 27:1;O;S	SSulfate
HexCer 45:1;4O	HexCer_AP		ST 27:2;O	ST
HexCer 50:3;3O	HexCer_HS		ST 28:1;O	ST
HexCer 52:0;4O	HexCer_AP		ST 28:3;O	ST
HexCer 52:1;4O HexCer 20:0;3O/32:1;(2OH)	HexCer_AP		TG 25:0 TG 8:0_8:0_9:0	TG
HexCer 52:6;4O	HexCer_AP		TG 26:0 TG 8:0_8:0_10:0	TG
HexCer 52:7;4O	HexCer_AP		TG 31:0 TG 9:0_10:0_12:0	TG
LPC 16:1	LPC		TG 36:0 TG 12:0_12:0_12:0	TG
LPC 17:0	LPC		TG 37:1 TG 10:0_10:0_17:1	TG
LPC 18:0	LPC		TG 38:1 TG 8:0_12:0_18:1	TG
LPC 18:3/0:0	LPC		TG 41:0 TG 12:0_14:0_15:0	TG
LPC 20:3/0:0	LPC		TG 43:1 TG 10:0_15:0_18:1	TG
LPC 22:4	LPC		TG 48:1 TG 14:0_16:0_18:1	TG
LPC O-20:2	EtherLPC		TG 48:2 TG 12:0_18:1_18:1	TG

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
LPE 15:0	LPE		TG 48:3;1O TG 14:1 18:2 16:0;1O	OxTG
LPE 16:0	LPE		TG 48:3;1O TG 15:0 15:0 18:3;1O	OxTG
LPE 16:1	LPE		TG 48:3 TG 16:1 16:1 16:1	TG
LPE 17:0	LPE		TG 49:2 TG 16:0 16:1 17:1	TG
LPE 18:0	LPE		TG 49:3 TG 15:0 16:1 18:2	TG
LPE 18:1	LPE		TG 50:1 TG 16:0 16:0 18:1	TG
LPE 18:2	LPE		TG 50:2;1O TG 14:0 18:1 18:1;1O	OxTG
LPE 20:1	LPE		TG 50:2;1O TG 16:0 16:0 18:2;1O	OxTG
LPE 20:3	LPE		TG 51:1 TG 16:0 17:0 18:1	TG
LPE 20:4	LPE		TG 51:2 TG 16:0 17:1 18:1	TG
LPE 22:4	LPE		TG 51:3;1O TG 16:0 17:1 18:2;1O	OxTG
LPE 22:6	LPE		TG 51:3 TG 16:1 17:1 18:1	TG
LPE O-10:0	EtherLPE		TG 51:3 TG 17:1 17:1 17:1	TG
LPE O-16:1	EtherLPE		TG 52:0 TG 16:0 18:0 18:0	TG
LPE O-17:1	EtherLPE		TG 52:1;1O TG 18:0 18:0 16:1;1O	OxTG
LPE O-18:2	EtherLPE		TG 52:2;1O TG 18:1 18:1 16:0;1O	OxTG
LPE O-20:4	EtherLPE		TG 52:2;2O TG 16:0 19:0 17:2;2O	OxTG
LPE O-22:2	EtherLPE		TG 52:2 TG 16:0 18:1 18:1	TG
LPE O-22:4	EtherLPE		TG 52:3;2O TG 16:0 18:1 18:2;2O	OxTG
LPG 18:1	LPG		TG 52:3;3O TG 19:0 17:2 16:1;3O	OxTG
LPG O-13:1	EtherLPG		TG 52:4;2O TG 16:0 18:1 18:3;2O	OxTG
MG 33:1	MG		TG 52:4;2O TG 16:0 18:2 18:2;2O	OxTG
MG 34:3	MG		TG 52:5;1O TG 16:1 18:2 18:2;1O	OxTG
MG 36:1	MG		TG 53:0 TG 15:0 16:0 22:0	TG
MG 37:1	MG		TG 53:2 TG 17:0 18:1 18:1	TG
NAE 13:0	NAE		TG 53:5 TG 17:1 17:2 19:2	TG
NAE 14:0	NAE		TG 54:0 TG 18:0 18:0 18:0	TG
NAE 15:4	NAE		TG 54:1;2O TG 18:0 18:1 18:0;2O	OxTG
NAE 19:2	NAE		TG 54:2;2O TG 18:1 18:1 18:0;2O	OxTG
NAE 20:2	NAE		TG 54:3;2O TG 19:0 18:2 17:1;2O	OxTG
NAGly 11:0;O	NAGly		TG 54:3 TG 18:1 18:1 18:1	TG
NAGly 13:1;O	NAGly		TG 54:4;2O TG 18:1 18:1 18:2;2O	OxTG
NAGly 14:0;O	NAGly		TG 54:4;3O TG 19:0 17:4 18:0;3O	OxTG
NAGly 15:0;O	NAGly		TG 54:5;1O TG 18:1 18:1 18:3;1O	OxTG
NAGly 16:0;O	NAGly		TG 54:6;2O TG 18:2 18:2 18:2;2O	OxTG
NAGly 18:0;O	NAGly		TG 54:7;1O TG 18:2 18:2 18:3;1O	OxTG
NAGly 18:5;O	NAGly		TG 55:1 TG 16:0 21:0 18:1	TG
NAGly 19:0;O	NAGly		TG 55:2 TG 19:0 18:1 18:1	TG

Metabolite and Lipid name	Class		Metabolite and Lipid Name	Class
NAGly 31:1;2O NAGly 16:0;O(FA 15:0)	NAGly		TG 55:3;1O TG 18:1 19:1 18:1;1O	OxTG
NAGlySer 15:1;O	NAGlySer		TG 56:0 TG 16:0_16:0_24:0	TG
NAGlySer 31:1;2O NAGlySer 16:0;O(FA 15:0)	NAGlySer		TG 56:1 TG 16:0_22:0_18:1	TG
NAGlySer 32:1;2O NAGlySer 17:0;O(FA 15:0)	NAGlySer		TG 56:2;1O TG 18:1 18:1 20:0;1O	OxTG
NAGlySer 33:1;2O NAGlySer 17:0;O(FA 16:0)	NAGlySer		TG 56:3;1O TG 18:1 18:1 20:1;1O	OxTG
NAGlySer 34:1;2O NAGlySer 17:0;O(FA 17:0)	NAGlySer		TG 56:5;1O TG 18:1 18:1 20:3;1O	OxTG
NAOrn 19:0;O	NAOrn		TG 57:0;2O TG 18:0 18:0 21:0;2O	OxTG
NAOrn 22:6;O	NAOrn		TG 57:7;1O TG 22:3 21:4 14:0;1O	OxTG
NAOrn 30:1;2O NAOrn 15:0;O(FA 15:0)	NAOrn		TG 57:8;1O TG 22:3 21:5 14:0;1O	OxTG
NAOrn 32:1;2O NAOrn 17:0;O(FA 15:0)	NAOrn		TG 58:1 TG 16:0_24:0_18:1	TG
PA 36:0 PA 18:0_18:0	PA		TG 58:10;3O TG 21:4 21:4 16:2;3O	OxTG
Pantothenic acid	Others		TG 58:3 TG 22:0_18:1_18:2	TG
PC 28:0	PC		TG 58:5 TG 18:0_18:2_22:3	TG
PC 28:0 PC 14:0_14:0	PC		TG 59:1 TG 16:0_25:0_18:1	TG
PC 30:1 PC 14:0_16:1	PC		TG 59:4 TG 23:0_18:2_18:2	TG
PC 31:1 PC 15:0_16:1	PC		TG 60:0 TG 18:0_20:0_22:0	TG
PC 31:2	PC		TG 60:1 TG 16:0_26:0_18:1	TG
PC 32:2	PC		TG 60:6 TG 18:1_20:1_22:4	TG
PC 32:3	PC		TG 61:1 TG 17:0_26:0_18:1	TG
PC 33:1	PC		TG 61:2 TG 25:0_18:1_18:1	TG
PC 33:2	PC		TG 62:0 TG 18:0_22:0_22:0	TG
PC 35:1	PC		TG 62:1 TG 18:0_26:0_18:1	TG
PC 35:4	PC		TG 63:2 TG 27:0_18:1_18:1	TG
PC 37:2 PC 19:0_18:2	PC		TG 64:2 TG 16:0_18:1_30:1	TG
PC 38:5	PC		TG 64:4 TG 18:1_28:1_18:2	TG
PC 39:2	PC		TG 66:3 TG 18:1_18:1_30:1	TG
PC 40:3	PC		VAE 4:0	VAE

Table L. Salivary metabolites and lipids identified in both users and controls.

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
LPE 16:0	LPE		PC O-36:0 PC O-20:0_16:0	EtherPC
LPE 18:2	LPE		PC O-36:1 PC O-18:0_18:1	EtherPC
PC 30:0	PC		PC O-36:1 PC O-20:1_16:0	EtherPC
PC 32:2	PC		PC O-36:2	EtherPC
PC 34:2	PC		PC O-36:2 PC O-18:1_18:1	EtherPC
PC 34:3	PC		PC O-36:3 PC O-18:1_18:2	EtherPC
PE 32:1	PE		PC O-36:3 PC O-18:3_18:0	EtherPC
PE 34:1	PE		PC O-36:4 PC O-16:0_20:4	EtherPC
LPC 18:1	LPC		PC O-36:4 PC O-18:2_18:2	EtherPC
(+)-2'-Deoxyuridine	Pyrimidine 2'-deoxyribonucleosides		PC O-36:6 PC O-16:2_20:4	EtherPC
(9Z,12R)-12-Hydroxyoctadec-9-enoic acid	Long-chain fatty acids		PC O-36:8 PC O-18:3_18:5	EtherPC
1,3-Dimethylxanthine	Xanthines		PC O-37:10	EtherPC

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
12-Hydroxyoctadecanoic acid	Long-chain fatty acids		PC O-37:5 PC O-17:1_20:4	EtherPC
13-HODE	Lineolic acids and derivatives		PC O-37:8 PC O-18:3_19:5	EtherPC
13-KODE	Lineolic acids and derivatives		PC O-37:9	EtherPC
9Z,12Z-Linoleic acid	Lineolic acids and derivatives		PC O-37:9 PC O-18:4_19:5	EtherPC
Acebutolol	Alkyl-phenylketones		PC O-38:0	EtherPC
ADENINE	6-aminopurines		PC O-38:0 PC O-22:0_16:0	EtherPC
Adenosine	Purine nucleosides		PC O-38:1	EtherPC
Arachidonic acid	Long-chain fatty acids		PC O-38:1 PC O-20:0_18:1	EtherPC
Benzoic acid	Benzoic acids		PC O-38:2	EtherPC
Creatinine	Alpha amino acids and derivatives		PC O-38:2 PC O-20:1_18:1	EtherPC
Deoxyuridine	Pyrimidine 2'-deoxyribonucleosides		PC O-38:3 PC O-18:0_20:3	EtherPC
Docosahexanoic acid	Very long-chain fatty acids		PC O-38:3 PC O-20:1_18:2	EtherPC
Eicosenoic acid	Long-chain fatty acids		PC O-38:4 PC O-16:0_22:4	EtherPC
Hydroxyisocaproic acid	Hydroxy fatty acids		PC O-38:4 PC O-18:0_20:4	EtherPC
HYPOXANTHINE	Hypoxanthines		PC O-38:4 PC O-18:1_20:3	EtherPC
Indole-3-carboxaldehyde	Indoles		PC O-38:4 PC O-20:2_18:2	EtherPC
Isatin	Indolines		PC O-38:5	EtherPC
ISOLEUCINE	Isoleucine and derivatives		PC O-38:5 PC O-16:1_22:4	EtherPC
Ketoleucine	Short-chain keto acids and derivatives		PC O-38:5 PC O-18:1_20:4	EtherPC
L-(-)-Phenylalanine	Phenylalanine and derivatives		PC O-38:5 PC O-20:3_18:2	EtherPC
Leucine	Leucine and derivatives		PC O-38:6	EtherPC
Levocetirizine	Diphenylmethanes		PC O-38:6 PC O-18:2_20:4	EtherPC
Linolenic acid	Lineolic acids and derivatives		PC O-38:7 PC O-16:1_22:6	EtherPC
Nervonic acid	Very long-chain fatty acids		PC O-38:8	EtherPC
Oleic acid	Long-chain fatty acids		PC O-38:8 PC O-18:3_20:5	EtherPC
PE 34:0	PE		PC O-38:8 PC O-18:4_20:4	EtherPC
PE 36:3	PE		PC O-39:1 PC O-23:1_16:0	EtherPC
PE 36:5	PE		PC O-39:10	EtherPC
PE 40:4	PE		PC O-39:4 PC O-19:0_20:4	EtherPC
PG 30:0	PG		PC O-40:0	EtherPC
PG 32:1	PG		PC O-40:1 PC O-24:1_16:0	EtherPC
PG 32:2	PG		PC O-40:2 PC O-22:1_18:1	EtherPC
PG 34:2	PG		PC O-40:3 PC O-22:1_18:2	EtherPC
PG 34:3	PG		PC O-40:4 PC O-18:0_22:4	EtherPC
PG 36:3	PG		PC O-40:4 PC O-22:2_18:2	EtherPC
phenyl pyruvic acid	Phenylpyruvic acid derivatives		PC O-40:5 PC O-16:0_24:5	EtherPC
Phenyllactate	Phenylpropanoic acids		PC O-40:5 PC O-18:1_22:4	EtherPC
PREGNENOLONE SULFATE	Sulfated steroids		PC O-40:5 PC O-20:1_20:4	EtherPC
Succinate	Dicarboxylic acids and derivatives		PC O-40:6 PC O-18:0_22:6	EtherPC
Uracil	Pyrimidones		PC O-40:6 PC O-18:1_22:5	EtherPC
Xanthine	Xanthines		PC O-40:7	EtherPC

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
1-pentadecanoyl-2-hydroxy-sn-glycero-3-phosphocholine	1-acyl-sn-glycero-3-phosphocholines		PC O-40:7 PC O-18:1_22:6	EtherPC
Decanoyl-L-Carnitine	Acyl carnitines		PC O-40:8	EtherPC
Hexanoyl-L-Carnitine	Acyl carnitines		PC O-41:1	EtherPC
Histamine	2-arylethylamines		PC O-41:3	EtherPC
N-ACETYLNEURAMINATE	N-acylneuraminic acids		PC O-41:8	EtherPC
N-Acetyltryptophan	N-acyl-alpha amino acids		PC O-42:3 PC O-18:3_24:0	EtherPC
Taurine	Organosulfonic acids		PC O-42:4 PC O-18:3_24:1	EtherPC
Tetradecanoyl-L-Carnitine	Acyl carnitines		PC O-42:4 PC O-22:0_20:4	EtherPC
VALINE	Valine and derivatives		PC O-42:4 PC O-24:2_18:2	EtherPC
Adenosine 5'-monophosphate			PC O-42:5	EtherPC
AHexCer 37:3;O3 AHexCer (O-12:0)25:3;O3	AHexCer		PC O-42:5 PC O-22:1_20:4	EtherPC
AHexCer 42:4;O2 AHexCer (O-15:1)27:3;O2	AHexCer		PC O-42:6 PC O-22:6_20:0	EtherPC
AHexCer 42:6;O2 AHexCer (O-14:1)28:5;O2	AHexCer		PC O-42:7	EtherPC
AHexCer 43:5;O3 AHexCer (O-15:1)28:4;O3	AHexCer		PC O-42:7 PC O-20:1_22:6	EtherPC
AHexCer 44:6;O2 AHexCer (O-16:0)28:6;O2	AHexCer		PC O-42:8	EtherPC
AHexCer 45:5;O3 AHexCer (O-15:1)30:4;O3	AHexCer		PC O-43:1	EtherPC
AHexCer 49:1;O3 AHexCer (O-15:1)34:0;O3	AHexCer		PC O-43:1 PC O-23:1_20:0	EtherPC
AHexCer 49:4;O3 AHexCer (O-16:2)33:2;O3	AHexCer		PC O-44:3 PC O-24:2_20:1	EtherPC
AHexCer 50:4;O3 AHexCer (O-16:2)34:2;O3	AHexCer		PC O-44:3 PC O-25:0_19:3	EtherPC
AHexCer 51:1;O3 AHexCer (O-18:0)33:1;O3	AHexCer		PC O-44:4 PC O-24:0_20:4	EtherPC
AHexCer 51:2;O3 AHexCer (O-16:2)35:0;O3	AHexCer		PC O-44:4 PC O-24:1_20:3	EtherPC
AHexCer 51:4;O3 AHexCer (O-12:0)39:4;O3	AHexCer		PC O-44:5 PC O-24:1_20:4	EtherPC
AHexCer 51:4;O3 AHexCer (O-16:2)21:1;O2 14:1;O	AHexCer		PC O-44:6 PC O-24:2_20:4	EtherPC
AHexCer 52:2;O3 AHexCer (O-15:0)21:1;O2 16:1;O	AHexCer		PC O-44:7	EtherPC
AHexCer 52:4;O3 AHexCer (O-16:2)18:1;O2 18:1;O	AHexCer		PC O-44:8	EtherPC
AHexCer 52:7;O2 AHexCer (O-16:2)36:5;O2	AHexCer		PC O-46:5 PC O-24:1_22:4	EtherPC
AHexCer 52:8;O3 AHexCer (O-16:1)36:7;O3	AHexCer		PC O-46:7	EtherPC
AHexCer 53:8;O2 AHexCer (O-16:2)37:6;O2	AHexCer		PC O-46:7 PC O-24:1_22:6	EtherPC
AHexCer 54:5;O2 AHexCer (O-17:2)37:3;O2	AHexCer		PC O-46:8	EtherPC
AHexCer 54:6;O2 AHexCer (O-15:0)20:1;O2 19:5	AHexCer		PC O-48:6	EtherPC
AHexCer 54:6;O3 AHexCer (O-15:0)21:1;O2 18:5;O	AHexCer		PE 28:0	PE
AHexCer 54:7;O2 AHexCer (O-15:1)21:1;O2 18:5	AHexCer		PE 28:0 PE 13:0_15:0	PE
AHexCer 54:7;O3 AHexCer (O-15:1)21:1;O2 18:5;O	AHexCer		PE 28:0 PE 14:0_14:0	PE
AHexCer 54:8;O2 AHexCer (O-16:2)38:6;O2	AHexCer		PE 29:0	PE
AHexCer 54:8;O2 AHexCer (O-18:1)36:7;O2	AHexCer		PE 29:0 PE 14:0_15:0	PE
AHexCer 54:8;O3 AHexCer (O-15:1)17:3;O2 22:4;O	AHexCer		PE 30:0 PE 14:0_16:0	PE
AHexCer 54:8;O3 AHexCer (O-15:1)39:7;O3	AHexCer		PE 30:0 PE 15:0_15:0	PE
AHexCer 55:6;O2 AHexCer (O-15:0)40:6;O2	AHexCer		PE 30:1 PE 16:0_14:1	PE
AHexCer 55:6;O3 AHexCer (O-16:0)19:2;O2 20:4;O	AHexCer		PE 31:0 PE 15:0_16:0	PE
AHexCer 55:6;O3 AHexCer (O-17:2)38:4;O3	AHexCer		PE 31:1 PE 15:0_16:1	PE
AHexCer 55:9;O3 AHexCer (O-14:0)41:9;O3	AHexCer		PE 31:2 PE 13:0_18:2	PE
AHexCer 56:10;O3 AHexCer (O-15:1)41:9;O3	AHexCer		PE 32:0	PE

