Effect of aging and methionine restriction on rat tissue metabolomic profiles

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TESI DOCTORAL

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Abstract

The aging process causes numerous changes in the organism at all levels of biological organization, reduced the maximum functional capabilities and homeostasis, and increases the probability of developing age-related diseases. All these changes are likely to originate from a small number of causes, operating continuously through lifespan and generating changes in the metabolome and more specifically in the lipidome of an organism. Metabolomics and the branch lipidomics allow studying the terminal downstream products of the genome, serving as direct signatures of biochemical activity.

In this sense, this thesis has been designed with the aim of: i) profile the metabolome and lipidome of five different tissues (heart, liver, kidney, skeletal muscle and adipose tissue) in healthy adult male rats ii) determine the effect of aging in the metabolome and lipidome of these five tissues and iii) evaluate the adaptive response of the metabolomic and lipidomic profiles to a methionine restriction in aged rats.

The results show the existence of a metabolomic and lipidomic specific profiles in the different tissues of adult male rats with general rules and patterns shared by tissues about metabolites distribution to cover basic cellular processes. The aging process produces specific changes in the metabolome and lipidome of the different mammalian tissues and methionine restriction partially reverts the change induced due to aging and/or generates a remodeling in the metabolome and lipidome in a tissue-specific manner.

Resumen

El proceso de envejecimiento causa numerosos cambios en todos los niveles biológicos en el organismo, reduciendo las capacidades funcionales máximas y la homeostasis, y aumenta la posibilidad de desarrollar enfermedades relacionadas con la edad. Todos estos cambios tienen probablemente su origen en un número pequeño de causas, que operan continuamente a lo largo de toda la vida y generan cambios en el metaboloma y más específicamente en el lipidoma de un organismo. La metabolómica y su rama lipidómica permiten el estudio de los productos terminales del genoma, sirviendo como huellas directas de la actividad bioquímica.

En este sentido, la presente tesis ha sido diseñada con el objetivo de i) perfilar el metaboloma y lipidoma de cinco tejidos diferentes (corazón, hígado, riñón, músculo esquelético y tejido adiposo) en ratas macho adultas sanas, ii) determinar el efecto del envejecimiento en el metaboloma y lipidoma de estos cinco tejidos y iii) evaluar la respuesta adaptativa del perfil metabolómico y lipidómico a una restricción de metionina en ratas viejas.

Los resultados muestran la existencia de perfiles metabolómicos y lipidómicos específicas en los diferentes tejidos de ratas macho adultas con unas reglas y patrones generales compartidos por los tejidos acerca de la distribución de los metabolitos para cubrir procesos celulares básicos. El proceso de envejecimiento genera cambios específicos en el metaboloma y lipidoma de los diferentes tejidos de mamíferos y la restricción de metionina revierte parcialmente los cambios inducidos por el envejecimiento y /o genera una remodelación en el metaboloma y lipidoma de manera específica para cada tejido.

Resum

El procés d'envelliment causa nombrosos canvis als organismes a tots els nivells d'organització biològica, es redueixen les capacitats funcionals i l'homeòstasi, i s'incrementa la probabilitat de desenvolupar malalties derivades de l'edat. Tots aquests canvis semblen originar-se per un petit nombre de causes que es donen al llarg de la vida i que van generant canvis en el metabolisme i, més específicament, en el lipidoma d'un organisme. La metabolòmica i la lipidòmica permeten estudiar els productes finals del genoma, servint així com a mostra de l'activitat bioquímica.

En aquest sentit, aquesta tesi s'ha dissenyat amb la idea de: i) fer el perfil metabolomic i lipidomic de cinc teixits (cor, fetge, ronyó, múscul esquelètic i teixit adipós) en rates adultes mascles sans ii) determinar l'efecte de l'envelliment en el metaboloma i el lipidoma d'aquests cinc teixits i iii) avaluar la resposta adaptativa dels perfils metabolòmic i lipidòmic a una dieta amb restricció de metionina en rates adultes.

Els resultats obtinguts mostren l'existència d'un perfil metabolòmic i lipidòmic específic en els diferents teixits de rates mascles adultes amb unes regles i patrons generals compartits pels teixits sobre la distribució dels metabòlits per cobrir processos cel·lulars bàsics. El procés d'envelliment genera canvis específics en el metaboloma i el lipidoma dels diferents teixits de mamífers i la restricció de metionina reverteix parcialment els canvis derivats de l'envelliment i/o genera una remodelació en el metaboloma i el lipidoma específic per cada teixit.