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
AHexCer 56:5;O2 AHexCer (O-16:0)40:5;O2	AHexCer		PE 32:0 PE 16:0_16:0	PE
AHexCer 56:6;O3 AHexCer (O-15:0)21:1;O2/20:5;O	AHexCer		PE 32:2 PE 14:0_18:2	PE
AHexCer 56:6;O3 AHexCer (O-16:0)40:6;O3	AHexCer		PE 32:2 PE 16:1_16:1	PE
AHexCer 56:7;O2 AHexCer (O-15:0)41:7;O2	AHexCer		PE 33:0 PE 15:0_18:0	PE
AHexCer 56:7;O2 AHexCer (O-22:6)34:1;O2	AHexCer		PE 33:1 PE 15:0_18:1	PE
AHexCer 56:9;O3 AHexCer (O-15:0)41:9;O3	AHexCer		PE 33:2 PE 15:0_18:2	PE
AHexCer 57:1;O3 AHexCer (O-18:0)39:1;O3	AHexCer		PE 34:0 PE 16:0_18:0	PE
AHexCer 57:4;O2 AHexCer (O-17:2)40:2;O2	AHexCer		PE 34:1;O PE 18:1_16:0;O	OxPE
AHexCer 58:1;O2 AHexCer (O-16:0)20:1;O2/22:0	AHexCer		PE 34:1 PE 16:0_18:1	PE
AHexCer 58:1;O3 AHexCer (O-16:0)42:1;O3	AHexCer		PE 34:2	PE
AHexCer 58:5;O3 AHexCer (O-17:2)20:1;O2/21:2;O	AHexCer		PE 34:2 PE 16:1_18:1	PE
AHexCer 58:5;O3 AHexCer (O-18:0)40:5;O3	AHexCer		PE 34:3 PE 16:0_18:3	PE
AHexCer 58:6;O3 AHexCer (O-18:1)40:5;O3	AHexCer		PE 34:3 PE 16:1_18:2	PE
AHexCer 58:7;O3 AHexCer (O-16:1)42:6;O3	AHexCer		PE 35:1	PE
AHexCer 58:8;O3 AHexCer (O-16:1)42:7;O3	AHexCer		PE 35:1 PE 17:0_18:1	PE
AHexCer 59:8;O2 AHexCer (O-18:0)41:8;O2	AHexCer		PE 35:2 PE 17:0_18:2	PE
AHexCer 60:10;O3 AHexCer (O-18:3)42:7;O3	AHexCer		PE 35:2 PE 17:1_18:1	PE
AHexCer 60:5;O3 AHexCer (O-16:2)18:1;O2/26:2;O	AHexCer		PE 35:4	PE
AHexCer 61:4;O3 AHexCer (O-16:0)45:4;O3	AHexCer		PE 36:1 PE 18:0_18:1	PE
AHexCer 63:6;O2 AHexCer (O-16:0)47:6;O2	AHexCer		PE 36:2 PE 18:1_18:1	PE
AHexCer 63:6;O3 AHexCer (O-16:1)47:5;O3	AHexCer		PE 36:3 PE 18:1_18:2	PE
AHexCer 72:8;O2 AHexCer (O-24:0)48:8;O2	AHexCer		PE 36:4 PE 16:0_20:4	PE
ASG 29:1;O;Hex;FA 16:0	AHexSIS		PE 37:4	PE
C18-Sphingosine	Others		PE 38:1 PE 18:0_20:1	PE
CAR 16:0	CAR		PE 38:2 PE 18:1_20:1	PE
CAR 16:1	CAR		PE 38:4 PE 18:0_20:4	PE
CAR 17:0	CAR		PE 38:7	PE
CAR 18:0	CAR		PE 40:0 PE 20:0_20:0	PE
CAR 18:2	CAR		PE 40:2 PE 18:1_22:1	PE
CAR 20:0	CAR		PE 40:5;O PE 18:2_22:3;O	OxPE
CAR 20:1	CAR		PE 40:6	PE
CAR 20:2	CAR		PE 40:6;O PE 18:2_22:4;O	OxPE
CAR 22:0	CAR		PE 42:1	PE
CAR 22:2	CAR		PE O-16:1	EtherPE
CE 16:0	CE		PE O-17:0	EtherPE
CE 18:0	CE		PE O-32:0	EtherPE
CE 18:1	CE		PE O-32:1	EtherPE
CE 18:2	CE		PE O-33:2 PE O-16:1_17:1	EtherPE
CE 18:3	CE		PE O-34:1 PE O-18:1_16:0	EtherPE
CE 20:1	CE		PE O-34:2 PE O-16:0_18:2	EtherPE
CE 20:3	CE		PE O-34:3 PE O-16:1_18:2	EtherPE
CE 20:4	CE		PE O-35:2 PE O-17:1_18:1	EtherPE
CE 20:5	CE		PE O-36:1	EtherPE
CE 21:3	CE		PE O-36:1 PE O-18:0_18:1	EtherPE
CE 22:5	CE		PE O-36:4	EtherPE

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
CE 22:6	CE		PE O-36:4 PE O-16:1_20:3	EtherPE
CE 25:0	CE		PE O-38:2 PE O-20:1_18:1	EtherPE
CE 26:0	CE		PE O-38:3 PE O-20:2_18:1	EtherPE
CE 26:4	CE		PE O-38:4 PE O-18:0_20:4	EtherPE
CE 27:0	CE		PE O-38:5 PE O-18:1_20:4	EtherPE
CE 28:0	CE		PE O-38:6 PE O-18:2_20:4	EtherPE
CE 28:4	CE		PE O-39:2	EtherPE
CE 30:0	CE		PE O-40:2 PE O-22:1_18:1	EtherPE
CE 31:0	CE		PE O-40:6 PE O-18:1_22:5	EtherPE
CE 32:0	CE		PE O-40:8 PE O-18:2_22:6	EtherPE
CE 33:0	CE		PE O-42:6 PE O-22:2_20:4	EtherPE
CE 34:1	CE		PE O-44:6 PE O-24:2_20:4	EtherPE
CE 35:0	CE		PE O-44:7 PE O-24:3_20:4	EtherPE
Cer 31:1;O2 Cer 17:1;O2/14:0	Cer_NS		PE O-45:6	EtherPE
Cer 32:0;O2 Cer 18:0;O2/14:0	Cer_NDS		PE P-29:0 PE P-14:0_15:0	EtherPE
Cer 33:1;O2 Cer 17:1;O2/16:0	Cer_NS		PE P-30:0 PE P-15:0_15:0	EtherPE
Cer 33:1;O4 Cer 18:0;O3/15:1(2OH)	Cer_AP		PE P-30:0 PE P-16:0_14:0	EtherPE
Cer 34:0;O2 Cer 18:0;O2/16:0	Cer_NDS		PE P-30:1 PE P-16:1_14:0	EtherPE
Cer 34:0;O2 Cer 19:0;O2/15:0	Cer_NDS		PE P-31:0 PE P-16:0_15:0	EtherPE
Cer 34:0;O3 Cer 17:0;O2/17:0;O	Cer_HDS		PE P-31:1 PE P-15:0_16:1	EtherPE
Cer 34:0;O3 Cer 18:0;O2/16:0(2OH)	Cer_ADS		PE P-32:0	EtherPE
Cer 34:0;O3 Cer 18:0;O2/16:0;O	Cer_HDS		PE P-32:0 PE P-16:0_16:0	EtherPE
Cer 34:1;O2 Cer 18:1;O2/16:0	Cer_NS		PE P-32:1 PE P-16:0_16:1	EtherPE
Cer 34:1;O2 Cer 19:0;O2/15:1	Cer_NDS		PE P-32:2 PE P-14:0_18:2	EtherPE
Cer 34:1;O3 Cer 18:1;O2/16:0;O	Cer_HS		PE P-33:0 PE P-16:0_17:0	EtherPE
Cer 34:1;O3 Cer 19:0;O2/15:1;O	Cer_HDS		PE P-33:1 PE P-16:0_17:1	EtherPE
Cer 34:1;O4 Cer 18:0;O3/16:1(2OH)	Cer_AP		PE P-33:2 PE P-15:0_18:2	EtherPE
Cer 34:1;O4 Cer 18:1;O3/16:0(2OH)	Cer_AP		PE P-33:2 PE P-16:1_17:1	EtherPE
Cer 34:2;O2 Cer 18:2;O2/16:0	Cer_NS		PE P-34:0	EtherPE
Cer 34:2;O3 Cer 18:2;O2/16:0;O	Cer_HS		PE P-34:0 PE P-18:0_16:0	EtherPE
Cer 35:0;O2 Cer 18:0;O2/17:0	Cer_NDS		PE P-34:1	EtherPE
Cer 35:0;O3 Cer 18:0;O2/17:0;O	Cer_HDS		PE P-34:1 PE P-16:0_18:1	EtherPE
Cer 35:0;O3 Cer 21:0;O2/14:0;O	Cer_HDS		PE P-34:2 PE P-16:0_18:2	EtherPE
Cer 35:1;O2 Cer 18:1;O2/17:0	Cer_NS		PE P-34:3 PE P-16:0_18:3	EtherPE
Cer 35:1;O3 Cer 18:0;O2/17:1;O	Cer_HDS		PE P-34:4	EtherPE
Cer 35:2;O2 Cer 18:2;O2/17:0	Cer_NS		PE P-35:1 PE P-17:0_18:1	EtherPE
Cer 35:2;O4 Cer 20:1;O3/15:1(2OH)	Cer_AP		PE P-35:2 PE P-17:0_18:2	EtherPE
Cer 35:3;O4 Cer 20:2;O3/15:1(2OH)	Cer_AP		PE P-35:4 PE P-15:0_20:4	EtherPE
Cer 36:0;O2 Cer 18:0;O2/18:0	Cer_NDS		PE P-36:0	EtherPE
Cer 36:0;O2 Cer 21:0;O2/15:0	Cer_NDS		PE P-36:0 PE P-20:0_16:0	EtherPE
Cer 36:0;O3 Cer 18:0;O2/18:0;O	Cer_HDS		PE P-36:1 PE P-18:0_18:1	EtherPE
Cer 36:0;O3 Cer 19:0;O2/17:0;O	Cer_HDS		PE P-36:2 PE P-16:0_20:2	EtherPE
Cer 36:0;O3 Cer 22:0;O2/14:0;O	Cer_HDS		PE P-36:2 PE P-18:1_18:1	EtherPE
Cer 36:0;O4 Cer 18:0;O3/18:0(2OH)	Cer_AP		PE P-36:3 PE P-16:0_20:3	EtherPE
Cer 36:1;O2 Cer 18:1;O2/18:0	Cer_NS		PE P-36:3 PE P-18:1_18:2	EtherPE
Cer 36:1;O3 Cer 18:0;O2/18:1;O	Cer_ADS		PE P-36:4 PE P-16:0_20:4	EtherPE
Cer 36:1;O3 Cer 18:1;O2/18:0;O	Cer_HS		PE P-36:4 PE P-18:2_18:2	EtherPE

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
Cer 36:1;O3 Cer 19:0;O2/17:1;O	Cer_HDS		PE P-36:5	EtherPE
Cer 36:1;O4 Cer 19:0;O3/17:1(2OH)	Cer_AP		PE P-36:5 PE P-16:0_20:5	EtherPE
Cer 36:1;O4 Cer 20:0;O3/16:1(2OH)	Cer_AP		PE P-37:2	EtherPE
Cer 36:1;O4 Cer 20:1;O3/16:0(2OH)	Cer_AP		PE P-37:4 PE P-17:0_20:4	EtherPE
Cer 36:2;O2 Cer 18:1;O2/18:1	Cer_NS		PE P-38:1	EtherPE
Cer 36:2;O2 Cer 18:2;O2/18:0	Cer_NS		PE P-38:1 PE P-20:0_18:1	EtherPE
Cer 36:2;O3 Cer 21:1;O2/15:1;O	Cer_HS		PE P-38:2	EtherPE
Cer 36:3;O2 Cer 18:1;O2/18:2	Cer_NS		PE P-38:2 PE P-18:0_20:2	EtherPE
Cer 37:0;O2 Cer 18:0;O2/19:0	Cer_NDS		PE P-38:2 PE P-20:1_18:1	EtherPE
Cer 37:0;O2 Cer 19:0;O2/18:0	Cer_NDS		PE P-38:3 PE P-18:0_20:3	EtherPE
Cer 37:0;O4 Cer 18:0;O3/19:0(2OH)	Cer_AP		PE P-38:3 PE P-20:1_18:2	EtherPE
Cer 37:1;O2 Cer 17:1;O2/20:0	Cer_NS		PE P-38:4	EtherPE
Cer 37:1;O2 Cer 18:1;O2/19:0	Cer_NS		PE P-38:4 PE P-16:0_22:4	EtherPE
Cer 37:1;O2 Cer 20:0;O2/17:1	Cer_NDS		PE P-38:4 PE P-18:0_20:4	EtherPE
Cer 38:0;O2 Cer 18:0;O2/20:0	Cer_NDS		PE P-38:5 PE P-18:1_20:4	EtherPE
Cer 38:0;O4 Cer 18:0;O3/20:0(2OH)	Cer_AP		PE P-38:6 PE P-16:0_22:6	EtherPE
Cer 38:1;O2 Cer 18:1;O2/20:0	Cer_NS		PE P-38:6 PE P-18:2_20:4	EtherPE
Cer 38:1;O3 Cer 18:1;O2/20:0;O	Cer_HS		PE P-39:4	EtherPE
Cer 38:1;O3 Cer 19:0;O2/19:1;O	Cer_HDS		PE P-40:1 PE P-22:0_18:1	EtherPE
Cer 38:1;O3 Cer 21:0;O2/17:1;O	Cer_HDS		PE P-40:2 PE P-22:1_18:1	EtherPE
Cer 38:1;O4 Cer 19:0;O3/19:1(2OH)	Cer_AP		PE P-40:3 PE P-22:1_18:2	EtherPE
Cer 38:2;O2 Cer 20:2;O2/18:0	Cer_NS		PE P-40:4	EtherPE
Cer 39:0;O2 Cer 20:0;O2/19:0	Cer_NDS		PE P-40:4 PE P-18:0_22:4	EtherPE
Cer 39:0;O4 Cer 18:0;O3/21:0(2OH)	Cer_AP		PE P-40:5 PE P-18:0_22:5	EtherPE
Cer 39:1;O2 Cer 16:1;O2/23:0	Cer_NS		PE P-40:6 PE P-18:0_22:6	EtherPE
Cer 39:1;O2 Cer 17:1;O2/22:0	Cer_NS		PE P-40:6 PE P-20:2_20:4	EtherPE
Cer 39:1;O4 Cer 18:1;O3/21:0(2OH)	Cer_AP		PE P-40:7 PE P-18:1_22:6	EtherPE
Cer 39:1;O4 Cer 22:0;O3/17:1(2OH)	Cer_AP		PE P-42:1 PE P-24:0_18:1	EtherPE
Cer 39:2;O3 Cer 18:1;O2/21:1;O	Cer_HS		PE P-42:2 PE P-24:1_18:1	EtherPE
Cer 40:0;O2 Cer 18:0;O2/22:0	Cer_NDS		PE P-42:4 PE P-22:0_20:4	EtherPE
Cer 40:0;O2 Cer 19:0;O2/21:0	Cer_NDS		PE P-42:4 PE P-24:2_18:2	EtherPE
Cer 40:0;O4 Cer 18:0;O3/22:0(2OH)	Cer_AP		PE P-42:5 PE P-22:1_20:4	EtherPE
Cer 40:1;O2 Cer 18:1;O2/22:0	Cer_NS		PE P-42:6 PE P-20:0_22:6	EtherPE
Cer 40:1;O3 Cer 16:1;O2/24:0;O	Cer_HS		PE P-42:6 PE P-22:2_20:4	EtherPE
Cer 40:1;O3 Cer 18:1;O2/22:0;O	Cer_HS		PE P-42:7 PE P-20:1_22:6	EtherPE
Cer 40:1;O3 Cer 19:0;O2/21:1;O	Cer_HDS		PE P-44:4 PE P-16:1_28:3	EtherPE
Cer 40:1;O4 Cer 18:1;O3/22:0(2OH)	Cer_AP		PE P-44:4 PE P-24:1_20:3	EtherPE
Cer 40:5;O4 Cer 18:0;O3/22:5(2OH)	Cer_AP		PE P-44:5 PE P-24:1_20:4	EtherPE
Cer 41:0;O2 Cer 18:0;O2/23:0	Cer_NDS		PE P-44:6 PE P-24:2_20:4	EtherPE
Cer 41:0;O4 Cer 18:0;O3/23:0(2OH)	Cer_AP		PE P-46:5 PE P-24:1_22:4	EtherPE
Cer 41:1;O2 Cer 17:1;O2/24:0	Cer_NS		PE P-46:7 PE P-24:1_22:6	EtherPE
Cer 41:1;O2 Cer 18:1;O2/23:0	Cer_NS		PEtOH 34:0 PEtOH 16:0_18:0	PEtOH
Cer 41:1;O3 Cer 17:1;O2/24:0;O	Cer_HS		PEtOH 38:3 PEtOH 16:0_22:3	PEtOH
Cer 41:1;O3 Cer 18:0;O2/23:1;O	Cer_HDS		PG 31:0 PG 15:0_16:0	PG
Cer 41:2;O2 Cer 17:1;O2/24:1	Cer_NS		PG 32:0 PG 16:0_16:0	PG
Cer 41:5;O2 Cer 19:0;O2/22:5	Cer_NDS		PG 32:1 PG 16:0_16:1	PG
Cer 42:0;O2 Cer 18:0;O2/24:0	Cer_NDS		PG 33:0 PG 15:0_18:0	PG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
Cer 42:0;O3 Cer 18:0;O2/24:0;O	Cer_HDS		PG 33:0 PG 16:0_17:0	PG
Cer 42:0;O3 Cer 22:0;O2/20:0;O	Cer_HDS		PG 33:1 PG 15:0_18:1	PG
Cer 42:0;O4 Cer 18:0;O3/24:0(2OH)	Cer_AP		PG 33:1 PG 16:0_17:1	PG
Cer 42:1;O2 Cer 18:1;O2/24:0	Cer_NS		PG 34:1 PG 16:0_18:1	PG
Cer 42:1;O3 Cer 18:1;O2/24:0;O	Cer_HS		PG 34:2 PG 16:0_18:2	PG
Cer 42:1;O3 Cer 19:0;O2/23:1;O	Cer_HDS		PG 35:1 PG 17:0_18:1	PG
Cer 42:1;O4 Cer 18:1;O3/24:0(2OH)	Cer_AP		PG 36:1 PG 18:0_18:1	PG
Cer 42:2;O2 Cer 18:1;O2/24:1	Cer_NS		PG 36:2 PG 18:1_18:1	PG
Cer 42:2;O3 Cer 18:1;O2/24:1;O	Cer_HS		PG 36:3 PG 18:1_18:2	PG
Cer 42:2;O3 Cer 27:1;O2/15:1;O	Cer_HS		PG 38:2 PG 18:1_20:1	PG
Cer 42:7;O3 Cer 18:1;O2/24:6;O	Cer_HS		PG 38:3 PG 18:1_20:2	PG
Cer 43:0;O2 Cer 18:0;O2/25:0	Cer_NDS		PG 40:2 PG 20:1_20:1	PG
Cer 43:0;O3	Cer_NP		PG O-32:1 PG O-16:1_16:0	EtherPG
Cer 43:0;O4 Cer 18:0;O3/25:0(2OH)	Cer_AP		PG O-32:2 PG O-17:2_15:0	EtherPG
Cer 43:1;O2 Cer 18:1;O2/25:0	Cer_NS		PG O-34:1 PG O-16:1_18:0	EtherPG
Cer 43:1;O3 Cer 18:1;O2/25:0;O	Cer_HS		PG O-34:2 PG O-16:1_18:1	EtherPG
Cer 43:1;O3 Cer 19:0;O2/24:1;O	Cer_HDS		PG O-36:1 PG O-18:1_18:0	EtherPG
Cer 43:1;O4 Cer 18:1;O3/25:0(2OH)	Cer_AP		PG O-36:3 PG O-20:3_16:0	EtherPG
Cer 43:2;O2 Cer 19:1;O2/24:1	Cer_NS		PG O-37:5 PG O-22:5_15:0	EtherPG
Cer 43:3;O4 Cer 17:2;O3/26:1(2OH)	Cer_AP		PI 34:1	PI
Cer 43:3;O4 Cer 18:2;O2/25:1;O2	Cer_EOS		PI 34:1 PI 16:0_18:1	PI
Cer 43:3;O4 Cer 26:1;O3/17:2(2OH)	Cer_AP		PI 34:2	PI
Cer 43:4;O4 Cer 19:3;O2/24:1;O2	Cer_EOS		PI 36:1	PI
Cer 43:5;O4 Cer 17:0;O3/26:5(2OH)	Cer_AP		PI 36:1 PI 18:0_18:1	PI
Cer 44:0;O2 Cer 18:0;O2/26:0	Cer_NDS		PI 36:2	PI
Cer 44:0;O3 Cer 18:0;O2/26:0;O	Cer_HDS		PI 36:2 PI 18:0_18:2	PI
Cer 44:0;O3 Cer 20:0;O2/24:0;O	Cer_HDS		PI 38:3	PI
Cer 44:0;O4 Cer 18:0;O3/26:0(2OH)	Cer_AP		PI 38:3 PI 18:0_20:3	PI
Cer 44:1;O2 Cer 18:1;O2/26:0	Cer_NS		PI 38:4	PI
Cer 44:1;O3 Cer 18:1;O2/26:0;O	Cer_HS		PI 40:4	PI
Cer 44:1;O3 Cer 19:0;O2/25:1;O	Cer_HDS		PS 36:1	PS
Cer 44:1;O4 Cer 18:0;O3/26:1(2OH)	Cer_AP		PS 36:1 PS 18:0_18:1	PS
Cer 44:1;O4 Cer 18:1;O3/26:0(2OH)	Cer_AP		PS 36:2	PS
Cer 44:1;O4 Cer 27:0;O3/17:1(2OH)	Cer_AP		PS 36:2 PS 18:0_18:2	PS
Cer 44:2;O2 Cer 18:1;O2/26:1	Cer_NS		PS 36:2 PS 18:1_18:1	PS
Cer 44:2;O3 Cer 18:1;O2/26:1;O	Cer_HS		PS 38:1	PS
Cer 44:6;O4 Cer 18:0;O3/26:6(2OH)	Cer_AP		SE 24:1;O3/22:5;O	LCAE
Cer 45:0;O2 Cer 20:0;O2/25:0	Cer_NDS		SE 24:1;O4/15:1;O	DCAE
Cer 45:0;O4 Cer 20:0;O3/25:0(2OH)	Cer_AP		SE 24:1;O4/16:1;O	DCAE
Cer 45:1;O2 Cer 18:1;O2/27:0	Cer_NS		SE 24:1;O4/17:1;O	DCAE
Cer 45:1;O2 Cer 19:0;O2/26:1	Cer_NDS		SE 24:1;O4/17:2;O	DCAE
Cer 45:1;O2 Cer 19:1;O2/26:0	Cer_NS		SE 24:2;O4/18:0	KDCAE
Cer 45:1;O3 Cer 18:1;O2/27:0;O	Cer_HS		SE 24:2;O4/20:1	KDCAE
Cer 45:1;O3 Cer 20:1;O2/25:0;O	Cer_HS		SE 24:2;O4/20:2	KDCAE
Cer 45:1;O4 Cer 19:1;O3/26:0(2OH)	Cer_AP		SE 24:2;O4/21:0;O	KDCAE
Cer 45:1;O4 Cer 20:0;O3/25:1(2OH)	Cer_AP		SE 27:2/22:2	DSMSE
Cer 45:2;O2 Cer 18:1;O2/27:1	Cer_NS		SE 28:1/8:0	CASE