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ABBREVIATIONS

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AMPK: AMP-activated protein kinase

ANOVA: analysis of variance

BHMT: betaine homocysteine methyltransferase

BHT: 2,6-Di-tert-butyl-4-methylphenol

BSA: Bovine serum albumin

CE: Cholesteryl ester

CGL: cystathionine-γ-lyase

COH: Cholesterol

CR: caloric restriction

DAG: diacylglycerol

DNA: deoxyribonucleic acid

EDTA: Ethylenediaminetetraacetic acid

ESI: electrospray ionization

FA: fatty acyls

FC: Fold change

FOXO: Forkhead box O

FXR: Farnesoid X receptor

GL: glycerolipids

GP: glycerophospholipids

GSH: Glutathione

GSSG: Glutathione disulfide

IGF-1: Insulin growth factor I

KCl: potassium chloride

LC ESI-QQQ MS/MS: liquid chromatography with electrospray ionization coupled to triple quadrupole mass spectrometry

LC ESI-QTOF MS/MS: liquid chromatography with electrospray ionization coupled to quadrupole time-of-flight mass spectrometry

LGP: lysoglycerophospholipid

LPA: lysophosphatidic acid

LPC: lysophosphatidylcholine

LPE: lysophosphatidylethanolamine

LPG: lysophosphatidylglycerol

LPI: lysophosphatidylinositol

m/z: mass-to-charge ratio

MFE: Molecular Feature Extractor

RMet: Restriction of methionine

MOPS: 3-(N-morpholino)propanesulfonic acid

MTBE: Methyl tert-butyl ether

mTOR: mammalian target of rapamycin

NAD: Nicotinamide adenine dinucleotide

PA: phosphatidic acid

PC: phosphatidylcholine

PCA: principal component analysis

PE: phosphatidylethanolamine

PG: phosphatidylglycerol

PI: phosphatidylinositol

PLS-DA: partial least squares discriminant analysis

PR: protein restriction

Pr: prenol lipids

ROS: reactive oxygen species

RT: retention time

SAM: S-adenosylmethionine

SDS: Sodium dodecyl sulfate

SHP: Small heterodimer partner

SIRT: sirtuin

SOD: Superoxide dismutase

SP: sphingolipids

SREBP: sterol receptor element binding protein

ST: sterol lipids

TAG: triacylglycerols

THF: Tetrahydrofolate

TRIS: Tris-(hydroxymethyl)-amino methane

INTRODUCTION

1. INTRODUCTION

1.1 Metabolomics

Metabolomic is the newest "omic" field and for the best understanding, we are going to review the definitions of terms like metabolite, metabolome or metabolic signature. **Metabolites**, according to Patti and collaborators, are small molecules that are chemically transformed during metabolism and, as such, they provide a functional read out of cellular state (*Patti et al. 2012*). Hence, the **metabolome** is defined as the collection of all the endogenous and exogenous metabolites of a cell, tissue or organism, resulting from the enzymatic activity and exposition to environmental stimulus such as diet. Those metabolites are required for growth, maintenance or normal function in a specific physiological state (*Harrigan and Goodacre 2003*). The metabolome, as a result of being the terminal downstream product of the genome, serves as direct indicator of biochemical activity and therefore is easier to correlate with the phenotype unlike genes and proteins, the functions of which are subject to epigenetic regulation and posttranslational modifications, respectively (*Goodacre et al. 2004*). The **metabolic signature** is a chemical fingerprint composed by several metabolites in a biological sample that can be associated with a physiological process and is a very useful tool in biomarkers discovery.