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
Cer 45:2;O3 Cer 19:2;O2/26:0;O	Cer_HS		SE 29:1/24:5	SISE
Cer 45:3;O4 Cer 17:2;O3/28:1(2OH)	Cer_AP		SE 29:1/26:5	SISE
Cer 46:0;O2 Cer 19:0;O2/27:0	Cer_NDS		SE 29:1/9:0	SISE
Cer 46:0;O2 Cer 20:0;O2/26:0	Cer_NDS		SHexCer 39:2;O3 SHexCer 18:0;O2/21:2;O	SHexCer
Cer 46:0;O3 Cer 18:0;O2/28:0;O	Cer_HDS		SL 32:0;O SL 17:0;O/15:0	SL
Cer 46:0;O3 Cer 20:0;O2/26:0;O	Cer_HDS		SL 34:0;O2 SL 17:0;O/17:0;O	SL
Cer 46:0;O4 Cer 18:0;O3/28:0(2OH)	Cer_AP		SL 51:9;O2	SL
Cer 46:0;O4 Cer 20:0;O3/26:0(2OH)	Cer_AP		SM 30:1;O2 SM 16:1;O2/14:0	SM
Cer 46:1;O2 Cer 18:1;O2/28:0	Cer_NS		SM 30:1;O2 SM 18:1;O2/12:0	SM
Cer 46:1;O3 Cer 18:1;O2/28:0;O	Cer_HS		SM 31:1;O2 SM 17:1;O2/14:0	SM
Cer 46:1;O3 Cer 19:0;O2/27:1;O	Cer_HDS		SM 32:1;O2 SM 16:1;O2/16:0	SM
Cer 46:1;O3 Cer 20:1;O2/26:0;O	Cer_HS		SM 32:1;O3	SM
Cer 46:1;O4 Cer 20:1;O3/26:0(2OH)	Cer_AP		SM 32:2;O2 SM 18:2;O2/14:0	SM
Cer 46:2;O2 Cer 18:1;O2/28:1	Cer_NS		SM 33:0;O3	SM
Cer 46:3;O4 Cer 18:2;O2/28:1;O2	Cer_EOS		SM 33:1;O2 SM 21:1;O2/12:0	SM
Cer 46:3;O4 Cer 21:1;O2/25:2;O2	Cer_EOS		SM 33:1;O3	SM
Cer 46:5;O4 Cer 18:0;O3/28:5(2OH)	Cer_AP		SM 33:2;O3	SM
Cer 47:0;O4 Cer 14:0;O3/33:0(2OH)	Cer_AP		SM 34:0;O2 SM 22:0;O2/12:0	SM
Cer 47:1;O2 Cer 20:1;O2/27:0	Cer_NS		SM 34:1;O2	SM
Cer 47:1;O3 Cer 20:0;O2/27:1;O	Cer_HDS		SM 34:1;O3	SM
Cer 47:1;O4 Cer 18:0;O3/29:1(2OH)	Cer_AP		SM 34:2;O2 SM 18:2;O2/16:0	SM
Cer 47:3;O2 Cer 19:0;O2/28:3	Cer_NDS		SM 34:2;O3	SM
Cer 47:8;O2 Cer 21:3;O2/26:5	Cer_NS		SM 34:3;O3	SM
Cer 47:9;O2 Cer 23:3;O2/24:6	Cer_NS		SM 35:1;O2 SM 18:1;O2/17:0	SM
Cer 48:0;O2 Cer 19:0;O2/29:0	Cer_NDS		SM 35:2;O2 SM 18:2;O2/17:0	SM
Cer 48:0;O3 Cer 18:0;O2/30:0;O	Cer_HDS		SM 35:3;O3	SM
Cer 48:0;O4 Cer 18:0;O3/30:0(2OH)	Cer_AP		SM 35:6;O3	SM
Cer 48:1;O2 Cer 20:1;O2/28:0	Cer_NS		SM 36:0;O2	SM
Cer 48:1;O3 Cer 18:1;O2/30:0;O	Cer_HS		SM 36:0;O2 SM 21:0;O2/15:0	SM
Cer 48:1;O3 Cer 21:0;O2/27:1;O	Cer_HDS		SM 36:0;O3	SM
Cer 48:2;O2 Cer 18:1;O2/30:1	Cer_NS		SM 36:1;O2	SM
Cer 48:2;O3 Cer 18:1;O2/30:1;O	Cer_HS		SM 36:1;O2 SM 18:1;O2/18:0	SM
Cer 48:2;O4 Cer 22:1;O2/26:1;O2	Cer_EOS		SM 36:1;O3	SM
Cer 48:5;O4 Cer 20:0;O3/28:5(2OH)	Cer_AP		SM 36:2;O2	SM
Cer 48:6;O2 Cer 18:1;O2/30:5	Cer_NS		SM 36:2;O2 SM 18:2;O2/18:0	SM
Cer 48:7;O3 Cer 18:1;O2/30:6;O	Cer_HS		SM 36:3;O2 SM 18:1;O2/18:2	SM
Cer 49:0;O2 Cer 23:0;O2/26:0	Cer_NDS		SM 36:3;O2 SM 21:0;O2/15:3	SM
Cer 49:2;O3 Cer 18:1;O2/31:1;O	Cer_HS		SM 36:4;O3	SM
Cer 49:6;O4 Cer 17:2;O3/32:4(2OH)	Cer_AP		SM 36:6;O3	SM
Cer 50:0;O2 Cer 21:0;O2/29:0	Cer_NDS		SM 37:0;O2	SM
Cer 50:0;O4 Cer 18:0;O3/32:0(2OH)	Cer_AP		SM 37:2;O3	SM
Cer 50:0;O4 Cer 20:0;O3/30:0(2OH)	Cer_AP		SM 37:6;O2	SM
Cer 50:1;O3 Cer 18:0;O2/32:1;O	Cer_HDS		SM 37:7;O3	SM
Cer 50:1;O3 Cer 18:1;O2/32:0;O	Cer_HS		SM 37:8;O3	SM
Cer 50:1;O3 Cer 19:1;O2/31:0;O	Cer_HS		SM 38:0;O2	SM
Cer 50:1;O4 Cer 18:0;O3/32:1(2OH)	Cer_AP		SM 38:0;O3	SM
Cer 50:2;O3 Cer 18:1;O2/32:1;O	Cer_HS		SM 38:1;O2 SM 16:1;O2/22:0	SM

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
Cer 50:3;O3 Cer 18:1;O2/32:2;O	Cer_HS		SM 38:1;O2 SM 18:1;O2/20:0	SM
Cer 51:2;O3 Cer 18:2;O2/33:0;O	Cer_HS		SM 38:1;O3	SM
Cer 51:2;O3 Cer 20:2;O2/31:0;O	Cer_HS		SM 38:2;O2 SM 23:0;O2/15:2	SM
Cer 52:0;O2 Cer 19:0;O2/33:0	Cer_NDS		SM 38:7;O3	SM
Cer 52:1;O4 Cer 18:0;O3/34:1(2OH)	Cer_AP		SM 39:1;O2 SM 18:1;O2/21:0	SM
Cer 52:2;O3 Cer 18:1;O2/34:1;O	Cer_HS		SM 39:8;O3	SM
Cer 52:2;O4 Cer 17:2;O3/35:0(2OH)	Cer_AP		SM 40:0;O2	SM
Cer 52:3;O3 Cer 18:1;O2/34:2;O	Cer_HS		SM 40:0;O3	SM
Cer 53:2;O3 Cer 19:2;O2/34:0;O	Cer_HS		SM 40:1;O2	SM
Cer 53:3;O3 Cer 18:2;O2/35:1;O	Cer_HS		SM 40:1;O2 SM 18:1;O2/22:0	SM
Cer 53:4;O2 Cer 19:0;O2/34:4	Cer_NDS		SM 40:1;O3	SM
Cer 54:0;O2 Cer 19:0;O2/35:0	Cer_NDS		SM 40:2;O2 SM 16:1;O2/24:1	SM
Cer 54:12;O4 Cer 18:2;O2/36:10;O2	Cer_EOS		SM 40:2;O2 SM 18:2;O2/22:0	SM
Cer 54:3;O3 Cer 18:1;O2/36:2;O	Cer_HS		SM 40:3;O2	SM
Cer 55:9;O4 Cer 21:3;O3/34:6(2OH)	Cer_AP		SM 40:8;O3	SM
Cer 56:0;O2 Cer 27:0;O2/29:0	Cer_NDS		SM 41:0;O2	SM
Cer 56:1;O2 Cer 18:1;O2/38:0	Cer_NS		SM 41:1;O2 SM 18:1;O2/23:0	SM
Cer 57:9;O4 Cer 21:3;O3/36:6(2OH)	Cer_AP		SM 41:1;O3	SM
Cer 59:5;O2 Cer 27:0;O2/32:5	Cer_NDS		SM 41:2;O2 SM 18:1;O2/23:1	SM
Cer 59:9;O4 Cer 23:3;O3/36:6(2OH)	Cer_AP		SM 41:7;O3	SM
Cer 60:0;O2 Cer 29:0;O2/31:0	Cer_NDS		SM 41:8;O3	SM
Cer 60:14;O4 Cer 18:2;O2/42:12;O2	Cer_EOS		SM 42:0;O2 SM 18:0;O2/24:0	SM
Cer 60:7;O2 Cer 22:1;O2/38:6	Cer_NS		SM 42:0;O3	SM
Cer 62:13;O4 Cer 19:1;O2/43:12;O2	Cer_EOS		SM 42:1;O2	SM
Cer 62:7;O3	Cer_NP		SM 42:1;O2 SM 18:1;O2/24:0	SM
Cer 63:12;O4 Cer 20:1;O2/43:11;O2	Cer_EOS		SM 42:1;O3	SM
Cer 63:13;O4 Cer 19:1;O2/44:12;O2	Cer_EOS		SM 42:2;O2	SM
Cer 63:13;O4 Cer 21:1;O2/42:12;O2	Cer_EOS		SM 42:2;O2 SM 18:1;O2/24:1	SM
Cer 63:14;O4 Cer 19:1;O2/44:13;O2	Cer_EOS		SM 42:2;O3	SM
Cer 64:7;O3	Cer_NP		SM 42:3;O2 SM 18:2;O2/24:1	SM
Cer 65:10;O4 Cer 21:1;O2/44:9;O2	Cer_EOS		SM 42:4;O2	SM
Cer 65:11;O4 Cer 18:2;O2/47:9;O2	Cer_EOS		SM 42:4;O3	SM
Cer 65:12;O4 Cer 21:1;O2/44:11;O2	Cer_EOS		SM 42:5;O3	SM
Cer 65:14;O4 Cer 21:1;O2/44:13;O2	Cer_EOS		SM 43:0;O2	SM
Cer 68:13;O4 Cer 22:2;O2/46:11;O2	Cer_EOS		SM 43:1;O3	SM
Cer 68:14;O4 Cer 22:2;O2/46:12;O2	Cer_EOS		SM 43:2;O2	SM
Cer 68:15;O4 Cer 22:2;O2/46:13;O2	Cer_EOS		SM 43:2;O2 SM 18:2;O2/25:0	SM
Cer 68:16;O4 Cer 22:3;O2/46:13;O2	Cer_EOS		SM 43:5;O3	SM
Cer 68:5;O4 Cer 18:2;O2/50:3;O2	Cer_EOS		SM 44:0;O2	SM
Cer 70:5;O4 Cer 18:2;O2/52:3;O2	Cer_EOS		SM 44:0;O3	SM
CL 55:2	CL		SM 44:1;O2	SM
CL 62:1	CL		SM 44:1;O2 SM 18:1;O2/26:0	SM
CL 72:8 CL 36:4_36:4	CL		SM 44:1;O2 SM 19:1;O2/25:0	SM
CL 74:0 CL 16:0_16:0_16:0_26:0	CL		SM 44:1;O3	SM
CL 75:11 CL 15:0_20:3_20:3_20:5	CL		SM 44:2;O2 SM 17:1;O2/27:1	SM
CL 80:4 CL 18:0_18:0_22:0_22:4	CL		SM 44:2;O2 SM 18:1;O2/26:1	SM
CL 80:4 CL 28:0_16:1_18:1_18:2	CL		SM 44:2;O3	SM

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
CL 84:12 CL 24:0_20:4_20:4_20:4	CL		SM 44:3;O2	SM
CL 90:1 CL 24:0_24:0_24:0_18:1	CL		SM 44:4;O2	SM
CoQ10	CoQ		SM 45:1;O2 SM 18:1;O2/27:0	SM
CoQ8	CoQ		SM 45:1;O3	SM
DG 10:0	DG		SM 45:2;O3	SM
DG 15:0	DG		SM 45:3;O3	SM
DG 17:0	DG		SM 45:6;O2	ASM
DG 18:0	DG		SM 45:7;O2	SM
DG 18:2	DG		SM 46:0;O2	SM
DG 19:0	DG		SM 46:1;O2	SM
DG 20:0 DG 8:0_12:0	DG		SM 46:1;O3	SM
DG 21:3	DG		SM 46:3;O2	SM
DG 22:0	DG		SM 46:5;O2	SM
DG 22:0 DG 10:0_12:0	DG		SM 46:6;O3	SM
DG 24:0 DG 12:0_12:0	DG		SM 46:7;O3	SM
DG 28:0 DG 12:0_16:0	DG		SM 47:2;O3	SM
DG 28:1 DG 10:0_18:1	DG		SM 47:3;O3	SM
DG 29:0 DG 14:0_15:0	DG		SM 47:4;O2	SM
DG 30:0 DG 14:0_16:0	DG		SM 47:4;O3	SM
DG 30:0 DG 15:0_15:0	DG		SM 48:2;O2	SM
DG 30:1 DG 14:0_16:1	DG		SM 48:2;O3	SM
DG 30:2 DG 14:1_16:1	DG		SM 50:1;O3	SM
DG 30:8	DG		SM 50:2;O2	SM
DG 31:0 DG 15:0_16:0	DG		SM 50:2;O3	SM
DG 31:1 DG 15:0_16:1	DG		SM 50:3;O3	SM
DG 31:2 DG 15:1_16:1	DG		SM 52:2;O3	SM
DG 32:0 DG 16:0_16:0	DG		SM 52:3;O3	SM
DG 32:1	DG		SM 56:8;O2	SM
DG 32:1 DG 16:0_16:1	DG		SM 56:9;O2	SM
DG 32:2 DG 16:1_16:1	DG		SPB 18:0;O2	DHSph
DG 33:0 DG 16:0_17:0	DG		SPB 18:0;O3	PhytoSph
DG 33:1 DG 15:0_18:1	DG		SPB 18:1;O2	Sph
DG 33:2 DG 15:0_18:2	DG		SPB 19:0;O2	DHSph
DG 34:0	DG		SPB 20:0;O2	DHSph
DG 34:0 DG 16:0_18:0	DG		SPB 22:0;O2	DHSph
DG 34:1	DG		SPB 24:0;O2	DHSph
DG 34:1 DG 16:0_18:1	DG		SPB 26:0;O2	DHSph
DG 34:2 DG 16:0_18:2	DG		ST 27:1;O	ST
DG 34:3 DG 16:1_18:2	DG		ST 27:2;O	ST
DG 35:1 DG 17:0_18:1	DG		ST 28:1;O	ST
DG 35:2 DG 17:0_18:2	DG		ST 28:2;O	ST
DG 35:2 DG 17:1_18:1	DG		ST 29:1;O	ST
DG 35:3 DG 17:1_18:2	DG		TG 24:0 TG 8:0_8:0_8:0	TG
DG 35:4 DG 15:0_20:4	DG		TG 26:0 TG 8:0_8:0_10:0	TG
DG 35:6	DG		TG 27:0 TG 5:0_9:0_13:0	TG
DG 36:0	DG		TG 28:0 TG 8:0_10:0_10:0	TG
DG 36:0 DG 18:0_18:0	DG		TG 28:1 TG 8:0_10:0_10:1	TG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
DG 36:1	DG		TG 29:0;O TG 10:0_10:0_9:0;O	OxTG
DG 36:1 DG 18:0_18:1	DG		TG 29:0 TG 5:0_10:0_14:0	TG
DG 36:2 DG 18:1_18:1	DG		TG 29:0 TG 8:0_9:0_12:0	TG
DG 36:3	DG		TG 29:1 TG 5:0_5:0_19:1	TG
DG 36:3 DG 18:1_18:2	DG		TG 29:1 TG 5:0_8:0_16:1	TG
DG 36:4 DG 16:0_20:4	DG		TG 30:0 TG 8:0_10:0_12:0	TG
DG 36:4 DG 18:2_18:2	DG		TG 30:0 TG 8:0_8:0_14:0	TG
DG 36:5 DG 16:1_20:4	DG		TG 30:1 TG 8:0_10:0_12:1	TG
DG 36:5 DG 18:2_18:3	DG		TG 30:2 TG 8:0_10:1_12:1	TG
DG 37:0	DG		TG 31:0 TG 8:0_8:0_15:0	TG
DG 37:2 DG 18:1_19:1	DG		TG 31:1 TG 5:0_8:0_18:1	TG
DG 37:4 DG 17:0_20:4	DG		TG 32:0 TG 8:0_12:0_12:0	TG
DG 37:6 DG 18:1_19:5	DG		TG 32:1;O TG 10:0_14:0_8:1;O	OxTG
DG 38:0 DG 16:0_22:0	DG		TG 32:1 TG 8:0_8:0_16:1	TG
DG 38:1	DG		TG 32:2 TG 10:0_10:1_12:1	TG
DG 38:1 DG 20:0_18:1	DG		TG 32:3;O2 TG 8:0_8:0_16:3;O2	OxTG
DG 38:2	DG		TG 33:1 TG 8:0_8:0_17:1	TG
DG 38:2 DG 18:1_20:1	DG		TG 34:0 TG 8:0_10:0_16:0	TG
DG 38:3	DG		TG 34:0 TG 8:0_12:0_14:0	TG
DG 38:3 DG 18:0_20:3	DG		TG 34:1 TG 8:0_8:0_18:1	TG
DG 38:4	DG		TG 34:2 TG 8:0_8:0_18:2	TG
DG 38:4 DG 18:0_20:4	DG		TG 34:3 TG 8:0_8:0_18:3	TG
DG 38:4 DG 18:1_20:3	DG		TG 35:0 TG 10:0_10:0_15:0	TG
DG 38:5 DG 18:1_20:4	DG		TG 35:0 TG 8:0_10:0_17:0	TG
DG 38:5 DG 18:2_20:3	DG		TG 36:0;O TG 12:0_16:0_8:0;O	OxTG
DG 38:6	DG		TG 36:0;O TG 14:0_14:0_8:0;O	OxTG
DG 38:6 DG 16:0_22:6	DG		TG 36:0 TG 10:0_12:0_14:0	TG
DG 38:6 DG 18:2_20:4	DG		TG 36:0 TG 12:0_12:0_12:0	TG
DG 39:10	DG		TG 36:1;O TG 8:0_10:0_18:1;O	OxTG
DG 39:2	DG		TG 36:1 TG 8:0_10:0_18:1	TG
DG 39:3	DG		TG 36:2 TG 8:0_10:0_18:2	TG
DG 39:5	DG		TG 36:3 TG 8:0_10:1_18:2	TG
DG 39:6	DG		TG 37:0 TG 12:0_12:0_13:0	TG
DG 39:7	DG		TG 37:0 TG 5:0_16:0_16:0	TG
DG 40:0 DG 16:0_24:0	DG		TG 37:1 TG 8:0_10:0_19:1	TG
DG 40:0 DG 20:0_20:0	DG		TG 37:2 TG 5:0_14:0_18:2	TG
DG 40:10	DG		TG 37:2 TG 5:0_14:1_18:1	TG
DG 40:4	DG		TG 38:0;O TG 14:0_16:0_8:0;O	OxTG
DG 40:4 DG 18:0_22:4	DG		TG 38:0;O TG 15:0_16:0_7:0;O	OxTG
DG 40:5	DG		TG 38:0;O2 TG 8:0_10:0_20:0;O2	OxTG
DG 40:5 DG 18:0_22:5	DG		TG 38:0 TG 12:0_12:0_14:0	TG
DG 40:6 DG 18:0_22:6	DG		TG 38:0 TG 8:0_12:0_18:0	TG
DG 41:2 DG 18:1_23:1	DG		TG 38:1;O TG 10:0_10:0_18:1;O	OxTG
DG 41:3	DG		TG 38:1;O TG 8:0_15:0_15:1;O	OxTG
DG 41:4	DG		TG 38:1 TG 8:0_12:0_18:1	TG
DG 41:5	DG		TG 38:1 TG 8:0_14:0_16:1	TG
DG 41:6	DG		TG 38:2;O TG 14:0_16:1_8:1;O	OxTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
DG 41:7	DG		TG 38:2 TG 8:0_12:0_18:2	TG
DG 42:0 DG 20:0_22:0	DG		TG 38:3 TG 8:0_12:0_18:3	TG
DG 42:1 DG 24:0_18:1	DG		TG 39:0;O TG 14:0_18:0_7:0;O	OxTG
DG 42:5	DG		TG 39:0 TG 8:0_15:0_16:0	TG
DG 42:6	DG		TG 39:1 TG 8:0_16:0_15:1	TG
DG 42:9	DG		TG 39:2 TG 5:0_16:0_18:2	TG
DG 43:0	DG		TG 39:2 TG 5:0_16:1_18:1	TG
DG 43:1 DG 25:0_18:1	DG		TG 39:3 TG 5:0_16:1_18:2	TG
DG 43:2	DG		TG 40:0;O TG 14:0_16:0_10:0;O	OxTG
DG 43:4	DG		TG 40:0 TG 10:0_14:0_16:0	TG
DG 43:6	DG		TG 40:0 TG 12:0_14:0_14:0	TG
DG 43:7	DG		TG 40:1;O TG 8:0_14:1_18:0;O	OxTG
DG 44:0	DG		TG 40:1 TG 10:0_12:0_18:1	TG
DG 44:1	DG		TG 40:2;O TG 8:0_14:0_18:2;O	OxTG
DG 44:1 DG 22:0_22:1	DG		TG 40:2 TG 10:0_12:0_18:2	TG
DG 44:3 DG 18:1_26:2	DG		TG 40:2 TG 8:0_16:1_16:1	TG
DG 45:1	DG		TG 40:3 TG 8:0_14:0_18:3	TG
DG 45:10	DG		TG 41:0;O TG 16:0_16:0_9:0;O	OxTG
DG 45:5	DG		TG 41:0 TG 12:0_13:0_16:0	TG
DG 45:6	DG		TG 41:1 TG 5:0_18:0_18:1	TG
DG 45:9	DG		TG 41:2 TG 5:0_18:1_18:1	TG
DG 46:0 DG 22:0_24:0	DG		TG 41:3 TG 5:0_18:1_18:2	TG
DG 46:10	DG		TG 41:4 TG 5:0_18:1_18:3	TG
DG 47:11	DG		TG 42:0;O TG 10:0_14:0_18:0;O	OxTG
DG 47:5	DG		TG 42:0;O TG 16:0_16:0_10:0;O	OxTG
DG 47:6	DG		TG 42:0 TG 12:0_14:0_16:0	TG
DG 47:8	DG		TG 42:0 TG 14:0_14:0_14:0	TG
DG 48:12	DG		TG 42:1 TG 12:0_12:0_18:1	TG
DG 48:13	DG		TG 42:1 TG 12:0_14:0_16:1	TG
DG 48:4	DG		TG 42:2 TG 12:0_12:1_18:1	TG
DG 48:6	DG		TG 42:2 TG 8:0_16:0_18:2	TG
DG 48:7	DG		TG 42:3 TG 12:0_12:0_18:3	TG
DG 48:8	DG		TG 42:3 TG 14:0_10:1_18:2	TG
DG 48:9	DG		TG 42:4 TG 10:1_14:1_18:2	TG
DG 50:8	DG		TG 42:4 TG 14:0_10:1_18:3	TG
DG 51:4	DG		TG 43:0 TG 14:0_14:0_15:0	TG
DG 51:6	DG		TG 43:1 TG 13:0_14:0_16:1	TG
DG 52:1	DG		TG 43:2 TG 13:0_15:1_15:1	TG
DG 52:10	DG		TG 43:3 TG 15:0_10:1_18:2	TG
DG 52:14	DG		TG 43:3 TG 8:0_17:1_18:2	TG
DG 52:3	DG		TG 44:0;O TG 10:0_16:0_18:0;O	OxTG
DG 52:9	DG		TG 44:0 TG 14:0_14:0_16:0	TG
DG O-31:1 DG O-17:0_14:1	EtherDG		TG 44:1;O TG 12:0_14:0_18:1;O	OxTG
DG O-34:1 DG O-17:0_17:1	EtherDG		TG 44:1 TG 12:0_14:0_18:1	TG
DG O-34:2 DG O-16:1_18:1	EtherDG		TG 44:2 TG 10:0_16:1_18:1	TG
DG O-34:2 DG O-17:0_17:2	EtherDG		TG 44:3 TG 10:1_16:1_18:1	TG
DG O-35:1 DG O-17:0_18:1	EtherDG		TG 44:3 TG 8:0_18:1_18:2	TG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
DG O-35:4 DG O-19:3_16:1	EtherDG		TG 44:4 TG 8:0_18:2_18:2	TG
DG O-36:1 DG O-19:0_17:1	EtherDG		TG 44:5 TG 8:0_16:0_20:5	TG
DG O-36:2 DG O-15:0_21:2	EtherDG		TG 45:1 TG 14:0_15:0_16:1	TG
DG O-36:2 DG O-18:1_18:1	EtherDG		TG 45:2 TG 14:0_15:1_16:1	TG
DG O-36:4 DG O-18:2_18:2	EtherDG		TG 45:3 TG 14:1_14:1_17:1	TG
DG O-36:5 DG O-16:1_20:4	EtherDG		TG 45:3 TG 14:1_15:1_16:1	TG
DG O-37:1 DG O-20:0_17:1	EtherDG		TG 45:7;O TG 15:1_22:5_8:1;O	OxTG
DG O-38:1 DG O-13:1_25:0	EtherDG		TG 46:0;O TG 12:0_16:0_18:0;O	OxTG
DG O-38:1 DG O-20:0_18:1	EtherDG		TG 46:1;O TG 14:0_14:0_18:1;O	OxTG
DG O-38:5 DG O-18:1_20:4	EtherDG		TG 46:1;O2 TG 14:0_14:0_18:1;O2	OxTG
DG O-38:6 DG O-18:2_20:4	EtherDG		TG 46:1 TG 12:0_16:0_18:1	TG
DG O-38:7 DG O-16:1_22:6	EtherDG		TG 46:2;O TG 14:0_14:0_18:2;O	OxTG
DG O-39:1 DG O-21:0_18:1	EtherDG		TG 46:2;O TG 16:0_18:0_12:2;O	OxTG
DG O-40:6 DG O-18:1_22:5	EtherDG		TG 46:2;O2 TG 19:0_18:2_9:0;O2	OxTG
DG O-40:8 DG O-18:2_22:6	EtherDG		TG 46:2 TG 14:0_16:1_16:1	TG
DG O-42:1 DG O-15:1_27:0	EtherDG		TG 46:3;O TG 15:0_17:1_14:2;O	OxTG
DG O-42:3 DG O-24:2_18:1	EtherDG		TG 46:3 TG 10:0_18:1_18:2	TG
DG O-44:1 DG O-17:1_27:0	EtherDG		TG 46:4;O TG 13:1_18:2_15:1;O	OxTG
DG O-44:1 DG O-26:0_18:1	EtherDG		TG 46:4 TG 10:0_18:2_18:2	TG
DG O-45:1 DG O-20:0_25:1	EtherDG		TG 46:5 TG 10:0_18:2_18:3	TG
DG O-46:1 DG O-21:0_25:1	EtherDG		TG 46:5 TG 8:0_16:0_22:5	TG
DG O-47:1 DG O-27:1_20:0	EtherDG		TG 47:2 TG 15:0_16:1_16:1	TG
DG O-50:1 DG O-24:0_26:1	EtherDG		TG 47:3;O2 TG 18:1_18:2_11:0;O2	OxTG
DGDG 24:0 DGDG 12:0_12:0	DGDG		TG 47:3 TG 14:1_16:1_17:1	TG
DGDG 26:0 DGDG 12:0_14:0	DGDG		TG 47:4 TG 12:0_17:1_18:3	TG
DGDG 28:0 DGDG 14:0_14:0	DGDG		TG 48:0;O TG 14:0_16:0_18:0;O	OxTG
DGDG 29:0 DGDG 14:0_15:0	DGDG		TG 48:0;O TG 16:0_16:0_16:0;O	OxTG
DGDG 30:0 DGDG 14:0_16:0	DGDG		TG 48:0 TG 16:0_16:0_16:0	TG
DGDG 31:0 DGDG 15:0_16:0	DGDG		TG 48:1;O TG 16:0_16:1_16:0;O	OxTG
DGDG 32:0 DGDG 15:0_17:0	DGDG		TG 48:1;O TG 16:0_19:0_13:1;O	OxTG
DGDG 32:0 DGDG 16:0_16:0	DGDG		TG 48:1 TG 14:0_16:0_18:1	TG
DGDG 32:1 DGDG 14:0_18:1	DGDG		TG 48:2;O2 TG 12:0_18:2_18:0;O2	OxTG
DGDG 32:1 DGDG 16:0_16:1	DGDG		TG 48:2 TG 16:0_14:1_18:1	TG
DGDG 32:2 DGDG 14:0_18:2	DGDG		TG 48:3;O TG 14:0_16:0_18:3;O	OxTG
DGDG 33:0 DGDG 15:0_18:0	DGDG		TG 48:3;O TG 16:1_18:1_14:1;O	OxTG
DGDG 33:1 DGDG 15:0_18:1	DGDG		TG 48:3 TG 14:0_16:1_18:2	TG
DGDG 33:2 DGDG 15:0_18:2	DGDG		TG 48:3 TG 16:1_16:1_16:1	TG
DGDG 34:0 DGDG 15:0_19:0	DGDG		TG 48:4 TG 12:0_18:2_18:2	TG
DGDG 34:0 DGDG 16:0_18:0	DGDG		TG 48:4 TG 14:1_16:1_18:2	TG
DGDG 34:1 DGDG 16:0_18:1	DGDG		TG 48:5 TG 12:0_18:2_18:3	TG
DGDG 34:2 DGDG 16:1_18:1	DGDG		TG 48:5 TG 12:1_18:2_18:2	TG
DGDG 34:3 DGDG 16:0_18:3	DGDG		TG 49:1 TG 15:0_16:0_18:1	TG
DGDG 35:1 DGDG 17:0_18:1	DGDG		TG 49:2;O TG 16:0_17:1_16:1;O	OxTG
DGDG 35:2 DGDG 17:1_18:1	DGDG		TG 49:2 TG 15:0_16:0_18:2	TG
DGDG 36:1 DGDG 18:0_18:1	DGDG		TG 49:3;O TG 16:1_19:1_14:1;O	OxTG
DGDG 36:2 DGDG 18:1_18:1	DGDG		TG 49:3;O2 TG 16:1_16:1_17:1;O2	OxTG
DGDG 36:3 DGDG 18:1_18:2	DGDG		TG 49:3;O4 TG 16:0_15:2_18:1;O4	OxTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
DGDG 37:1 DGDG 15:0_22:1	DGDG		TG 49:3 TG 15:0_16:1_18:2	TG
DGDG 38:1 DGDG 18:0_20:1	DGDG		TG 49:4;O TG 16:0_19:2_14:2;O	OxTG
DGDG 38:2 DGDG 18:1_20:1	DGDG		TG 49:4 TG 15:1_16:1_18:2	TG
DGDG 38:3 DGDG 18:1_20:2	DGDG		TG 49:7 TG 15:1_15:1_19:5	TG
DMPE 32:0 DMPE 16:0_16:0	DMPE		TG 50:0;O TG 16:0_16:0_18:0;O	OxTG
DMPE 34:1 DMPE 16:0_18:1	DMPE		TG 50:0 TG 16:0_16:0_18:0	TG
DMPE 43:9	DMPE		TG 50:1;O TG 16:0_16:0_18:1;O	OxTG
DMPE 49:2	DMPE		TG 50:1;O TG 16:0_18:1_16:0;O	OxTG
FA 16:0	FA		TG 50:1;O2 TG 16:0_16:0_18:1;O2	OxTG
FA 16:0;O2	OxFA		TG 50:1 TG 16:0_16:0_18:1	TG
FA 17:0	FA		TG 50:2;O TG 16:0_16:0_18:2;O	OxTG
FA 17:1	FA		TG 50:2;O TG 16:0_16:1_18:1;O	OxTG
FA 18:0(2OH)	OxFA		TG 50:2;O TG 16:0_18:1_16:1;O	OxTG
FA 18:0;O2	OxFA		TG 50:2 TG 16:0_16:0_18:2	TG
FA 18:0;O3	OxFA		TG 50:2 TG 16:0_16:1_18:1	TG
FA 18:1;O	OxFA		TG 50:3;O TG 16:0_16:0_18:3;O	OxTG
FA 18:1;O2	OxFA		TG 50:3;O TG 16:1_16:1_18:1;O	OxTG
FA 18:1;O3	OxFA		TG 50:3;O TG 16:1_18:2_16:0;O	OxTG
FA 18:2;O	OxFA		TG 50:3;O2 TG 16:0_16:0_18:3;O2	OxTG
FA 20:3	FA		TG 50:3;O2 TG 17:1_17:1_16:1;O2	OxTG
FA 20:3;O2	OxFA		TG 50:3 TG 16:0_16:1_18:2	TG
FA 20:3;O3	OxFA		TG 50:3 TG 16:1_16:1_18:1	TG
FA 20:4;O	OxFA		TG 50:4;O TG 16:0_16:1_18:3;O	OxTG
FA 20:4;O2	OxFA		TG 50:4;O TG 17:1_18:2_15:1;O	OxTG
FA 20:4;O4	OxFA		TG 50:4;O2 TG 16:0_16:1_18:3;O2	OxTG
FA 22:1;O3	OxFA		TG 50:4 TG 16:1_16:1_18:2	TG
FA 22:6;O	OxFA		TG 50:5 TG 16:1_16:2_18:2	TG
FA 22:6;O3	OxFA		TG 50:6 TG 12:0_18:2_20:4	TG
FA 24:0	FA		TG 50:7;O TG 17:2_17:2_16:3;O	OxTG
FA 25:0	FA		TG 51:0 TG 17:0_17:0_17:0	TG
FA 26:0	FA		TG 51:1;O TG 16:0_17:1_18:0;O	OxTG
FA 26:0(2OH)	OxFA		TG 51:1;O2 TG 8:0_8:0_9:0;O(FA 26:0)	TG_EST
FA 28:0	FA		TG 51:1 TG 16:0_17:0_18:1	TG
FA 28:1	FA		TG 51:2 TG 16:0_17:1_18:1	TG
FA 30:1	FA		TG 51:3;O TG 15:0_18:1_18:2;O	OxTG
FA 32:0	FA		TG 51:3;O3 TG 17:1_18:2_16:0;O3	OxTG
FAHFA 42:1;O FAHFA 16:0/26:0;O	FAHFA		TG 51:3 TG 16:1_17:1_18:1	TG
HBMP 50:1 HBMP 16:0_16:0_18:1	HBMP		TG 51:3 TG 17:1_17:1_17:1	TG
HBMP 52:2 HBMP 18:1/16:0_18:1	HBMP		TG 51:4;O TG 18:1_18:1_15:2;O	OxTG
HBMP 52:3 HBMP 18:1/16:0_18:2	HBMP		TG 51:4 TG 15:0_18:2_18:2	TG
HBMP 52:4 HBMP 18:2/16:0_18:2	HBMP		TG 51:5;O3 TG 16:0_15:2_20:3;O3	OxTG
HBMP 54:2 HBMP 18:0/18:1_18:1	HBMP		TG 51:5 TG 15:1_18:2_18:2	TG
HBMP 54:3 HBMP 18:1/18:0_18:2	HBMP		TG 51:6;O TG 18:2_18:2_15:2;O	OxTG
Hex2Cer 34:1;O2 Hex2Cer 18:1;O2/16:0	Hex2Cer		TG 51:6;O2 TG 16:1_18:3_17:2;O2	OxTG
Hex2Cer 34:2;O2 Hex2Cer 18:2;O2/16:0	Hex2Cer		TG 52:0 TG 16:0_18:0_18:0	TG
Hex2Cer 36:1;O2 Hex2Cer 18:1;O2/18:0	Hex2Cer		TG 52:1;O TG 16:0_18:0_18:1;O	OxTG
Hex2Cer 36:2;O2 Hex2Cer 18:1;O2/18:1	Hex2Cer		TG 52:1;O TG 16:0_18:1_18:0;O	OxTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
Hex2Cer 38:1;O2 Hex2Cer 18:1;O2/20:0	Hex2Cer		TG 52:1;O2 TG 13:0_18:1_21:0;O2	OxTG
Hex2Cer 38:2;O2 Hex2Cer 18:1;O2/20:1	Hex2Cer		TG 52:1;O2 TG 16:0_18:0_18:1;O2	OxTG
Hex2Cer 40:0;O2 Hex2Cer 18:0;O2/22:0	Hex2Cer		TG 52:1 TG 16:0_18:0_18:1	TG
Hex2Cer 40:1;O2 Hex2Cer 18:1;O2/22:0	Hex2Cer		TG 52:1 TG 18:0_18:0_16:1	TG
Hex2Cer 40:2;O2 Hex2Cer 18:1;O2/22:1	Hex2Cer		TG 52:2;O TG 16:0_18:1_18:1;O	OxTG
Hex2Cer 40:3;O2 Hex2Cer 18:1;O2/22:2	Hex2Cer		TG 52:2;O TG 18:0_18:1_16:1;O	OxTG
Hex2Cer 41:1;O2 Hex2Cer 18:1;O2/23:0	Hex2Cer		TG 52:2;O2 TG 16:0_18:2_18:0;O2	OxTG
Hex2Cer 41:2;O2 Hex2Cer 18:1;O2/23:1	Hex2Cer		TG 52:2 TG 16:0_18:1_18:1	TG
Hex2Cer 42:1;O2 Hex2Cer 18:1;O2/24:0	Hex2Cer		TG 52:2 TG 18:0_16:1_18:1	TG
Hex2Cer 42:2;O2 Hex2Cer 18:1;O2/24:1	Hex2Cer		TG 52:2 TG 18:0_17:1_17:1	TG
Hex2Cer 42:3;O2 Hex2Cer 18:1;O2/24:2	Hex2Cer		TG 52:3;O TG 16:0_18:1_18:2;O	OxTG
Hex2Cer 42:4;O2 Hex2Cer 18:1;O2/24:3	Hex2Cer		TG 52:3;O TG 16:0_18:2_18:1;O	OxTG
Hex2Cer 43:1;O2 Hex2Cer 21:1;O2/22:0	Hex2Cer		TG 52:3;O TG 18:1_18:2_16:0;O	OxTG
Hex2Cer 43:2;O2 Hex2Cer 19:1;O2/24:1	Hex2Cer		TG 52:3;O2 TG 15:1_17:2_20:0;O2	OxTG
Hex2Cer 44:0;O2 Hex2Cer 21:0;O2/23:0	Hex2Cer		TG 52:3;O2 TG 16:0_18:1_18:2;O2	OxTG
Hex2Cer 44:1;O2 Hex2Cer 18:1;O2/26:0	Hex2Cer		TG 52:3;O2 TG 19:0_15:2_18:1;O2	OxTG
Hex2Cer 44:2;O2 Hex2Cer 18:1;O2/26:1	Hex2Cer		TG 52:3;O4 TG 17:1_17:2_18:0;O4	OxTG
Hex2Cer 44:3;O2 Hex2Cer 18:1;O2/26:2	Hex2Cer		TG 52:3 TG 16:0_18:1_18:2	TG
Hex2Cer 44:8;O2	Hex2Cer		TG 52:3 TG 16:1_18:1_18:1	TG
Hex3Cer 44:1;O2	Hex3Cer		TG 52:3 TG 17:1_17:1_18:1	TG
HexCer 34:0;O2 HexCer 18:0;O2/16:0	HexCer_NDS		TG 52:3 TG 19:0_15:1_18:2	TG
HexCer 34:1;O2 HexCer 18:1;O2/16:0	HexCer_NS		TG 52:4;O TG 16:0_18:2_18:2;O	OxTG
HexCer 34:1;O3 HexCer 18:1;O2/16:0;O	HexCer_HS		TG 52:4;O TG 16:0_18:3_18:1;O	OxTG
HexCer 36:0;O2 HexCer 18:0;O2/18:0	HexCer_NDS		TG 52:4;O TG 18:2_18:2_16:0;O	OxTG
HexCer 36:1;O2 HexCer 18:1;O2/18:0	HexCer_NS		TG 52:4;O2 TG 16:0_18:1_18:3;O2	OxTG
HexCer 36:3;O3	HexCer_HDS		TG 52:4;O2 TG 18:1_18:1_16:2;O2	OxTG
HexCer 38:0;O2 HexCer 18:0;O2/20:0	HexCer_NDS		TG 52:4;O2 TG 19:0_17:4_16:0;O2	OxTG
HexCer 38:0;O4 HexCer 18:0;O3/20:0(2OH)	HexCer_AP		TG 52:4 TG 12:1_22:1_18:2	TG
HexCer 38:1;O2 HexCer 18:1;O2/20:0	HexCer_NS		TG 52:4 TG 16:1_18:1_18:2	TG
HexCer 38:6;O2 HexCer 18:1;O2/20:5	HexCer_NS		TG 52:4 TG 17:1_17:1_18:2	TG
HexCer 39:0;O2	HexCer_NDS		TG 52:5;O TG 16:1_18:2_18:2;O	OxTG
HexCer 39:0;O4 HexCer 18:0;O3/21:0(2OH)	HexCer_AP		TG 52:5;O TG 18:2_18:2_16:1;O	OxTG
HexCer 39:1;O4 HexCer 18:0;O3/21:1(2OH)	HexCer_AP		TG 52:5;O2 TG 16:0_18:2_18:3;O2	OxTG
HexCer 40:0;O2 HexCer 18:0;O2/22:0	HexCer_NDS		TG 52:5 TG 16:1_18:2_18:2	TG
HexCer 40:0;O4 HexCer 18:0;O3/22:0(2OH)	HexCer_AP		TG 52:6;O TG 18:2_18:2_16:2;O	OxTG
HexCer 40:1;O2 HexCer 18:1;O2/22:0	HexCer_NS		TG 52:6;O2 TG 16:1_18:2_18:3;O2	OxTG
HexCer 40:1;O3 HexCer 18:1;O2/22:0;O	HexCer_HS		TG 52:6 TG 16:1_18:2_18:3	TG
HexCer 40:4;O3	HexCer_HS		TG 52:7 TG 16:0_16:3_20:4	TG
HexCer 41:0;O2 HexCer 18:0;O2/23:0	HexCer_NDS		TG 52:7 TG 18:1_16:3_18:3	TG
HexCer 41:0;O4 HexCer 18:0;O3/23:0(2OH)	HexCer_AP		TG 52:7 TG 18:2_18:2_16:3	TG
HexCer 41:1;O2 HexCer 18:1;O2/23:0	HexCer_NS		TG 53:0;O2 TG 14:0_18:0_21:0;O2	OxTG
HexCer 41:1;O3 HexCer 18:1;O2/23:0;O	HexCer_HS		TG 53:0 TG 14:0_15:0_24:0	TG
HexCer 41:3;O3 HexCer 17:2;O2/24:1;O	HexCer_HS		TG 53:1;O TG 18:0_18:0_17:1;O	OxTG
HexCer 42:0;O2 HexCer 18:0;O2/24:0	HexCer_NDS		TG 53:1 TG 17:0_18:0_18:1	TG
HexCer 42:0;O3 HexCer 18:0;O2/24:0;O	HexCer_HDS		TG 53:2;O2 TG 19:0_16:2_18:0;O2	OxTG
HexCer 42:0;O4 HexCer 18:0;O3/24:0(2OH)	HexCer_AP		TG 53:2 TG 17:0_18:1_18:1	TG
HexCer 42:1;O2 HexCer 18:1;O2/24:0	HexCer_NS		TG 53:3;O TG 18:1_19:1_16:1;O	OxTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
HexCer 42:1;O3 HexCer 18:1;O2/24:0;O	HexCer_HS		TG 53:3 TG 17:0_18:1_18:2	TG
HexCer 42:1;O4 HexCer 18:0;O3/24:1(2OH)	HexCer_AP		TG 53:4;O2 TG 18:0_17:4_18:0;O2	OxTG
HexCer 42:2;O2 HexCer 18:1;O2/24:1	HexCer_NS		TG 53:4 TG 17:1_18:1_18:2	TG
HexCer 42:2;O3	HexCer_HS		TG 53:5 TG 17:1_18:2_18:2	TG
HexCer 42:3;O2 HexCer 18:1;O2/24:2	HexCer_NS		TG 53:6 TG 15:0_18:2_20:4	TG
HexCer 43:0;O2 HexCer 18:0;O2/25:0	HexCer_NDS		TG 53:7;O TG 18:2_18:2_17:3;O	OxTG
HexCer 43:0;O4 HexCer 18:0;O3/25:0(2OH)	HexCer_AP		TG 53:7;O3 TG 18:2_17:4_18:1;O3	OxTG
HexCer 43:1;O2 HexCer 18:1;O2/25:0	HexCer_NS		TG 54:0;O TG 16:0_18:0_20:0;O	OxTG
HexCer 43:1;O3 HexCer 18:1;O2/25:0;O	HexCer_HS		TG 54:0;O2 TG 15:0_18:0_21:0;O2	OxTG
HexCer 43:4;O3	HexCer_HS		TG 54:0 TG 18:0_18:0_18:0	TG
HexCer 44:0;O3 HexCer 18:0;O2/26:0;O	HexCer_HDS		TG 54:1;O TG 16:0_18:1_20:0;O	OxTG
HexCer 44:0;O4 HexCer 18:0;O3/26:0(2OH)	HexCer_AP		TG 54:1;O TG 18:0_18:0_18:1;O	OxTG
HexCer 44:1;O2 HexCer 18:1;O2/26:0	HexCer_NS		TG 54:1;O2 TG 15:0_18:0_21:1;O2	OxTG
HexCer 44:1;O3 HexCer 18:1;O2/26:0;O	HexCer_HS		TG 54:1 TG 18:0_18:0_18:1	TG
HexCer 44:1;O4 HexCer 18:0;O3/26:1(2OH)	HexCer_AP		TG 54:2;O TG 18:0_18:1_18:1;O	OxTG
HexCer 44:2;O2 HexCer 18:1;O2/26:1	HexCer_NS		TG 54:2;O TG 18:1_18:1_18:0;O	OxTG
HexCer 44:2;O3 HexCer 18:1;O2/26:1;O	HexCer_HS		TG 54:2;O2 TG 18:0_18:2_18:0;O2	OxTG
HexCer 44:2;O4 HexCer 18:0;O3/26:2(2OH)	HexCer_AP		TG 54:2;O2 TG 18:1_18:1_18:0;O2	OxTG
HexCer 44:6;O2 HexCer 18:1;O2/26:5	HexCer_NS		TG 54:2;O3 TG 19:0_17:2_18:0;O3	OxTG
HexCer 44:7;O3 HexCer 18:1;O2/26:6;O	HexCer_HS		TG 54:2 TG 18:0_18:1_18:1	TG
HexCer 45:1;O2	HexCer_NDS		TG 54:3;O TG 18:1_18:1_18:1;O	OxTG
HexCer 45:1;O2 HexCer 18:1;O2/27:0	HexCer_NS		TG 54:3;O2 TG 18:1_18:1_18:1;O2	OxTG
HexCer 45:1;O4 HexCer 19:0;O3/26:1(2OH)	HexCer_AP		TG 54:3;O2 TG 19:0_18:1_17:2;O2	OxTG
HexCer 45:5;O3	HexCer_HS		TG 54:3;O2 TG 19:1_18:2_17:0;O2	OxTG