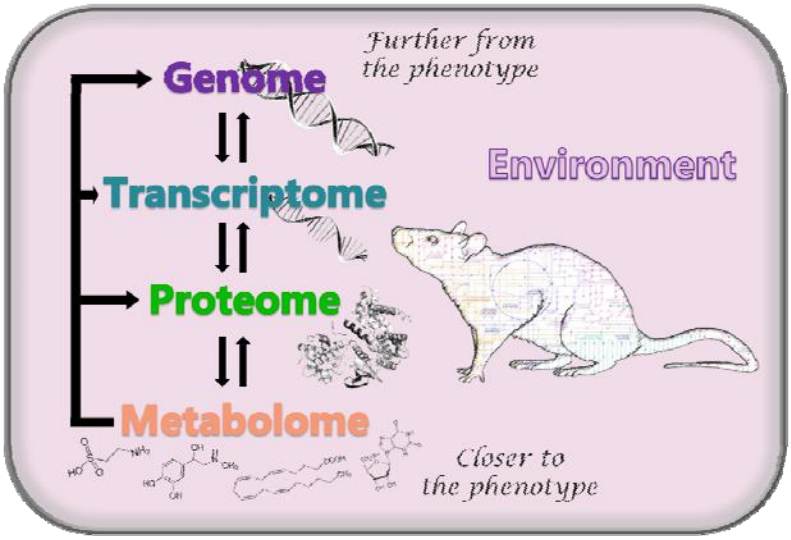

Figure 1. The classical view of the central dogma of the biology with the "-omes" representation. In this biological organization the information flow goes from the genome to the transcriptome, to the proteome and then as the downstream biochemical end products, the metabolome, closer to the phenotype. However, each tier of organization depends on the other and on the environment, which has a crucial impact on every level. Metabolomics aims to define the metabolome and to identify changes in every level that correlate with the phenotype. Adapted from (*Griffin and Shockcor 2004*).

Metabolomics was defined in the 1990s to describe techniques aimed at measuring the metabolites present within a cell, tissue or organism during a genetic alteration or physiological stimulus (*Nicholson et al. 1999*). In this context, metabolomics has become a powerful approach that has been widely adopted for clinical diagnostics. With developments in analytical technologies, it is now possible to rapidly measure thousands of metabolites simultaneously from only minimal amounts of sample (*Patti et al. 2012*).

1.1.1. Past, present and future of metabolomics

As the writer James Baldwin said "If you know whence you came, there are absolutely no limitations to where you can go", the birth of the metabolomic field and its current status is the fruit of decades of research in physics, chemistry and biology.

1.1.1.1. A little bit of history

From the first elementary determinations of small organic molecules such as lactic, citric or oxalic acids by Lavoisier to the 114113 metabolite entries of the Human Metabolome Database, important technological and computational advances have taken place, and were those that have led to the creation of metabolomics as a new way of studying and understanding classical biochemistry (*Lavoisier 1789*; *Wishart et al. 2007*). One crucial moment in the history of the biochemistry was in 1842 when for the first time Justus von Liebig published the *Animal Chemistry* composed by metabolic equations describing physiological processes without any other tool than his knowledge of organic chemistry (*Liebig 1842*). Since then, and thanks to the use radioactive isotopes, from 1940 there was an exponential growth of the research in biochemistry. By that time, Archer Martin and Richard Synge were developing different chromatographic methods such as gas chromatography (*Martin and Synge 1941*). The development of this analytical technique allowed that before the sixties the biosynthetic pathways of practically all classes of biological molecules had been elucidated. Technologies continued in expansion and the spectrometry field was revolutionized with the appearance of both techniques needed to understand nowadays metabolomics field. On the one hand, the nuclear magnetic resonance (NMR) thanks to Isidor Rabi who earned the Nobel Prize of Physics in 1944, and on the other hand, the mass spectrometry (MS) thanks to Hans Dehmelt and Wolfgang Paul, laureates of the Nobel Prize of Physics for the development of the ion trap technique in the 1950s and 1960s (*Boesch 2004*; *Griffiths 2008*). In the meantime, Donald Nicholson compiled all the known metabolic reactions in one map composed only of about 20

metabolic pathways (*Nicholson 2006*). The achieves of McLafferty and collaborators were also truly meaningful to the metabolomics field due to in 1956 they coupled a gas chromatographer to a mass spectrometer for the first time, introduced the collision-induced dissociation (CID) in 1967 and coupled also high performance liquid chromatography (HPLC) to mass spectrometry equipment in 1974 (*Vanlear and Mclafferty 1969*; *Arpino et al. 1974*). It was not until 1989 when the electrospray ionization (ESI) was developed by the Nobel Prize of Chemistry John Bennet Fenn, which allowed in 1994 the first untargeted metabolomic study carried out by Cravatt and collaborators (*Fenn et al. 1989*; *Lerner et al. 1994*).