HexCer 45:6;O2	HexCer_NDS		TG 54:3;O3 TG 19:0_17:3_18:0;O3	OxTG
HexCer 46:0;O2 HexCer 20:0;O2/26:0	HexCer_NDS		TG 54:3;O4 TG 14:0_22:3_18:0;O4	OxTG
HexCer 46:0;O3 HexCer 20:0;O2/26:0;O	HexCer_HDS		TG 54:3 TG 18:1_18:1_18:1	TG
HexCer 46:0;O4 HexCer 18:0;O3/28:0(2OH)	HexCer_AP		TG 54:4;O TG 18:1_18:2_18:1;O	OxTG
HexCer 46:0;O4 HexCer 20:0;O3/26:0(2OH)	HexCer_AP		TG 54:4;O TG 18:2_18:2_18:0;O	OxTG
HexCer 46:1;O2 HexCer 18:1;O2/28:0	HexCer_NS		TG 54:4;O2 TG 15:1_15:1_9:0;O(FA 15:1)	TG_EST
HexCer 46:1;O3	HexCer_HS		TG 54:4;O2 TG 18:0_18:1_18:3;O2	OxTG
HexCer 46:1;O3 HexCer 18:1;O2/28:0;O	HexCer_HS		TG 54:4;O2 TG 18:1_18:1_18:2;O2	OxTG
HexCer 46:1;O4 HexCer 18:0;O3/28:1(2OH)	HexCer_AP		TG 54:4;O2 TG 18:1_18:2_18:1;O2	OxTG
HexCer 46:2;O2 HexCer 18:1;O2/28:1	HexCer_NS		TG 54:4;O2 TG 18:1_19:1_17:2;O2	OxTG
HexCer 46:2;O3 HexCer 18:1;O2/28:1;O	HexCer_HS		TG 54:4;O2 TG 18:2_18:2_18:0;O2	OxTG
HexCer 46:5;O3	HexCer_HS		TG 54:4;O3 TG 19:0_17:4_18:0;O3	OxTG
HexCer 47:10;O4 HexCer 16:3;O2/31:7;O2	HexCer_EOS		TG 54:4;O4 TG 14:1_22:3_18:0;O4	OxTG
HexCer 47:5;O2	HexCer_NDS		TG 54:4;O4 TG 18:2_18:2_18:0;O4	OxTG
HexCer 48:0;O3	HexCer_HDS		TG 54:4 TG 18:1_18:1_18:2	TG
HexCer 48:1;O3	HexCer_HS		TG 54:5;O TG 18:1_18:2_18:2;O	OxTG
HexCer 48:12;O4	HexCer_EOS		TG 54:5;O TG 18:1_19:1_17:3;O	OxTG
HexCer 48:4;O3	HexCer_HS		TG 54:5;O TG 18:2_18:2_18:1;O	OxTG
HexCer 48:5;O4 HexCer 20:2;O2/28:3;O2	HexCer_EOS		TG 54:5;O TG 19:1_18:2_17:2;O	OxTG
HexCer 49:9;O3	HexCer_HS		TG 54:5;O2 TG 18:1_18:1_18:3;O2	OxTG
HexCer 50:0;O3	HexCer_HDS		TG 54:5;O2 TG 18:1_18:2_18:2;O2	OxTG
HexCer 50:1;O3 HexCer 18:0;O2/32:1;O	HexCer_HDS		TG 54:5;O2 TG 18:2_18:2_18:1;O2	OxTG
HexCer 50:1;O4 HexCer 18:0;O3/32:1(2OH)	HexCer_AP		TG 54:5;O2 TG 18:2_18:3_18:0;O2	OxTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
HexCer 50:2;O3 HexCer 18:1;O2/32:1;O	HexCer_HS		TG 54:5;O3 TG 19:0_17:4_18:1;O3	OxTG
HexCer 50:2;O4 HexCer 18:0;O3/32:2(2OH)	HexCer_AP		TG 54:5;O4 TG 19:0_17:4_18:1;O4	OxTG
HexCer 51:5;O2	HexCer_NDS		TG 54:5 TG 18:1_18:1_18:3	TG
HexCer 51:9;O3	HexCer_HS		TG 54:5 TG 18:1_18:2_18:2	TG
HexCer 52:1;O4 HexCer 18:0;O3/34:1(2OH)	HexCer_AP		TG 54:6;O TG 18:2_18:2_18:2;O	OxTG
HexCer 52:2;O4 HexCer 18:0;O3/34:2(2OH)	HexCer_AP		TG 54:6;O2 TG 18:1_18:2_18:3;O2	OxTG
HexCer 52:3;O3 HexCer 18:1;O2/34:2;O	HexCer_HS		TG 54:6;O2 TG 18:2_18:2_18:2;O2	OxTG
HexCer 52:4;O2	HexCer_NDS		TG 54:6;O3 TG 18:2_18:2_18:2;O3	OxTG
HexCer 52:5;O3 HexCer 18:1;O2/34:4;O	HexCer_HS		TG 54:6 TG 18:1_18:2_18:3	TG
HexCer 52:6;O4 HexCer 18:2;O2/34:4;O2	HexCer_EOS		TG 54:6 TG 18:2_18:2_18:2	TG
HexCer 52:7;O4 HexCer 18:2;O2/34:5;O2	HexCer_EOS		TG 54:7;O TG 18:1_18:3_18:3;O	OxTG
HexCer 52:7;O4 HexCer 18:3;O2/34:4;O2	HexCer_EOS		TG 54:7;O2 TG 18:2_18:2_18:3;O2	OxTG
HexCer 52:8;O4 HexCer 18:2;O2/34:6;O2	HexCer_EOS		TG 54:7;O2 TG 18:2_18:3_18:2;O2	OxTG
HexCer 53:10;O4 HexCer 18:2;O2/35:8;O2	HexCer_EOS		TG 54:7 TG 18:2_18:2_18:3	TG
HexCer 53:4;O2	HexCer_NDS		TG 54:8 TG 18:2_18:3_18:3	TG
HexCer 54:10;O4 HexCer 21:2;O2/33:8;O2	HexCer_EOS		TG 55:0 TG 15:0_16:0_24:0	TG
HexCer 54:5;O2	HexCer_NDS		TG 55:1;O2 TG 18:0_18:1_19:0;O2	OxTG
HexCer 55:10;O4	HexCer_EOS		TG 55:1 TG 14:0_25:0_16:1	TG
HexCer 55:5;O3	HexCer_HS		TG 55:2;O TG 15:1_18:1_22:0;O	OxTG
HexCer 55:6;O2	HexCer_NDS		TG 55:2 TG 21:0_16:1_18:1	TG
HexCer 55:6;O3	HexCer_HS		TG 55:3;O TG 19:0_16:3_20:0;O	OxTG
HexCer 55:9;O3	HexCer_HS		TG 55:3;O2 TG 19:0_18:2_18:1;O2	OxTG
HexCer 56:14;O4 HexCer 19:3;O2/37:11;O2	HexCer_EOS		TG 55:3;O3 TG 15:0_22:3_18:0;O3	OxTG
HexCer 57:10;O4 HexCer 20:1;O2/37:9;O2	HexCer_EOS		TG 55:3 TG 18:1_18:1_19:1	TG
HexCer 66:5;O4 HexCer 18:2;O2/48:3;O2	HexCer_EOS		TG 55:4;O2 TG 16:0_18:4_21:0;O2	OxTG
HexCer 68:5;O4 HexCer 18:2;O2/50:3;O2	HexCer_EOS		TG 55:4 TG 18:1_19:1_18:2	TG
HexCer 68:6;O4 HexCer 18:2;O2/50:4;O2	HexCer_EOS		TG 55:5;O4 TG 19:0_18:2_18:3;O4	OxTG
LPC 14:0	LPC		TG 55:5 TG 17:0_18:2_20:3	TG
LPC 15:0	LPC		TG 55:6 TG 17:1_18:2_20:3	TG
LPC 15:0/0:0	LPC		TG 55:7;O2 TG 18:1_20:4_17:2;O2	OxTG
LPC 15:1/0:0	LPC		TG 55:7 TG 17:1_18:2_20:4	TG
LPC 16:0	LPC		TG 55:9;O TG 18:2_18:2_19:5;O	OxTG
LPC 16:0/0:0	LPC		TG 56:0;O2 TG 18:0_18:0_20:0;O2	OxTG
LPC 16:1	LPC		TG 56:0 TG 16:0_18:0_22:0	TG
LPC 17:0/0:0	LPC		TG 56:1;O TG 18:0_18:1_20:0;O	OxTG
LPC 17:1	LPC		TG 56:1;O2 TG 18:0_18:0_20:1;O2	OxTG
LPC 18:0	LPC		TG 56:1;O4 TG 18:0_18:0_20:1;O4	OxTG
LPC 18:0/0:0	LPC		TG 56:1 TG 18:0_20:0_18:1	TG
LPC 18:1/0:0	LPC		TG 56:12;O3 TG 20:5_20:5_16:2;O3	OxTG
LPC 18:2	LPC		TG 56:2;O TG 18:1_18:1_20:0;O	OxTG
LPC 18:3/0:0	LPC		TG 56:2;O2 TG 18:0_17:1_21:1;O2	OxTG
LPC 19:1/0:0	LPC		TG 56:2;O2 TG 19:1_19:1_18:0;O2	OxTG
LPC 20:0	LPC		TG 56:2 TG 20:0_18:1_18:1	TG
LPC 20:1	LPC		TG 56:3;O TG 18:1_18:1_20:1;O	OxTG
LPC 20:1/0:0	LPC		TG 56:3;O2 TG 19:0_19:3_18:0;O2	OxTG
LPC 20:2	LPC		TG 56:3 TG 18:1_18:1_20:1	TG
LPC 20:2/0:0	LPC		TG 56:4;O TG 18:1_18:1_20:2;O	OxTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
LPC 20:3	LPC		TG 56:4;O TG 18:2_18:2_20:0;O	OxTG
LPC 20:4	LPC		TG 56:4;O2 TG 18:2_18:2_20:0;O2	OxTG
LPC 20:4/0:0	LPC		TG 56:4;O2 TG 21:0_15:3_20:1;O2	OxTG
LPC 22:1	LPC		TG 56:4;O2 TG 21:0_15:4_20:0;O2	OxTG
LPC 22:4/0:0	LPC		TG 56:4;O3 TG 18:2_18:2_20:0;O3	OxTG
LPC 22:5	LPC		TG 56:4 TG 18:1_20:1_18:2	TG
LPC 22:6	LPC		TG 56:4 TG 19:0_11:1_26:3	TG
LPC 24:0/0:0	LPC		TG 56:4 TG 19:0_19:0_18:4	TG
LPC 24:1/0:0	LPC		TG 56:5;O TG 15:0_19:3_22:2;O	OxTG
LPC 26:0	LPC		TG 56:5;O TG 20:1_18:2_18:2;O	OxTG
LPC 26:1/0:0	LPC		TG 56:5 TG 18:1_18:1_20:3	TG
LPC O-16:0	EtherLPC		TG 56:6 TG 18:1_18:2_20:3	TG
LPC O-16:1	EtherLPC		TG 56:7;O TG 18:1_18:2_20:4;O	OxTG
LPC O-17:1	EtherLPC		TG 56:7 TG 18:2_18:2_20:3	TG
LPC O-18:0	EtherLPC		TG 56:8;O TG 18:2_18:2_20:4;O	OxTG
LPC O-18:1	EtherLPC		TG 56:8 TG 18:2_18:2_20:4	TG
LPC O-18:2	EtherLPC		TG 56:9 TG 16:1_18:2_22:6	TG
LPC O-20:0	EtherLPC		TG 57:0;O2 TG 18:0_18:0_21:0;O2	OxTG
LPC O-20:1	EtherLPC		TG 57:0 TG 15:0_16:0_26:0	TG
LPC O-20:2	EtherLPC		TG 57:1;O2 TG 18:0_18:1_21:0;O2	OxTG
LPC O-22:0	EtherLPC		TG 57:1 TG 16:0_25:0_16:1	TG
LPC O-22:1	EtherLPC		TG 57:2;O2 TG 18:0_18:1_21:1;O2	OxTG
LPC O-22:2	EtherLPC		TG 57:2 TG 23:0_16:1_18:1	TG
LPC O-24:0	EtherLPC		TG 57:3;O2 TG 18:1_18:1_21:1;O2	OxTG
LPC O-24:1	EtherLPC		TG 57:3 TG 21:0_18:1_18:2	TG
LPC O-24:2	EtherLPC		TG 57:5;O TG 18:1_18:1_21:3;O	OxTG
LPC O-26:1	EtherLPC		TG 57:5;O2 TG 18:1_18:4_21:0;O2	OxTG
LPC O-26:2	EtherLPC		TG 57:5 TG 18:1_18:1_21:3	TG
LPE 14:0	LPE		TG 57:6;O2 TG 18:1_18:4_21:1;O2	OxTG
LPE 15:0	LPE		TG 57:6 TG 17:0_18:2_22:4	TG
LPE 16:1	LPE		TG 57:7 TG 17:0_18:1_22:6	TG
LPE 17:0	LPE		TG 57:7 TG 21:1_18:3_18:3	TG
LPE 18:0	LPE		TG 57:8;O2 TG 22:3_21:5_14:0;O2	OxTG
LPE 18:1	LPE		TG 57:8;O2 TG 22:4_22:4_13:0;O2	OxTG
LPE 20:4	LPE		TG 57:8 TG 17:1_18:1_22:6	TG
LPE 22:4	LPE		TG 57:9 TG 17:1_18:2_22:6	TG
LPE 22:6	LPE		TG 58:0;O2 TG 18:0_19:0_21:0;O2	OxTG
LPE O-18:0	EtherLPE		TG 58:0 TG 16:0_18:0_24:0	TG
LPE O-18:1	EtherLPE		TG 58:1;O2 TG 16:0_16:0_10:0;O(FA 16:0)	TG_EST
LPE O-18:3	EtherLPE		TG 58:1;O2 TG 18:0_19:1_21:0;O2	OxTG
LPE O-18:4	EtherLPE		TG 58:1 TG 16:0_24:0_18:1	TG
LPE O-19:2	EtherLPE		TG 58:10 TG 18:2_18:2_22:6	TG
LPE O-20:1	EtherLPE		TG 58:11 TG 18:1_20:5_20:5	TG
LPE O-20:2	EtherLPE		TG 58:2;O TG 18:1_18:1_22:0;O	OxTG
LPE O-20:4	EtherLPE		TG 58:2;O TG 22:0_18:1_18:1;O	OxTG
LPE P-16:0	EtherLPE		TG 58:2;O2 TG 18:0_18:0_8:0;O(FA 14:1)	TG_EST
LPE P-16:1	EtherLPE		TG 58:3 TG 22:0_18:1_18:2	TG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
LPE P-17:0	EtherLPE		TG 58:4;O2 TG 18:0_18:4_22:0;O2	OxTG
LPE P-18:0	EtherLPE		TG 58:4 TG 18:1_22:1_18:2	TG
LPE P-18:1	EtherLPE		TG 58:4 TG 19:0_17:2_22:2	TG
LPE P-18:2	EtherLPE		TG 58:5;O2 TG 18:0_19:4_21:1;O2	OxTG
LPE P-20:0	EtherLPE		TG 58:5 TG 18:0_18:1_22:4	TG
LPE P-20:1	EtherLPE		TG 58:6;O TG 19:0_22:3_17:3;O	OxTG
LPE P-22:0	EtherLPE		TG 58:6 TG 18:1_18:1_22:4	TG
LPE P-22:1	EtherLPE		TG 58:7 TG 18:1_18:2_22:4	TG
LPE P-22:2	EtherLPE		TG 58:8;O TG 22:3_22:5_14:0;O	OxTG
LPE P-24:1	EtherLPE		TG 58:8 TG 18:0_18:2_22:6	TG
LPE P-24:2	EtherLPE		TG 58:8 TG 18:1_18:2_22:5	TG
LPG 16:0	LPG		TG 58:9 TG 18:2_20:3_20:4	TG
LPS 18:0	LPS		TG 59:0;O2 TG 18:0_20:0_21:0;O2	OxTG
MG 19:0	MG		TG 59:0 TG 16:0_17:0_26:0	TG
MG 22:0	MG		TG 59:1;O2 TG 18:0_20:1_21:0;O2	OxTG
MG 27:0	MG		TG 59:2 TG 23:0_18:1_18:1	TG
MG 29:1	MG		TG 59:3 TG 18:1_18:1_23:1	TG
MG 31:1	MG		TG 59:3 TG 24:0_17:1_18:2	TG
MG 34:1	MG		TG 59:4 TG 18:1_23:1_18:2	TG
MG 34:2	MG		TG 59:5;O2 TG 20:1_18:4_21:0;O2	OxTG
MG 34:3	MG		TG 59:5 TG 16:0_23:1_20:4	TG
MG 35:1	MG		TG 59:7;O4 TG 15:0_22:3_22:4;O4	OxTG
MG 36:0	MG		TG 59:8;O2 TG 18:1_22:6_19:1;O2	OxTG
MG 36:1	MG		TG 60:0 TG 18:0_20:0_22:0	TG
MG 36:2	MG		TG 60:1;O2 TG 18:0_18:0_8:0;O(FA 16:0)	TG_EST
MG 36:3	MG		TG 60:1;O4 TG 18:0_22:0_20:1;O4	OxTG
MG 36:6	MG		TG 60:10 TG 18:1_18:4_24:5	TG
MG 37:0	MG		TG 60:15 TG 20:5_20:5_20:5	TG
MG 37:1	MG		TG 60:2;O2 TG 18:0_21:2_21:0;O2	OxTG
MG 38:1	MG		TG 60:2;O3 TG 18:0_22:1_20:1;O3	OxTG
MG 38:4	MG		TG 60:2 TG 24:0_18:1_18:1	TG
MG 38:8	MG		TG 60:3 TG 20:1_20:1_20:1	TG
MGDG 32:1 MGDG 14:0_18:1	MGDG		TG 60:3 TG 24:0_18:1_18:2	TG
MGDG 36:1 MGDG 16:0_20:1	MGDG		TG 60:4 TG 18:1_24:1_18:2	TG
MGDG 36:2 MGDG 18:1_18:1	MGDG		TG 60:5 TG 24:1_18:2_18:2	TG
MGDG 36:3 MGDG 18:1_18:2	MGDG		TG 60:6 TG 18:1_20:1_22:4	TG
MGDG 36:4 MGDG 18:2_18:2	MGDG		TG 60:9 TG 10:0_24:2_26:7	TG
MGDG 36:5 MGDG 18:2_18:3	MGDG		TG 60:9 TG 18:1_20:3_22:5	TG
MGDG 43:10	MGDG		TG 60:9 TG 5:0_25:1_30:8	TG
MGDG O-31:1 MGDG O-15:1_16:0	EtherMGDG		TG 61:0 TG 16:0_16:0_29:0	TG
MMPE 32:1	MMPE		TG 61:2 TG 25:0_18:1_18:1	TG
NAE 14:0	NAE		TG 61:3 TG 25:0_18:1_18:2	TG
NAE 16:0	NAE		TG 61:4 TG 25:0_18:2_18:2	TG
NAE 17:0	NAE		TG 61:6 TG 18:1_23:1_20:4	TG
NAE 17:2	NAE		TG 62:0 TG 18:0_22:0_22:0	TG
NAE 18:1	NAE		TG 62:10 TG 18:1_22:4_22:5	TG
NAE 18:2	NAE		TG 62:11 TG 18:1_22:4_22:6	TG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
NAE 18:3	NAE		TG 62:14 TG 20:4_20:4_22:6	TG
NAE 19:2	NAE		TG 62:2 TG 26:0_18:1_18:1	TG
NAE 20:0	NAE		TG 62:3 TG 26:0_18:1_18:2	TG
NAE 20:1	NAE		TG 62:4 TG 18:1_26:1_18:2	TG
NAE 20:2	NAE		TG 62:5 TG 18:1_18:2_26:2	TG
NAE 20:3	NAE		TG 62:6 TG 18:2_18:2_26:2	TG
NAE 20:4	NAE		TG 62:7 TG 20:0_18:3_24:4	TG
NAE 20:5	NAE		TG 62:8 TG 20:1_20:3_22:4	TG
NAE 24:6	NAE		TG 62:9 TG 18:1_22:4_22:4	TG
NAE 28:4	NAE		TG 63:0 TG 18:0_22:0_23:0	TG
NAGly 18:5	NAGly		TG 63:2 TG 27:0_18:1_18:1	TG
NAGly 32:1;O2 NAGly 17:0;O(FA 15:0)	NAGly		TG 63:3 TG 27:0_18:1_18:2	TG
NAGly 34:3;O2 NAGly 18:1;O(FA 16:1)	NAGly		TG 63:4 TG 27:0_18:2_18:2	TG
NAGly 36:2;O2 NAGly 17:0;O(FA 19:1)	NAGly		TG 63:5 TG 27:1_18:2_18:2	TG
NAGlySer 32:1;O2 NAGlySer 17:0;O(FA 15:0)	NAGlySer		TG 64:0 TG 18:0_22:0_24:0	TG
NAGlySer 33:1;O2 NAGlySer 17:0;O(FA 16:0)	NAGlySer		TG 64:1;O2 TG 22:0_22:0_20:1;O2	OxTG
NAGlySer 34:1;O2 NAGlySer 17:0;O(FA 17:0)	NAGlySer		TG 64:11 TG 20:3_22:4_22:4	TG
NAOrn 16:0;O	NAOrn		TG 64:2 TG 28:0_18:1_18:1	TG
NAOrn 28:1;O2 NAOrn 12:0;O(FA 16:0)	NAOrn		TG 64:3 TG 28:0_18:1_18:2	TG
NAOrn 30:1;O2 NAOrn 14:0;O(FA 16:0)	NAOrn		TG 64:4 TG 18:1_28:1_18:2	TG
NAOrn 30:1;O2 NAOrn 15:0;O(FA 15:0)	NAOrn		TG 64:5 TG 18:0_18:0_28:5	TG
NAOrn 31:1;O2 NAOrn 16:0;O(FA 15:0)	NAOrn		TG 64:5 TG 28:1_18:2_18:2	TG
NAOrn 32:1;O2 NAOrn 17:0;O(FA 15:0)	NAOrn		TG 64:6 TG 20:1_24:1_20:4	TG
NAOrn 32:2;O2 NAOrn 16:1;O(FA 16:0)	NAOrn		TG 64:7 TG 24:1_18:2_22:4	TG
NAOrn 34:0	NAOrn		TG 64:9 TG 18:0_18:4_28:5	TG
NATau 18:0	NATau		TG 65:0 TG 15:0_24:0_26:0	TG
PC 19:1	PC		TG 65:1 TG 23:0_24:0_18:1	TG
PC 28:0	PC		TG 65:2 TG 15:0_18:1_32:1	TG
PC 29:0	PC		TG 65:3 TG 18:1_18:1_29:1	TG
PC 29:0 PC 14:0_15:0	PC		TG 65:4 TG 16:1_17:1_32:2	TG
PC 29:3	PC		TG 65:6 TG 18:0_23:1_24:5	TG
PC 30:1	PC		TG 66:0 TG 22:0_22:0_22:0	TG
PC 30:1 PC 12:0_18:1	PC		TG 66:1 TG 22:0_22:0_22:1	TG
PC 31:0 PC 15:0_16:0	PC		TG 66:3 TG 16:1_18:1_32:1	TG
PC 31:1	PC		TG 66:4 TG 18:1_30:1_18:2	TG
PC 31:1 PC 15:0_16:1	PC		TG 66:5 TG 30:1_18:2_18:2	TG
PC 32:0	PC		TG 66:6 TG 18:1_26:1_22:4	TG
PC 32:0 PC 16:0_16:0	PC		TG 66:7 TG 26:1_20:3_20:3	TG
PC 32:1	PC		TG 67:1 TG 24:0_25:0_18:1	TG
PC 32:1 PC 16:0_16:1	PC		TG 67:2 TG 25:0_18:1_24:1	TG
PC 32:2 PC 16:1_16:1	PC		TG 68:0 TG 22:0_22:0_24:0	TG
PC 33:0 PC 16:0_17:0	PC		TG 68:1;O2 TG 15:0_18:0_18:0;O(FA 17:0)	TG_EST
PC 33:1	PC		TG 68:1 TG 24:0_26:0_18:1	TG
PC 33:1 PC 15:0_18:1	PC		TG 68:2;O2 TG 16:0_18:0_16:0;O(FA 18:1)	TG_EST
PC 33:1 PC 16:0_17:1	PC		TG 68:2 TG 18:0_18:1_32:1	TG
PC 33:2	PC		TG 68:3;O2 TG 18:0_18:1_14:1;O(FA 18:0)	TG_EST
PC 33:2 PC 15:0_18:2	PC		TG 68:3 TG 18:1_18:1_32:1	TG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
PC 33:2 PC 15:1_18:1	PC		TG 68:4 TG 18:1_32:1_18:2	TG
PC 33:3	PC		TG 68:5 TG 18:1_18:2_32:2	TG
PC 33:3 PC 15:1_18:2	PC		TG 70:2;O2 TG 18:0_18:1_18:0;O(FA 16:0)	TG_EST
PC 34:0 PC 16:0_18:0	PC		TG 70:2 TG 26:0_18:1_26:1	TG
PC 34:1	PC		TG 70:3;O2 TG 18:0_14:1_24:0;O(FA 14:1)	TG_EST
PC 34:1 PC 16:0_18:1	PC		TG 70:3;O2 TG 18:1_18:1_18:0;O(FA 16:0)	TG_EST
PC 34:2 PC 16:0_18:2	PC		TG 70:3 TG 26:0_26:1_18:2	TG
PC 34:3 PC 16:0_18:3	PC		TG 70:4;O2 TG 16:0_18:1_18:1;O(FA 18:1)	TG_EST
PC 34:3 PC 16:1_18:2	PC		TG 70:4 TG 18:1_34:1_18:2	TG
PC 34:4 PC 14:0_20:4	PC		TG 70:6 TG 18:2_18:2_34:2	TG
PC 35:0	PC		TG 71:2;O2 TG 18:0_18:1_17:0;O(FA 18:0)	TG_EST
PC 35:1	PC		TG 72:2;O2 TG 18:0_18:0_18:0;O(FA 18:1)	TG_EST
PC 35:1 PC 17:0_18:1	PC		TG 72:7;O2 TG 18:1_18:2_18:2;O(FA 18:1)	TG_EST
PC 35:2	PC		TG 74:3;O2 TG 16:0_18:2_24:0;O(FA 16:0)	TG_EST
PC 35:2 PC 17:0_18:2	PC		TG 76:8;O2 TG 18:1_18:1_22:4;O(FA 18:1)	TG_EST
PC 35:2 PC 17:1_18:1	PC		TG 76:9;O2 TG 14:1_22:3_18:1;O(FA 22:3)	TG_EST
PC 35:3	PC		TG 78:0 TG 24:0_24:0_30:0	TG
PC 35:3 PC 17:1_18:2	PC		TG 78:1;O2 TG 18:0_18:0_24:0;O(FA 18:0)	TG_EST
PC 35:4	PC		TG 78:2;O2 TG 18:0_18:0_24:0;O(FA 18:1)	TG_EST
PC 35:5	PC		TG 78:3;O2 TG 18:1_18:1_24:0;O(FA 18:0)	TG_EST
PC 35:5 PC 15:1_20:4	PC		TG 78:7;O2 TG 22:3_22:3_17:0;O(FA 17:0)	TG_EST
PC 35:6	PC		TG 79:0 TG 25:0_26:0_28:0	TG
PC 35:6 PC 15:1_20:5	PC		TG 80:10;O2 TG 18:1_18:1_22:4;O(FA 22:3)	TG_EST
PC 36:0 PC 18:0_18:0	PC		TG O-34:0 TG O-14:0_10:0_10:0	EtherTG
PC 36:1 PC 18:0_18:1	PC		TG O-34:1 TG O-10:0_9:0_15:1	EtherTG
PC 36:2	PC		TG O-34:1 TG O-18:1_8:0_8:0	EtherTG
PC 36:2 PC 18:1_18:1	PC		TG O-34:1 TG O-9:0_11:0_14:1	EtherTG
PC 36:3	PC		TG O-36:1 TG O-18:1_9:0_9:0	EtherTG
PC 36:3 PC 18:1_18:2	PC		TG O-36:3 TG O-20:3_8:0_8:0	EtherTG
PC 36:4	PC		TG O-44:0 TG O-12:0_16:0_16:0	EtherTG
PC 36:5	PC		TG O-44:3 TG O-14:1_15:1_15:1	EtherTG
PC 36:5 PC 16:0_20:5	PC		TG O-46:1 TG O-12:0_16:0_18:1	EtherTG
PC 36:6	PC		TG O-46:2 TG O-12:0_16:0_18:2	EtherTG
PC 37:0	PC		TG O-46:3 TG O-12:0_16:1_18:2	EtherTG
PC 37:1	PC		TG O-46:3 TG O-16:1_15:1_15:1	EtherTG
PC 37:2	PC		TG O-48:0 TG O-17:0_15:0_16:0	EtherTG
PC 37:5	PC		TG O-48:1 TG O-16:0_16:0_16:1	EtherTG
PC 37:6	PC		TG O-48:2 TG O-16:0_16:1_16:1	EtherTG
PC 37:7	PC		TG O-48:2 TG O-16:1_16:0_16:1	EtherTG
PC 38:1 PC 18:0_20:1	PC		TG O-48:3 TG O-12:0_18:1_18:2	EtherTG
PC 38:2	PC		TG O-48:3 TG O-16:1_15:1_17:1	EtherTG
PC 38:2 PC 18:1_20:1	PC		TG O-48:4 TG O-12:0_18:2_18:2	EtherTG
PC 38:3 PC 18:0_20:3	PC		TG O-48:4 TG O-18:2_15:1_15:1	EtherTG
PC 38:3 PC 20:1_18:2	PC		TG O-49:1 TG O-17:1_16:0_16:0	EtherTG
PC 38:4	PC		TG O-49:4 TG O-17:1_15:1_17:2	EtherTG
PC 38:4 PC 18:0_20:4	PC		TG O-50:1 TG O-16:0_16:0_18:1	EtherTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
PC 38:4 PC 18:1_20:3	PC		TG O-50:2 TG O-16:0_16:1_18:1	EtherTG
PC 38:5 PC 18:1_20:4	PC		TG O-50:3 TG O-16:1_17:1_17:1	EtherTG
PC 38:6 PC 16:0_22:6	PC		TG O-50:4 TG O-18:2_15:1_17:1	EtherTG
PC 38:6 PC 18:2_20:4	PC		TG O-50:5 TG O-16:1_17:2_17:2	EtherTG
PC 39:1	PC		TG O-51:2 TG O-17:0_17:1_17:1	EtherTG
PC 39:2	PC		TG O-51:3 TG O-19:1_16:1_16:1	EtherTG
PC 39:3	PC		TG O-51:4 TG O-17:1_17:1_17:2	EtherTG
PC 39:4	PC		TG O-52:0 TG O-18:0_16:0_18:0	EtherTG
PC 39:5	PC		TG O-52:1 TG O-16:0_18:0_18:1	EtherTG
PC 39:6	PC		TG O-52:3 TG O-16:0_18:1_18:2	EtherTG
PC 39:7	PC		TG O-52:4 TG O-12:0_19:0_21:4	EtherTG
PC 40:1	PC		TG O-52:4 TG O-20:2_15:1_17:1	EtherTG
PC 40:2	PC		TG O-52:4 TG O-8:0_22:2_22:2	EtherTG
PC 40:3	PC		TG O-52:5 TG O-13:0_17:3_22:2	EtherTG
PC 40:4	PC		TG O-52:5 TG O-16:1_18:2_18:2	EtherTG
PC 40:5	PC		TG O-52:7 TG O-18:2_16:0_18:5	EtherTG
PC 40:6	PC		TG O-53:3 TG O-17:1_18:1_18:1	EtherTG
PC 40:7 PC 18:1_22:6	PC		TG O-53:4 TG O-20:2_16:1_17:1	EtherTG
PC 40:8 PC 18:2_22:6	PC		TG O-54:2 TG O-18:0_18:1_18:1	EtherTG
PC 41:6	PC		TG O-54:3 TG O-20:1_17:1_17:1	EtherTG
PC 42:0 PC 15:0_27:0	PC		TG O-54:4 TG O-16:0_19:0_19:4	EtherTG
PC 42:1	PC		TG O-54:4 TG O-17:0_16:0_21:4	EtherTG
PC 42:2	PC		TG O-54:4 TG O-18:1_17:2_19:1	EtherTG
PC 42:3	PC		TG O-54:5 TG O-16:1_19:0_19:4	EtherTG
PC 42:4	PC		TG O-54:7 TG O-16:2_19:0_19:5	EtherTG
PC 42:5	PC		TG O-55:10 TG O-15:0_20:5_20:5	EtherTG
PC 42:6	PC		TG O-55:4 TG O-16:1_19:0_20:3	EtherTG
PC 44:1	PC		TG O-55:9 TG O-17:3_19:3_19:3	EtherTG
PC 44:2	PC		TG O-56:2 TG O-16:0_19:0_21:2	EtherTG
PC 44:4	PC		TG O-56:2 TG O-20:0_18:1_18:1	EtherTG
PC 46:3	PC		TG O-56:2 TG O-20:2_18:0_18:0	EtherTG
PC 46:4	PC		TG O-56:3 TG O-20:0_18:1_18:2	EtherTG
PC 51:8	PC		TG O-56:4 TG O-16:4_20:0_20:0	EtherTG
PC 52:9	PC		TG O-56:4 TG O-18:2_19:1_19:1	EtherTG
PC O-23:3	EtherPC		TG O-56:4 TG O-18:4_19:0_19:0	EtherTG
PC O-29:0	EtherPC		TG O-56:5 TG O-18:0_18:1_20:4	EtherTG
PC O-29:1	EtherPC		TG O-56:7 TG O-16:2_19:0_21:5	EtherTG
PC O-30:0 PC O-16:0_14:0	EtherPC		TG O-56:7 TG O-18:5_16:0_22:2	EtherTG
PC O-30:1	EtherPC		TG O-56:8 TG O-16:1_18:1_22:6	EtherTG
PC O-30:1 PC O-16:1_14:0	EtherPC		TG O-57:10 TG O-15:0_21:5_21:5	EtherTG
PC O-31:0 PC O-16:0_15:0	EtherPC		TG O-57:11 TG O-17:1_20:5_20:5	EtherTG
PC O-31:1 PC O-16:1_15:0	EtherPC		TG O-57:12 TG O-18:3_19:4_20:5	EtherTG
PC O-32:0	EtherPC		TG O-57:3 TG O-21:3_18:0_18:0	EtherTG
PC O-32:0 PC O-16:0_16:0	EtherPC		TG O-57:5 TG O-19:5_19:0_19:0	EtherTG
PC O-32:1 PC O-16:0_16:1	EtherPC		TG O-57:6 TG O-21:4_18:1_18:1	EtherTG
PC O-32:1 PC O-16:1_16:0	EtherPC		TG O-57:7 TG O-21:4_18:1_18:2	EtherTG
PC O-32:2 PC O-16:1_16:1	EtherPC		TG O-58:1 TG O-18:0_18:1_22:0	EtherTG