Developments in analytical techniques for DNA and proteins produced the explosion of genomics in the eighties and proteomics in the nineties being the metabolites relegated to the background. It has been recently that the scientific community has reconsidered the pre-established idea that cell metabolome sticks to the metabolic routes taught in the biochemistry subject at the university, which were discovered and mapped before 1960 (*Labaer 2002*). The Nobel Prize in Physiology Ernst Boris Chain classified the study of the cellular metabolism in three different periods: i) pre-isotope era, in which the enzymatic activities of different metabolic pathways were determined *in vitro* or outside the cell; ii) the isotope era, in which the metabolite transformations were characterized by radioactive labeling, and iii) the era of biochemical genetics, in which the expression of enzymes was manipulated in order to establish the sequence of metabolic reactions (*Chain 1965*). Hence, welcome to the new era, metabolomics, marked by technological and computational advances that will allow us to study new aspects of metabolism and elucidate unknown operational details of cell regulation in different physiological states (*Yanes 2015*).

1.1.1.2. Enabling technologies for metabolomics

Metabolomics aims to detect, quantify and elucidate the structure and function of metabolites, which are characterized by a great physical-chemical diversity in their molecular structures. This diversity is reflected in a wide range of polarities, molecular weights, functional groups, stability and chemical reactivity, among other important properties. Therefore, metabolomics needs to use technologies that allow it to fulfill its goal. Nowadays there is a wide range of platforms and configurations available for this purpose. The two core technologies for the metabolite analysis are NMR and MS, whose characteristics are summarized in Table 1. Both present pros and cons to be used for metabolomics (*Emwas 2015*). NMR spectroscopy, which is used almost exclusively for analyzing small analytes in the blood, requires relatively little sample preparation and is non-

destructive, allowing further analysis. However, the method tends to have low sensitivity and can detect only highly abundant metabolites (*Keun and Athersuch 2011*). On the other hand, MS allows the determination of metabolites masses with such high precision and accuracy that compounds can be identified unambiguously in complex mixtures, and it is, therefore, applicable to a wide range of biological samples. Moreover of its sensitivity, MS provides the detailed structural information necessary for the characterization of novel metabolites, and the selectivity required for the determination of individual species (*Metz et al. 2007*).

Table 1. Comparison of the two core technologies for the metabolomic analysis. Adapted from (*Nagrath et al. 2011*).

Characteristics	**NMR**	**MS**
Sensitivity	Medium	High
Sample preparation	Easy. Non-destructive	Separation methods are needed to increase peak identification
Limitations	Not widely used in clinics, need special training to use the equipment and not high throughput for metabolite analysis	Not widely used in clinics, need special training to use the equipment and high cost
Reproducibility	High	Low for biofluids
Resolution	High	High
Quantification	Easy	Difficult
Throughput	Low	High

Several choices are available as well amongst the chromatographic techniques such as gas chromatography (GC), capillary electrophoresis (CE) or liquid chromatography (LC). GC has high reproducibility and analytical sensitivity however, it is only applicable to volatile and thermally stable compounds (*Moco et al. 2007*). CE is only applicable to polar charged compounds, also has limited robustness and analytical reproducibility although it consumes very little amount of sample (*Ramautar et al. 2009*). Finally, LC has high reproducibility, analytical sensitivity, and besides that, it offers many chromatographic variants that have enabled a greatly increase in the number and classes of metabolites studied in a single experiment (*Metz et al. 2007*).

Regarding the ionization process, several types of sources are available. Amongst them, Matrix-Assisted Laser Desorption/Ionization (MALDI) and ESI have had a profound effect on mass spectrometry because they generate charged intact biomolecules into the gas phase (Siuzdak 2004). Chemical Ionization (CI), Electron Ionization (EI), Atmospheric Pressure Chemical Ionization (APCI) are sources of ionization that can not be used for all types of compounds. For example, EI is a very energetic source that allows high reproducibility and generates high fragmentation of the chemical structures but it is only suitable for gas phase ionization of

volatile and thermally stable compounds (*Chait 1972*). Main advantages and disadvantages of ESI and MALDI are shown in Table 2.

Table 2. Advantages and disadvantaged of the ionization sources Matrix-Assisted Laser Desorption/Ionization (MALDI) and Electrospray Ionization (ESI).

Ionization Source	Advantages	Disadvantages
Electrospray Ionization (ESI)	High range of ionizable compounds Softest ionization method (does not break chemical structures) Easily adapted to LC and mass analyzers	Ions redundancy due to the formation of multiple adducts
Matrix-Assisted Laser Desorption/Ionization (MALDI)	Soft ionization with little to no fragmentation observed	Matrix background (a problem for compounds under 700 Da) Possibility of photodegradation

Finally, several choices are also available amongst mass analyzers. Differences among them are based on the mass range, dynamic range, sensitivity, resolution, mass accuracy and final economic cost. Advantages and disadvantages are always combined in one instrument as Dr. Jekyll and Mr. Hyde are combined in one person (*Brunnée 1987*). The time of flight (TOF) alone or combined with a quadrupole (QTOF) has elevated masses range, high sensitivity and dynamic range but an average resolution. The opposite situation happens with the Orbitrap or the Fourier transform ion cyclotron resonance (FC-ICR). Quadrupole (Q), triple quadrupole (QQQ) and ion trap have lower resolution and mass accuracy although for the quadrupoles the sensitivity and the dynamic range are very high.

As it can be appreciated, diversity amongst technologies in ionization sources and mass analyzers translates into a variety of possibilities but also makes it very important to choose the right platform when designing a good metabolomics experiment.

1.1.1.3. Metabolomics experimental design

A good experimental design is the key of success. First of all, it is important to define the number of metabolites that you want to measure. Second, the chemical properties of those metabolites will determine the best sample preparation and instrumental configuration. In metabolomics, there are two main approaches depending on the number of metabolites to be measured, targeted and untargeted metabolomics (*León et al. 2013*).

Targeted metabolomics measures a specific list of metabolites, typically from one or more related metabolic pathways suspected of being of interest. This selective approach is usually conditioned by a specific biochemical question, or hypothesis, that motivates the investigation

of a particular pathway and metabolites. This method may be effective for pharmacokinetic studies, as well as for measuring the metabolic effect of genetic modifications on a given enzyme. The main advantages are its specificity, quantitative reproducibility, high sensitivity (very low detection and quantification limits) and high performance (*Roberts et al. 2012*).

Untargeted metabolomics is a broad scope analysis which aim is to measure simultaneously as many metabolites as possible without having a pre-established hypothesis. It is highly useful for metabolite profiling, for comparing metabolomes in different conditions or moments but to be successful it is necessary to design carefully the experiment. The number and matrix of the samples, sample processing, chromatographic method and analysis platform are main issues to decide before starting an experiment in order to get a future hypothesis, discover new biomarkers or metabolic signatures associated to a concrete physiological process or pathology. In addition, sophisticated computational tools are required to analyze the great amount of data obtained for just one experiment (*Patti et al. 2012*).

1.1.1.4. Data analysis

Data analysis is one of the most crucial process in metabolomics research and the one that requires more time and efforts. The goal of data analysis is to find significant changes and to validate the data obtained with the biological samples. Bioinformatics tools allow one to perform data analysis, including organized data matrix construction and statistical analysis (*Goodacre et al. 2004*). Data analysis will be different depending on the type of experiment, targeted or untargeted, and the data flow is represented in Figure 2. In both strategies, the first type of data obtained is the raw chromatogram data. In the targeted approach, the goal of the quantification of the measured metabolites is to acquire highly sensitive and reproducible data. For that reason, normalization, by means of internal standards, external standards and total signal, should also be optimized for each research purpose (*Roberts et al. 2012*). On the other hand, the raw chromatogram data in an untargeted metabolomics experiment is much more complex. It is needed a software capable of detect and align the peaks, filter possible contaminants, artefacts, background ions and degenerate features appears and finally, include complex adducts forms to the corresponding molecule (*Mahieu and Patti 2017*). Then, the next step is the search for significant metabolites, which will be identified by matching their tandem mass spectrometry data against experimental MS/MS data from known metabolites contained in public or private databases (*Moco et al. 2007*). Multivariable analysis is a convenient way to extract the metabolites of interest from metabolomics data. Right after, the methods and terms

used in this work have been briefly described. For that goal, algorithms are classified in two groups depending on if they are unsupervised or supervised.