Metabolite and Lipid name	Class		Metabolite and Lipid name	Class
PC O-32:3 PC O-16:2_16:1	EtherPC		TG O-58:10 TG O-18:2_20:4_20:4	EtherTG
PC O-33:0 PC O-17:0_16:0	EtherPC		TG O-58:3 TG O-16:1_21:1_21:1	EtherTG
PC O-33:1	EtherPC		TG O-58:3 TG O-22:0_18:1_18:2	EtherTG
PC O-33:1 PC O-15:0_18:1	EtherPC		TG O-58:4 TG O-22:1_18:1_18:2	EtherTG
PC O-33:1 PC O-24:1_9:0	EtherPC		TG O-58:5 TG O-18:0_18:1_22:4	EtherTG
PC O-33:2 PC O-16:1_17:1	EtherPC		TG O-58:5 TG O-18:0_19:0_21:5	EtherTG
PC O-33:3 PC O-14:1_19:2	EtherPC		TG O-58:6 TG O-16:1_21:0_21:5	EtherTG
PC O-33:3 PC O-15:1_18:2	EtherPC		TG O-58:6 TG O-22:2_18:2_18:2	EtherTG
PC O-33:6	EtherPC		TG O-58:7 TG O-20:2_16:4_22:1	EtherTG
PC O-34:0 PC O-18:0_16:0	EtherPC		TG O-58:8 TG O-16:4_21:2_21:2	EtherTG
PC O-34:1 PC O-16:0_18:1	EtherPC		TG O-58:8 TG O-22:6_18:1_18:1	EtherTG
PC O-34:2 PC O-16:0_18:2	EtherPC		TG O-58:9 TG O-22:5_18:2_18:2	EtherTG
PC O-34:2 PC O-16:1_18:1	EtherPC		TG O-59:10 TG O-16:1_21:5_22:4	EtherTG
PC O-34:3	EtherPC		TG O-59:10 TG O-16:3_21:5_22:2	EtherTG
PC O-34:3 PC O-16:1_18:2	EtherPC		TG O-59:9 TG O-15:3_22:3_22:3	EtherTG
PC O-34:3 PC O-18:2_16:1	EtherPC		TG O-59:9 TG O-16:2_21:5_22:2	EtherTG
PC O-35:0	EtherPC		TG O-60:4 TG O-16:4_22:0_22:0	EtherTG
PC O-35:1 PC O-17:0_18:1	EtherPC		TG O-60:6 TG O-20:1_18:1_22:4	EtherTG
PC O-35:2	EtherPC		TG O-60:7 TG O-20:0_19:5_21:2	EtherTG
PC O-35:3	EtherPC		TG O-61:10 TG O-21:4_18:1_22:5	EtherTG
PC O-35:3 PC O-17:1_18:2	EtherPC		Tryptophan	Others
PC O-35:6	EtherPC		VAE 22:3	VAE
PC O-35:6 PC O-16:2_19:4	EtherPC		VAE 23:0	VAE
PC O-35:7	EtherPC		VAE 24:5	VAE
PC O-35:8	EtherPC			