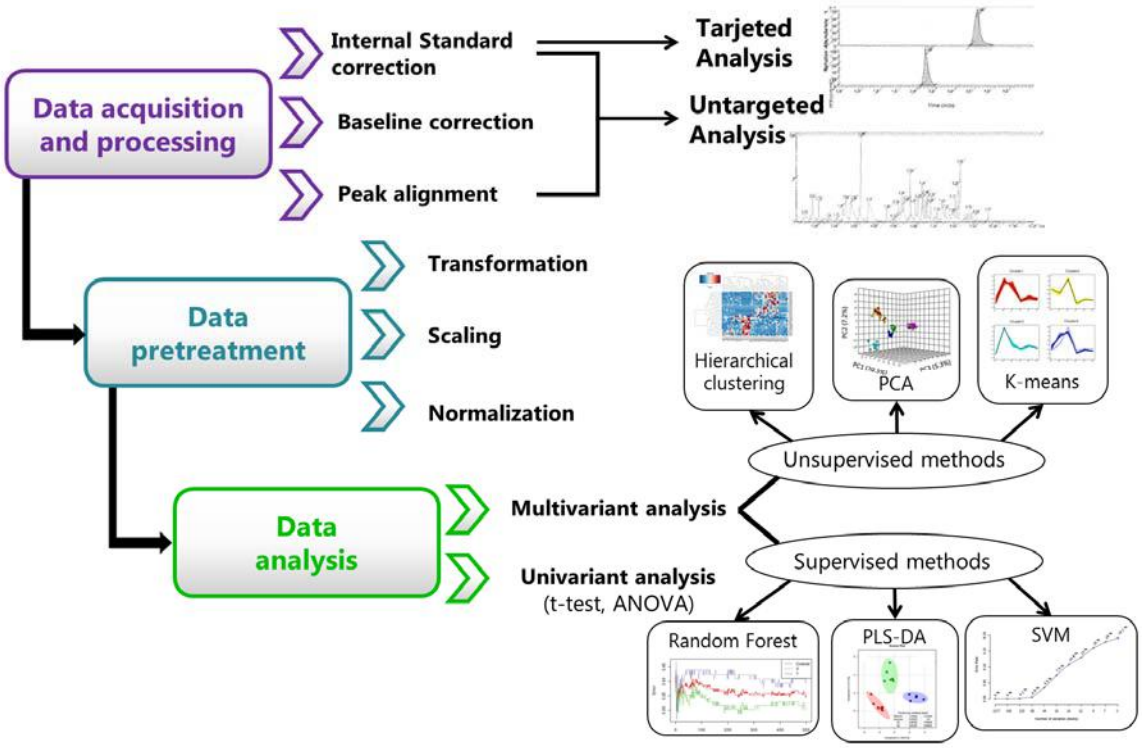

Figure 2. Data flow in a metabolomic study. The untargeted metabolomic comprise a more complex data processing involving baseline correction and peak alignment. The internal standard calibration it is applied to both approaches, targeted and untargeted. In fact, in the targeted approach each compound can be quantified respect to a specific class standard. Data pretreatment is equally performed in both approaches and the choice of the statistical analysis will depend on the experimental design and data interpretation. Among the statistical test, PCA is a useful tool to represent the samples variability and to identify outliers among them.

Unsupervised methods are exploratory methods that help you find patterns inside a set of samples. A powerful unsupervised multivariate tool for outlier identification and variability representation is the principal component analysis (PCA). PCA is the most frequently used method in metabolomics study for data mining. This method divides the data into three parts or components based on the data variance, which can be represented in 2D or 3D and the metabolites contributing to the differences among samples can be identified. Each component of the PCA is accompanied by the contribution ratio, represented by a percentage, which represents the amount of information explained by that principal component (*Putri et al. 2013*). Another multivariate method used frequently in untargeted metabolomics is the hierarchical clustering. In this analysis the mass and retention time for each compound, is expressed by a vector represented by a point in multidimensional space (*Ren et al. 2015*). The distances

between these points are calculated, and the clustering procedure will depend on those distances. Distance functions (such as Pearson or Euclidean) and clustering algorithm (average, centroid or the most used in metabolomics ward) have to be chosen carefully due to different clustering algorithms can give different results on the same data (*Benton et al. 2015*). Other unsupervised clustering method often used in metabolomics analysis is k-means.

Supervised methods use some type of response variable to discover patterns associated with the response, meaning that the algorithm will analyze each sample taking into account the experimental groups to which they belong. Inside this group a useful tool in the multivariate analysis is the partial least square discriminant analysis (PLS-DA). The PLS-DA can perform both classification and feature selection and the optimal number of components is selected by a cross-validation method. This is a supervised method because the partial least square is an algorithm that constructs the informative axis correlated to the supervised variables. PLS-DA method tends to over fit the data and therefore the model needs to be validated to see whether the separation is statistically significant or is due to random noise and this is done using permutation tests (*Pérez-Enciso and Tenenhaus 2003*). Other supervised methods often used in metabolomics analysis are random forest for clustering and support vector machine for modeling.