APPENDIX C

Table M. Description of the abbreviations used for lipid subclasses

Abbreviation	Lipid subclass
ADGGA	Acyl diacylglycerol glucuronide
AHexBRS	Acylhexosyl brassicasterol
AHexCAS	Acylhexosyl campesterol
AHexCer	Acylhexosylceramide
AHexCS	Acylhexosyl cholesterol
AHexSIS	Acylhexosyl sitosterol
AHexSTS	Acylhexosyl stigmaterol
ASM	Acylsphingomyelin
BASulfateST	Cholic acid sulfate
BileAcid	Cholic acid
BMP	Bismonoacylglycerophosphate
BRSE	Brassicasterol ester
CAR	Acylcarinitine
CASE	Campesterol ester
CE	Cholesteryl ester
Cer-ADS	Ceramide alpha-hydroxy fatty acid-dihydrosphingosine

Abbreviation	Lipid subclass
Cer-AP	Ceramide alpha-hydroxy fatty acid-phytospingosine
Cer-AS	Ceramide alpha-hydroxy fatty acid-sphingosine
Cer-BDS	Ceramide beta-hydroxy fatty acid-dihydrosphingosine
Cer-BS	Ceramide beta-hydroxy fatty acid-sphingosine
Cer-EBDS	Ceramide Esterified beta-hydroxy fatty acid dihydrosphingosine
Cer-EODS	Ceramide Esterified omega-hydroxy fatty acid dihydrosphingosine
Cer-EOS	Ceramide Esterified omega-hydroxy fatty acid-sphingosine
Cer-HDS	Ceramide hydroxy fatty acid-dihydrosphingosine
Cer-HS	Ceramide hydroxy fatty acid-sphingosine
Cer-NDS	Dihydroceramide
Cer-NP	Ceramide with phytospingosine
Cer-NS	Ceramide
CerP	Ceramide 1-phosphates
Cholesterol	Cholesterol
CL	Cardiolipin
CoQ	Coenzyme Q
DCAE	Esterified deoxycholic acid
DG	Diacylglycerol
DGCC	Diacylglycerol-3-O-carboxyhydroxymethylcholine
DGDG	Digalactosyldiacylglycerol
DGGA	Diacylglycerol glucuronide
DGTS/A	Diacylglycerol trimethylhomoserine
DHSph	Sphinganine
DLCL	Dilysocardiolipin
EtherDG	Ether-linked diacylglycerol
EtherDGDG	Ether-linked digalactosyldiacylglycerol
EtherLPC	Ether-linked lysophosphatidylcholine
EtherLPE	Ether-linked lysophosphatidylethanolamine
EtherLPG	Ether-linked lysophosphatidylglycerol
EtherMGDG	Ether-linked monogalactosyldiacylglycerol
EtherOxPE	Ether-linked oxidized phosphatidylethanolamine
EtherPC	Ether-linked phosphatidylcholine
EtherPE	Ether-linked phosphatidylethanolamine
EtherPE(P)	Ether-linked phosphatidylethanolamine
EtherPG	Ether-linked phosphatidylglycerol
EtherPI	Ether-linked phosphatidylinositol
EtherPS	Ether-linked phosphatidylserine
EtherSMGDG	Semino lipid
EtherTG	Ether-linked triacylglycerol
FA	Free fatty acid
GM3	Ganglioside GM3
HBMP	Hemibismonoacylglycerophosphate
Hex2Cer	Lactosylceramide
Hex3Cer	Gb3
HexCer-ADS	Hexosylceramide alpha-hydroxy fatty acid dihydrosphingosine
HexCer-AS	Hexosylceramide alpha-hydroxy fatty acid-sphingosine
HexCer-BDS	Hexosylceramide beta-hydroxy fatty acid-dihydrosphingosine

Abbreviation	Lipid subclass
HexCer-BS	Hexosylceramide beta-hydroxy fatty acid-sphingosine
HexCer-EOS	Hexosylceramide Esterified omega-hydroxy fatty acid sphingosine
HexCer-HDS	Hexosylceramide hydroxyfatty acid-dihydrosphingosine
HexCer-HS	Hexosylceramide hydroxyfatty acid-sphingosine
HexCer-NDS	Hexosyldihydroceramide
HexCer-NP	Hexosylceramide non-hydroxyfatty acid-phytospingosine
HexCer-NS	Hexosylceramide
LDGCC	Lysodiacylglyceryl-3-O-carboxyhydroxymethylcholine
LDGTS/A	Lysodiacylglyceryl trimethylhomoserine
LNAPE	N-acyl-lysophosphatidylethanolamine
LNAPS	N-acyl-lysophosphatidylserine
LPC	Lysophosphatidylcholine
LPE	Lysophosphatidylethanolamine
LPG	Lysophosphatidylglycerol
LPI	Lysophosphatidylinositol
LPS	Lysophosphatidylserine
MG	Monoacylglycerol
MGDG	Monogalactosyldiacylglycerol
MLCL	Lysocardiolipin
NAE	N acyl ethanolamine
NAGly	N acyl glycine
NAGlySer	N acyl glycil serine
NAOrn	N acyl ornithine
OxPC	Oxidized phosphatidylcholine
OxPE	Oxidized phosphatidylethanolamine
OxPG	Oxidized phosphatidylglycerol
OxPI	Oxidized phosphatidylinositol
OxPS	Oxidized phosphatidylserine
OxTG	Oxidized triglyceride
PA	Phosphatidic acid
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PE-Cer	Ceramide phosphoethanolamine
PE-Cer+O	Oxidized ceramide phosphoethanolamine
PG	Phosphatidylglycerol
PhytoSph	Phytosphingosine
PI	Phosphatidylinositol
PI-Cer+O	Oxidized ceramide phosphoinositol
PS	Phosphatidylserine
SHex	Stigmasterol hexoside
SHexCer	Sulfatide
SHexCer+O	Oxidized sulfatide
SISE	Sitosterol ester
SL	Sulfonolipid
SL+O	Oxidized sulfonolipid
SM	Sphingomyelin
SM+O	Oxidized sphingomyelin

Abbreviation	Lipid subclass
Sph	Sphingosine
SQDG	Sulfoquinovosyl diacylglycerol
STSE	Stigmasterol ester
TG	Triacylglycerol
TG-EST	Triacylglycerol estolides
VAE	Vitamin A fatty acid ester
Vitamin D	Vitamin D
Vitamin E	Vitamin E

APPENDIX D

Table N. Summary of MS-DIAL parameters used for feature detection, alignment and compound identification in salivary metabolomics and lipidomics analyses.

Data Type	Metabolomics	Lipidomics
Data collections		
MS1 Tolerance	0.01-0.02	0.01
MS2 Tolerance	0.5	0.05
Peak Detection		
Minimum Peak Height	1000	1000
Mass Slice	0.1	0.1
MS2 Deconvolution		
Sigma Window	0.5	0.5
MS/MS Abundance Cut Off	0	0
Identification		
MSP File	MSMS-public-experimentspectra-neg/pos-VS19	MS-DIAL library
Retention Time Tolerance	100	100
Accurate MS1	0.01-0.02	0.01-0.02
Accurate MS2	0.05 (HR) 0.5 (LR)	0.05 (HR) 0.5 (LR)
Score Cut off	70-80	70-80
Positive Adducts		
	+H ⁺ (+1.0073)	+H ⁺ (+1.0073)
	+NH ₄ ⁺ (+18.0338)	+NH ₄ ⁺ (+18.0338)
	+Na ⁺ (+22.9892)	+Na ⁺ (+22.9892)
	+H ⁺ -H ₂ O (-17.0022)	+H ⁺ -H ₂ O (-17.0022)
	+H ⁺ -2H ₂ O (-30.0022)	+H ⁺ -2H ₂ O (-30.0022)
Negative Adducts		
	-H ⁻ (-1.0073)	-H ⁻ (-1.0073)
	-H-H ₂ O ⁻ (-18.0022)	-H-H ₂ O ⁻ (-18.0022)
Alignment		
Reference File	Central QC	Central QC
Retention Time Tolerance	0.1	0.1
MS1 Tolerance	0.015	0.015
Sample Average/Blank Average	10	10

APPENDIX E

Table O. Summary of preliminary analysis on hair and oral fluid taken in the two study groups: 24 subjects who tested positive for at least one substance of abuse in hair and 6 also in oral fluid (test group) and 11 subjects who tested negative (controls group)

Negative samples (Control group)			Positive samples (Test group)		
Sample #	Hair	Oral fluid	Sample#	Hair	Oral fluid
24	-	-	12	Alcohol	-
25	-	-	63	Methadone	Methadone
85	-	-	97	Demozepam	-

Negative samples (Control group)			Positive samples (Test group)		
90	-	-	128	Methadone	Methadone
92	-	-	133	Ketazolam	Ketazolam
93	-	-	134	Ketazolam	Ketazolam
149	-	-	156	Demozepam	-
154	-	-	165	Zolpidem	
213	-	-	177	Delorazepam	
243	-	-	186	Zolpidem, Midazolam	-
249	-	-	187	Cocaine	-
			189	Cannabinoids, Methamphetamine	
			192	Cocaine	
			193	Alprazolam, Diazepam	Diazepam
			194	Phenazepam	
			198	Estazolam	-
			227	Cannabinoids	-
			230	Cocaine	-
			234	Midazolam	-
			240	Zolpidem	-
			247	Cocaine, Cannabinoids, ketamine, MDMA	
			248	Cocaine	Cocaine
			263	Clobazam	-
			266	Cannabinoids	-

APPENDIX F

In Appendix F, the results of the volcano plots are reported, showing the metabolites and lipids that were found to be down- and upregulated, together with their corresponding fold change (FC), $\log_2(\text{FC})$, p-value and $-\log_{10}(\text{p})$ values for each phase of this study. Specifically, Table P presents the results of the volcano plot obtained from the comparison between saliva and whole blood samples collected from healthy and young subjects. Table Q lists the compounds that showed statistically significant variations between adults and young individuals (aging study). Table R summarizes the metabolites and lipids that significantly differed between subjects with Alzheimer's disease (AD) and cognitively healthy controls, while Table S reports the volcano plot results derived from the comparison between individuals using psychoactive substances and the corresponding control group.

Table P. Summary of metabolites and lipids that significantly differ between oral fluid and whole blood samples taken from healthy and young individuals. P-value < 0.05 and fold change > 2.

Compounds Name	FC	$\log_2(\text{FC})$	p-values	$-\log_{10}(\text{p})$
1-Methylguanine	8.3628	3.064	3.56E-11	10.449
2-Piperidinone	1393.9	10.445	1.22E-20	19.913

Compounds Name	FC	log2(FC)	p-values	-log10(p)
3-Indolepropionic acid	2.4448	1.2897	0.006354	2.1969
6-Hydroxypurine	0.15304	-2.7081	1.12E-08	7.9499
7-Methylxanthine	0.47005	-1.0891	0.035478	1.45
Adenine	26.575	4.732	7.22E-13	12.141
Adenosine	2.4967	1.32	6.94E-05	4.1588
Alpha-ketoisovaleric acid	0.38873	-1.3631	1.24E-07	6.9077
Capric acid	5.0035	2.3229	1.51E-15	14.821
CAR 16:0	0.033316	-4.9076	1.98E-13	12.704
CE 18:2	0.13568	-2.8817	2.01E-14	13.697
CE 18:3	0.072274	-3.7904	8.85E-12	11.053
CE 20:3	0.1346	-2.8932	3.04E-13	12.518
CE 20:4	0.074888	-3.7391	1.69E-15	14.772
CE 20:5	0.081079	-3.6245	2.72E-10	9.5652
CE 22:6	0.10289	-3.2808	1.38E-11	10.861
Cer 42:1;2O Cer 18:1;2O/24:0	0.024547	-5.3483	4.12E-16	15.385
Cer 42:2;2O Cer 18:1;2O/24:1	0.039512	-4.6616	9.96E-14	13.002
Cholesterol sulfate	2.2062	1.1416	4.48E-05	4.3487
DG 38:4 DG 18:0_20:4	8.5505	3.096	2.46E-08	7.6094
FA 18:2	71.506	6.16	2.95E-16	15.53
FA 20:3	5.4447	2.4449	1.69E-09	8.7717
Hex2Cer 34:1;2O Hex2Cer 18:1;2O/16:0	4.68	2.2265	9.31E-05	4.0311
Hex2Cer 40:1;2O Hex2Cer 18:1;2O/22:0	4.4966	2.1688	0.000134	3.8732
Hex2Cer 42:1;2O Hex2Cer 18:1;2O/24:0	3.7732	1.9158	0.00065	3.1872
Hex2Cer 42:2;2O Hex2Cer 18:1;2O/24:1	9.3686	3.2278	1.59E-06	5.7999
Hex2Cer 42:3;2O Hex2Cer 18:1;2O/24:2	5.5539	2.4735	1.57E-05	4.8044
Hex2Cer 44:2;2O Hex2Cer 18:1;2O/26:1	5.6023	2.486	2.06E-06	5.6861
Inosine	0.45667	-1.1308	0.000868	3.0617
L-Carnitine	0.26611	-1.9099	4.22E-07	6.3746
Leucinic acid	16.735	4.0648	1.93E-12	11.714
LPC 16:0	0.40268	-1.3123	4.94E-07	6.3062
LPC 16:0/0:0	0.37476	-1.416	9.33E-10	9.0302
LPC 16:1/0:0	0.23239	-2.1054	2.42E-07	6.6171
LPC 17:0/0:0	0.26398	-1.9215	6.24E-09	8.2046
LPC 18:0	0.10388	-3.267	1.42E-12	11.848
LPC 18:0/0:0	0.106	-3.2378	1.08E-11	10.968
LPC 18:1	2.5235	1.3355	0.016927	1.7714
LPC 18:1/0:0	0.38841	-1.3643	3.28E-07	6.4836
LPC 18:2	0.26042	-1.9411	3.80E-08	7.4201
LPC 20:4	0.18627	-2.4245	2.14E-08	7.6703
LPE 20:4	0.33188	-1.5913	5.99E-07	6.2225
LPE O-16:1	2.805	1.488	0.000745	3.1279
LPE O-18:1	4.1292	2.0459	3.24E-05	4.4897
LPE-N (FA)36:1 LPE-N (FA 18:0)18:1	0.18922	-2.4018	3.59E-11	10.445
L-Phenylalanine	4.6942	2.2309	2.06E-06	5.6861
L-Proline	3.9888	1.996	0.0014	2.8538
L-Tryptophan	0.17038	-2.5532	2.58E-11	10.589
N-Acetyl-L-phenylalanine	0.41874	-1.2559	0.00011	3.957

Compounds Name	FC	log2(FC)	p-values	-log10(p)
Niacinamide	0.041468	-4.5919	1.84E-19	18.736
PC 28:0 PC 14:0_14:0	0.2379	-2.0716	0.000144	3.8424
PC 29:0	0.25318	-1.9818	3.37E-05	4.4723
PC 31:0 PC 15:0_16:0	0.47811	-1.0646	0.000582	3.2348
PC 32:0 PC 16:0_16:0	0.17182	-2.541	1.37E-09	8.8619
PC 32:1 PC 16:0_16:1	0.12784	-2.9676	1.15E-08	7.9403
PC 33:0 PC 16:0_17:0	0.27049	-1.8863	1.62E-07	6.7905
PC 33:2 PC 15:0_18:2	0.1021	-3.292	8.98E-12	11.047
PC 34:0 PC 16:0_18:0	0.099397	-3.3307	5.93E-12	11.227
PC 34:1 PC 16:0_18:1	0.079394	-3.6548	5.37E-14	13.27
PC 34:2 PC 16:0_18:2	0.039482	-4.6627	1.22E-16	15.912
PC 34:3 PC 16:0_18:3	0.069423	-3.8484	4.79E-12	11.32
PC 34:3 PC 16:1_18:2	0.064626	-3.9517	1.72E-12	11.764
PC 35:1 PC 17:0_18:1	0.26029	-1.9418	4.48E-08	7.3489
PC 35:2 PC 17:0_18:2	0.092245	-3.4384	9.55E-13	12.02
PC 35:3	0.26389	-1.922	4.59E-08	7.3378
PC 36:0 PC 18:0_18:0	0.21161	-2.2405	5.45E-09	8.2635
PC 36:1 PC 18:0_18:1	0.13424	-2.8971	3.85E-11	10.414
PC 36:2 PC 18:1_18:1	0.072845	-3.779	1.20E-14	13.92
PC 36:3 PC 18:1_18:2	0.073021	-3.7755	1.11E-13	12.956
PC 36:4 PC 16:0_20:4	0.029468	-5.0847	5.85E-17	16.232
PC 36:4 PC 18:2_18:2	0.10117	-3.3051	5.12E-12	11.291
PC 36:5 PC 16:0_20:5	0.020393	-5.6158	5.37E-14	13.27
PC 36:5 PC 18:2_18:3	0.23323	-2.1002	2.03E-06	5.6935
PC 38:1	0.35034	-1.5132	3.86E-06	5.4139
PC 38:4 PC 18:0_20:4	0.033897	-4.8827	2.77E-17	16.557
PC 38:5 PC 18:1_20:4	0.054529	-4.1968	1.20E-14	13.92
PC 38:6 PC 16:0_22:6	0.024614	-5.3444	2.12E-16	15.674
PC 38:6 PC 18:2_20:4	0.042665	-4.5508	2.85E-15	14.546
PC 40:8	0.21809	-2.197	1.19E-08	7.9254
PC O-31:0	0.099666	-3.3268	8.32E-12	11.08
PC O-31:1	2.9566	1.564	0.003024	2.5194
PC O-32:0	2.3227	1.2158	0.035823	1.4458
PC O-32:1	2.5261	1.3369	0.029293	1.5332
PC O-34:0	0.36409	-1.4576	6.88E-05	4.1621
PC O-34:3	0.15715	-2.6698	5.30E-10	9.2759
PC O-36:4	0.11499	-3.1204	1.12E-11	10.949
PC O-36:5	0.093129	-3.4246	4.42E-13	12.354
PC O-37:10	0.22884	-2.1276	8.94E-10	9.0485
PC O-37:8	0.45396	-1.1394	9.09E-05	4.0413
PC O-38:1	8.033	3.0059	2.14E-08	7.6701
PC O-38:5	0.19382	-2.3672	5.17E-09	8.2863
PC O-38:6	0.11404	-3.1323	4.78E-12	11.321
PC O-39:10	0.039382	-4.6663	3.09E-20	19.511
PC O-40:1	4.7698	2.2539	3.37E-05	4.4723
PC O-40:3	17.208	4.105	0.018911	1.7233
PC O-40:5	0.37457	-1.4167	3.25E-05	4.4875

Compounds Name	FC	log2(FC)	p-values	-log10(p)
PC O-40:6	0.2241	-2.1578	1.54E-08	7.8124
PC O-40:7	0.15642	-2.6765	7.55E-10	9.1223
PC O-42:3	3.624	1.8576	0.010203	1.9913
PC O-44:6	0.48038	-1.0577	0.000696	3.1576
PE 30:0 PE 14:0_16:0	14.107	3.8184	8.10E-10	9.0917
PE 32:0 PE 16:0_16:0	0.29026	-1.7846	9.74E-08	7.0113
PE 34:0 PE 16:0_18:0	0.14133	-2.8229	1.44E-10	9.8422
PE 34:1 PE 16:0_18:1	0.070101	-3.8344	1.20E-13	12.92
PE 34:2 PE 16:0_18:2	0.15845	-2.6579	1.32E-10	9.8786
PE 34:3 PE 16:0_18:3	0.17878	-2.4838	6.50E-10	9.1869
PE 35:1 PE 17:0_18:1	0.20556	-2.2824	3.97E-09	8.4012
PE 36:1;2O PE 18:1_18:0;2O	0.1407	-2.8293	2.04E-08	7.6907
PE 36:1 PE 18:0_18:1	0.46982	-1.0898	0.001025	2.9892
PE 36:2 PE 18:1_18:1	0.056901	-4.1354	1.11E-13	12.954
PE 36:3 PE 18:1_18:2	0.022467	-5.4761	2.77E-17	16.557
PE 36:4 PE 16:0_20:4	0.007314	-7.0951	1.81E-20	19.743
PE 36:4 PE 18:2_18:2	0.035137	-4.8309	2.27E-14	13.644
PE 38:3 PE 18:0_20:3	0.49328	-1.0195	0.001454	2.8374
PE 38:4 PE 18:0_20:4	0.02301	-5.4416	3.38E-16	15.471
PE 38:4 PE 18:1_20:3	0.062011	-4.0113	4.13E-15	14.384
PE 38:5 PE 18:1_20:4	0.003546	-8.1396	8.57E-22	21.067
PE 38:6 PE 16:0_22:6	0.020426	-5.6134	3.80E-19	18.42
PE 40:4 PE 18:0_22:4	0.099475	-3.3295	5.66E-12	11.247
PE 40:5 PE 18:1_22:4	0.028965	-5.1095	4.62E-16	15.335
PE 40:6 PE 18:1_22:5	0.34647	-1.5292	3.51E-06	5.4547
PE O-34:3 PE O-16:1_18:2	3.0098	1.5897	9.38E-05	4.0277
PE O-35:2 PE O-17:1_18:1	2.6031	1.3802	0.007143	2.1461
PE O-36:5 PE O-16:1_20:4	0.24626	-2.0218	1.54E-08	7.8121
PE O-36:6 PE O-16:1_20:5	0.24197	-2.0471	8.25E-08	7.0838
PE O-37:5 PE O-17:1_20:4	0.3706	-1.4321	1.29E-06	5.8903
PE O-38:5 PE O-16:1_22:4	0.45977	-1.121	0.000802	3.096
PE O-38:5 PE O-18:1_20:4	0.00944	-6.727	3.09E-20	19.511
PE O-38:6 PE O-18:2_20:4	0.13179	-2.9237	4.22E-13	12.375
PE O-38:7 PE O-16:1_22:6	0.14178	-2.8183	3.62E-11	10.441
PE O-38:7 PE O-18:2_20:5	0.10536	-3.2465	2.20E-12	11.657
PE O-39:7 PE O-17:1_22:6	0.29155	-1.7782	3.80E-08	7.4201
PE O-40:4 PE O-22:2_18:2	0.26455	-1.9184	1.57E-06	5.8037
PE O-40:5 PE O-18:1_22:4	0.036016	-4.7952	4.62E-16	15.335
PE O-40:7 PE O-18:1_22:6	0.052858	-4.2417	6.38E-15	14.195
PE O-40:8 PE O-18:2_22:6	0.07643	-3.7097	5.37E-14	13.27
PE O-42:3 PE O-24:2_18:1	8.6234	3.1083	5.34E-09	8.2729
PE O-42:4 PE O-24:2_18:2	7.4414	2.8956	6.93E-09	8.1596
PE O-44:6 PE O-24:2_20:4	3.5296	1.8195	0.00012	3.9202
PE P-36:4 PE P-16:0_20:4	0.20088	-2.3156	6.24E-09	8.2046
PE P-38:4 PE P-16:0_22:4	0.011687	-6.419	9.74E-21	20.012
PE P-38:4 PE P-16:1_22:3	0.18678	-2.4206	1.06E-08	7.9766
PE P-38:5 PE P-18:1_20:4	0.095523	-3.388	4.78E-12	11.321

Compounds Name	FC	log2(FC)	p-values	-log10(p)
PE P-38:6 PE P-16:0 22:6	0.10953	-3.1906	1.49E-11	10.828
PE P-40:4 PE P-18:0 22:4	0.023902	-5.3867	1.40E-15	14.855
PE P-40:5 PE P-18:0 22:5	0.077451	-3.6906	2.31E-12	11.636
PE P-40:6 PE P-18:0 22:6	0.037124	-4.7515	1.82E-14	13.74
PE P-40:6 PE P-18:1 22:5	0.11581	-3.1102	3.56E-11	10.449
PE P-40:7 PE P-18:1 22:6	0.059988	-4.0592	5.04E-14	13.298
PE P-42:3 PE P-24:1 18:2	3.0917	1.6284	0.0011	2.9586
PI 38:4	0.42476	-1.2353	0.00075	3.1249
PS 36:1 PS 18:0 18:1	2.0313	1.0224	0.009144	2.0389
PS 40:6 PS 18:0 22:6	0.037011	-4.7559	9.54E-13	12.02
PS O-37:2 PS O-19:0 18:2	0.23155	-2.1106	6.24E-09	8.2046
PS O-41:4 PS O-19:0 22:4	0.2926	-1.773	9.23E-08	7.0346
Pyrrolidonecarboxylic acid	0.28769	-1.7974	3.37E-07	6.4727
SHexCer 40:0;2O	0.19016	-2.3947	6.76E-10	9.1702
SM 34:0;3O	0.20904	-2.2582	1.52E-06	5.819
SM 34:1;2O SM 18:1;2O/16:0	0.11435	-3.1284	8.32E-12	11.08
SM 34:1;3O	0.1999	-2.3227	3.14E-07	6.5033
SM 34:2;2O SM 18:2;2O/16:0	0.048423	-4.3682	6.38E-15	14.195
SM 35:3;3O	0.21344	-2.2281	6.24E-09	8.2046
SM 36:1;2O SM 18:1;2O/18:0	0.061991	-4.0118	8.23E-15	14.085
SM 36:1;3O	0.20309	-2.2998	1.12E-06	5.9526
SM 40:0;2O	0.33712	-1.5686	1.03E-05	4.9881
SM 42:1;2O SM 18:1;2O/24:0	0.041135	-4.6035	2.50E-13	12.602
SM 42:1;3O	0.37853	-1.4015	0.000131	3.8834
SM 42:2;2O SM 18:1;2O/24:1	0.054081	-4.2087	1.60E-14	13.796
SM 43:1;2O SM 18:1;2O/25:0	0.070151	-3.8334	8.28E-14	13.082
SM 43:4;3O	0.4264	-1.2297	0.000223	3.652
ST 27:1;O	0.13946	-2.842	1.33E-14	13.875
ST 27:1;O;S	0.008898	-6.8122	9.27E-17	16.033
TG 54:4 TG 18:1 18:1 18:2	3.1349	1.6484	0.002078	2.6824
TG 54:5 TG 18:1 18:2 18:2	5.2196	2.3839	0.001477	2.8306
TG 54:6 TG 18:2 18:2 18:2	9.4147	3.2349	7.62E-06	5.1181
TG 54:7 TG 18:2 18:2 18:3	5.054	2.3374	0.0219	1.6596
TG 58:8 TG 18:1 18:1 22:6	0.37927	-1.3987	0.000181	3.7421
TG 58:9 TG 18:1 18:2 22:6	0.33462	-1.5794	6.33E-05	4.1983
Trigonelline	2.5168	1.3316	0.002449	2.6111
Urea	7.6112	2.9281	2.08E-06	5.6813
Uridine	297.16	8.2151	8.06E-12	11.093
VAE 25:1	0.37706	-1.4071	1.52E-06	5.819

Table Q. Summary of metabolites and lipids that significantly differ between adult and young individuals to study aging processes. P-value < 0.05 and fold change > 2.

Compounds Name	FC	log2(FC)	p-values	-log10(p)
LPC 22:4	0.021359	-5.549	6.0662e-24	23.217
TG 62:1 TG 18:0 26:0 18:1	0.10978	-3.1873	0.00307	2.5128
TG 59:1 TG 16:0 25:0 18:1	0.14674	-2.7687	0.00307	2.5128

Compounds Name	FC	log2(FC)	p-values	-log10(p)
VAE 4:0	6.5436	2.7101	0.00307	2.5128
TG 56:0 TG 16:0 16:0 24:0	0.17151	-2.5437	0.00307	2.5128
TG 63:2 TG 27:0 18:1 18:1	0.12211	-3.0338	0.003632	2.4399
TG 61:1 TG 17:0 26:0 18:1	0.12646	-2.9833	0.003632	2.4399
TG 60:0 TG 18:0 20:0 22:0	0.14439	-2.792	0.003632	2.4399
TG 54:5;1O TG 18:1 18:1 18:3;1O	0.12871	-2.9578	0.004854	2.3139
TG 60:1 TG 16:0 26:0 18:1	0.14454	-2.7905	0.004854	2.3139
TG 56:3;1O TG 18:1 18:1 20:1;1O	0.15724	-2.6689	0.005433	2.265
TG 50:2;1O TG 14:0 18:1 18:1;1O	0.1723	-2.537	0.009685	2.0139
TG 61:2 TG 25:0 18:1 18:1	0.13214	-2.9198	0.010676	1.9716
TG 54:0 TG 18:0 18:0 18:0	0.22864	-2.1289	0.011666	1.9331
TG 55:1 TG 16:0 21:0 18:1	0.19132	-2.3859	0.014307	1.8445
Palmitoylcarnitine cation	0.36268	-1.4632	0.014307	1.8445
TG 64:2 TG 16:0 18:1 30:1	0.13973	-2.8393	0.014446	1.8403
TG 58:1 TG 16:0 24:0 18:1	0.18166	-2.4607	0.017635	1.7536
TG 55:3;1O TG 18:1 19:1 18:1;1O	0.30925	-1.6932	0.018615	1.7301
PE 39:5;O PE 22:4 17:1;O	0.37808	-1.4032	0.022995	1.6384
NAE 14:0	0.40726	-1.296	0.028613	1.5434
DG 32:0 DG 15:0 17:0	0.132	-2.9214	0.029864	1.5249
TG 54:7;1O TG 18:2 18:2 18:3;1O	0.1659	-2.5916	0.029892	1.5244
TG 56:1 TG 16:0 22:0 18:1	0.21639	-2.2083	0.029892	1.5244
TG 56:2;1O TG 18:1 18:1 20:0;1O	0.26441	-1.9191	0.029892	1.5244
LPE 16:0	0.19708	-2.3432	0.031251	1.5051
LPC 18:2	0.27469	-1.8641	0.031251	1.5051
TG 66:3 TG 18:1 18:1 30:1	0.18297	-2.4503	0.033124	1.4799
TG 50:2;1O TG 16:0 16:0 18:2;1O	0.28948	-1.7885	0.033124	1.4799
TG 54:6;2O TG 18:2 18:2 18:2;2O	0.15009	-2.7361	0.040202	1.3957
FA 20:4	5.5234	2.4656	0.040784	1.3895
TG 55:2 TG 19:0 18:1 18:1	0.21716	-2.2032	0.040784	1.3895
TG 51:3;1O TG 16:0 17:1 18:2;1O	0.27879	-1.8427	0.040784	1.3895
PE O-40:7 PE O-18:1 22:6	0.36408	-1.4577	0.040784	1.3895
LPE 20:4	0.46157	-1.1154	0.040784	1.3895
PE O-32:2 PE O-16:1 16:1	0.14597	-2.7763	0.041681	1.3801
DG 32:1 DG 14:0 18:1	0.27957	-1.8387	0.041681	1.3801
TG 49:2 TG 16:0 16:1 17:1	0.32558	-1.6189	0.041681	1.3801
PI 20:0	0.46903	-1.0922	0.041681	1.3801
PC 31:1 PC 15:0 16:1	0.094416	-3.4048	0.043285	1.3637
PE O-33:2 PE O-17:1 16:1	0.18921	-2.4019	0.043285	1.3637
PE O-34:3 PE O-16:1 18:2	0.20504	-2.286	0.043285	1.3637
FA 22:5;O	4.216	2.0759	0.043285	1.3637
PE O-36:5 PE O-16:1 20:4	0.34116	-1.5515	0.043285	1.3637
LPE 18:2	0.36439	-1.4564	0.043285	1.3637
TG 59:4 TG 23:0 18:2 18:2	0.45513	-1.1356	0.043285	1.3637
PE 39:7;O PE 22:6 17:1;O	0.47824	-1.0642	0.043285	1.3637
PE 38:5;O PE 18:2 20:3;O	0.27788	-1.8475	0.047071	1.3272
PC 42:0	0.34151	-1.55	0.047071	1.3272
CL 76:7 CL 18:1 18:1 18:1 22:4	0.21402	-2.2242	0.048157	1.3173

Compounds Name	FC	log2(FC)	p-values	-log10(p)
TG 52:4;2O TG 16:0_18:1_18:3;2O	0.26968	-1.8907	0.048157	1.3173
TG 52:0 TG 16:0_18:0_18:0	0.41913	-1.2545	0.048157	1.3173
TG 62:0 TG 18:0_22:0_22:0	0.18729	-2.4167	0.048955	1.3102
PE O-38:7 PE O-16:1_22:6	0.24732	-2.0155	0.048955	1.3102
PG O-38:5 PG O-18:2_20:3	0.2571	-1.9596	0.048955	1.3102
TG 56:5;1O TG 18:1_18:1_20:3;1O	0.26371	-1.9229	0.048955	1.3102
TG 51:1 TG 16:0_17:0_18:1	0.31236	-1.6787	0.048955	1.3102
PC O-37:10	0.35887	-1.4784	0.048955	1.3102
TG 53:5 TG 17:1_17:2_19:2	0.40313	-1.3107	0.048955	1.3102
PE O-39:7 PE O-17:1_22:6	0.40849	-1.2916	0.048955	1.3102

Table R. Summary of metabolites and lipids that significantly differ between patients with Alzheimer's disease and control group to study disease processes. P-value < 0.05 and fold change > 2.

Compounds Name	FC	log2(FC)	p-values	-log10(p)
DG 37:0 DG 15:0_22:0	2.0646	1.0458	4.08E-06	5.3892
PC O-31:6	2.2959	1.1991	6.85E-06	5.164
Pantothenic acid	0.075096	-3.7351	1.83E-05	4.7365
5'-Deoxy-5'-Methylthioadenosine	0.15602	-2.6802	0.000155	3.8098
FA 36:10	4.4763	2.1623	0.000263	3.5806
LPC 17:0	2.9848	1.5776	0.000455	3.3423
DG 50:3 DG 16:1_34:2	0.15864	-2.6562	0.000646	3.19
PG 36:3 PG 18:1_18:2	0.22303	-2.1647	0.000973	3.0119
PG 33:0 PG 16:0_17:0	0.22569	-2.1476	0.002069	2.6843
LPC O-20:2	5.9219	2.5661	0.002998	2.5232
LPC 18:3/0:0	2.9665	1.5688	0.003585	2.4455
LPC 20:3/0:0	4.194	2.0683	0.003796	2.4207
TG 54:1;2O TG 18:0_18:1_18:0;2O	5.3175	2.4107	0.004652	2.3324
LPC 18:0	2.943	1.5573	0.004652	2.3324
PE 36:4 PE 18:1_18:3	0.37337	-1.4213	0.004652	2.3324
PI 40:4	2.5792	1.3669	0.004805	2.3183
LPE 22:6	2.8431	1.5075	0.005405	2.2672
PC O-38:8	2.2778	1.1876	0.007149	2.1458
ST 27:2;O	2.9355	1.5536	0.008444	2.0735
PE 35:2 PE 17:0_18:2	0.35216	-1.5057	0.008558	2.0676
PG 31:0 PG 15:0_16:0	0.32184	-1.6356	0.012106	1.917
NAE 14:0	3.8838	1.9575	0.014069	1.8517
PE 40:0 PE 20:0_20:0	0.34947	-1.5168	0.014069	1.8517
LPE O-18:2	2.4357	1.2844	0.014255	1.846
PG 40:3 PG 20:1_20:2	0.17262	-2.5343	0.016493	1.7827
PS 36:4 PS 18:2_18:2	0.37311	-1.4223	0.018459	1.7338
HexCer 42:0;4O HexCer 18:0;3O/24:0;(2OH)	0.42614	-1.2306	0.018459	1.7338
PC O-37:10	2.773	1.4715	0.019416	1.7118
PE 44:0 PE 22:0_22:0	0.36966	-1.4357	0.019416	1.7118
PS 36:1	2.0172	1.0123	0.019416	1.7118
PE 42:0 PE 20:0_22:0	0.35222	-1.5054	0.019547	1.7089
PE 34:2 PE 16:0_18:2	0.28625	-1.8047	0.022029	1.657

PG 34:2 PG 16:0_18:2	0.38746	-1.3679	0.022029	1.657
CL 98:1 CL 28:0_28:0_28:0_14:1	0.26134	-1.936	0.0239	1.6216
PE 32:2 PE 16:1_16:1	0.29221	-1.7749	0.0239	1.6216
PI 20:0	2.0071	1.0051	0.0239	1.6216
PE 34:2 PE 16:1_18:1	0.074729	-3.7422	0.0241	1.618
LPC 16:1	2.2211	1.1512	0.027109	1.5669
PG 38:2 PG 18:1_20:1	0.37444	-1.4172	0.027344	1.5631
LPE O-22:2	2.6328	1.3966	0.027344	1.5631
TG 52:2;1O TG 18:1_18:1_16:0;1O	0.39436	-1.3424	0.027344	1.5631
HexCer 42:0;3O	0.47231	-1.0822	0.028252	1.549
PE O-32:2 PE O-16:1_16:1	0.43533	-1.1998	0.028396	1.5467
Cer 44:2;3O Cer 18:1;2O/26:1;O	2.3868	1.2551	0.029258	1.5337
CE 18:2	3.2038	1.6798	0.030153	1.5207
PE 33:1 PE 15:0_18:1	0.29248	-1.7736	0.03518	1.4537
PE 33:2 PE 15:0_18:2	0.21353	-2.2275	0.036812	1.434
NAE 15:4	2.7196	1.4434	0.036812	1.434
PC O-37:3	2.3946	1.2598	0.036812	1.434
NAOrn 15:0;O	2.474	1.3068	0.038348	1.4163
SM 43:2;2O SM 18:1;2O/25:1	2.0073	1.0053	0.038348	1.4163
PC 40:6 PC 20:3_20:3	2.3129	1.2097	0.038564	1.4138
PC O-37:1 PC O-19:0_18:1	0.46081	-1.1178	0.038646	1.4129
FA 20:4;O	3.0018	1.5858	0.045174	1.3451
PE 32:1 PE 16:0_16:1	0.20385	-2.2944	0.047533	1.323
PE P-42:7 PE P-20:1_22:6	3.3147	1.7289	0.048323	1.3158

Table S. Summary of metabolites and lipids that significantly differ between users of psychoactive substances and control group to study how drugs vary salivary lipidomic and metabolic profiles. P-value < 0.05 and fold change > 2.

Compounds Name	FC	log2(FC)	p-values	-log10(p)
PC O-31:1 PC O-16:1_15:0	2.2546	1.1729	0.000365	3.4377
Succinate	3.2654	1.7073	0.002735	2.5631
DG 48:12	0.27534	-1.8607	0.006743	2.1712
TG 52:2;O TG 18:0_18:1_16:1;O	2.4594	1.2983	0.0093	2.0315
FA 20:4;O4	0.43688	-1.1947	0.010673	1.9717
PC O-29:1	3.0175	1.5934	0.010683	1.9713
LPE O-18:1	0.3835	-1.3827	0.011416	1.9425
DG 52:10	0.30553	-1.7106	0.013242	1.878
Hexanoyl-L-Carnitine	2.7441	1.4564	0.016373	1.7859
PE 28:0	0.29256	-1.7732	0.016831	1.7739
DG O-34:2 DG O-16:1_18:1	0.38664	-1.3709	0.018479	1.7333
PE O-33:2 PE O-16:1_17:1	0.47211	-1.0828	0.02614	1.5827
PE 29:0	0.26289	-1.9275	0.027779	1.5563
PC O-40:5 PC O-16:0_24:5	0.30454	-1.7153	0.031186	1.506
PE P-31:1 PE P-15:0_16:1	0.27218	-1.8774	0.0318	1.4976
LPE P-22:1	0.47619	-1.0704	0.033305	1.4775
CAR 18:0	0.35279	-1.5031	0.034943	1.4566
DG 33:2 DG 15:0_18:2	0.4481	-1.1581	0.03583	1.4458
PG 40:2 PG 20:1_20:1	0.46024	-1.1196	0.037095	1.4307

Compounds Name	FC	log2(FC)	p-values	-log10(p)
Cer 39:2;O3 Cer 18:1;O2/21:1;O	0.43867	-1.1888	0.0381	1.4191
Hex2Cer 34:1;O2 Hex2Cer 18:1;O2/16:0	2.3935	1.2591	0.03945	1.404
PE 28:0 PE 13:0_15:0	0.28011	-1.8359	0.042054	1.3762
HexCer 48:5;O4 HexCer 20:2;O2/28:3;O2	0.23457	-2.0919	0.042096	1.3758
PC O-43:1	2.5312	1.3398	0.043299	1.3635
PG 34:2	0.44148	-1.1796	0.04343	1.3622
TG 45:7;O TG 15:1_22:5_8:1;O	0.30424	-1.7167	0.044234	1.3542
CL 80:4 CL 28:0_16:1_18:1_18:2	0.33547	-1.5757	0.045328	1.3436
HexCer 40:4;O3	0.48237	-1.0518	0.045362	1.3433