1.1.1.5. Future perspective: the "-omics" integration

From the recent past it became obvious that metabolomics is a scientific field which develops with an enormous speed which makes it already difficult to follow the increasing numbers of scientific publications presenting the development of novel instrumentation, methodologies, or exciting applications in biology (*Nielsen 2006*). Because of these facts, we must be aware of the urgent need to define appropriate data standards, which is fundamental in order to compare data from different experiments. In addition, the standardization of analytical methods and sample preparation will also facilitate this task and will allow the comparison between experiments from different laboratories or institutions. In the untargeted metabolomic approach, a crucial step is the identification of the metabolites and therefore, the need to develop appropriate and updated libraries of mass spectra of the different available platforms (GC-MS, LC-MS, NMR, MALDI…)(*Dias and Koal 2016*). Finally, Nielsen and collaborators go beyond and talk about that future metabolomic studies must focus on the accurate measurement of the concentrations of unambiguously identified metabolites (*Nielsen and Oliver 2005*). And for that goal, databases of metabolite concentrations in cells that are grown in

several well-defined conditions must be developed, if metabolomic data wants to be integrated meaningfully with data from another “omics” approaches.

Nowadays, the “omics” technologies approaches allow us to analyze molecules at different cellular levels, obtaining a great amount of data. Any single ‘‘omics’’ approach may not be sufficient to characterize the complexity of biological systems. Genomics, transcriptomics, proteomics, metabolomics, lipidomics, glycomics, fluxomics are the main “omics” technologies that integrated will enable to elucidate a broader picture of the behavior of a cell (*Weckwerth 2003*; *Cortassa et al. 2015*). Hence, systems biology emerges as a new interdisciplinary field that focuses on the complex interactions in biological systems by the combination of all the data obtained from the different “omics” approaches. However, the integration of diverse ‘‘omics’’ data sets possess major challenges to bioinformaticians and computational infrastructures. As it has been discussed with the metabolomic studies, systems biology demands standards that make data sets from different sources (labs, platforms, technologies) reliable and comparable for integration on a broad scale (*Kitano 2002*).

We are only at the beginning of drawing the complete picture of the complex cellular processes and that further integrative ‘‘omics’’ approaches will be necessary to elucidate the molecular network controlling the cell fate. The best is yet to come.

1.1.2. Lipidomics

Lipidomics can be seen as a sub-discipline of the metabolomics that is only focused on the lipid species but it is defined as a scientific discipline dedicated to the lipidome. The lipidome is the comprehensive and quantitative description of a set of lipid species constituting a cell, tissue or organism (*Van Meer 2005a*; *Shevchenko and Simons 2010*).

Furthermore, lipidomics can be subdivided into membrane, organelle, metabolism and mediator lipidomics which address either the comprehensive and quantitative description of membrane lipid constituents, or the structural characterization and quantification of low abundant bioactive lipid species, respectively (*Serhan et al. 2006*).

Lipidomics has come a long way in the past decade and thanks to the development and advances in analytical instrumentations, the value of lipidomic analysis have been firmly established. Lipidomics studies have found their place amongst the other “omics” approaches and these analysis are currently a key part in the evaluation of a biological system or process (*Wenk 2005*). This growth in the field has incited instrument manufacturers to develop more robust, faster,

simpler, and (one hopes) cheaper instruments to accommodate a rapidly expanding number of users (*Merrill et al. 2013*).

1.1.2.1. Lipid definition and classification

Lipids exhibit notable structural diversity, determined by factors such as variable chain length, biochemical transformations such as oxidations, reductions, substitutions, ring-forming transformations, as well as modification with sugar residues and other functional groups of different biosynthetic origin (*Fahy et al. 2011*). Although there are no consistent assessments of the number of discrete lipid compounds in nature, likely due to the technical challenges of elucidating chemical structures, it is estimated that the cellular lipid profile comprises more than 1000 different molecular species (*Van Meer 2005b*) and the number of lipid species can be estimated around 200,000 (*Yetukuri et al. 2008*).

The concept "lipid" has been defined as any group of organic compounds that are insoluble in water but soluble in organic solvents (*Smith 2000*). Currently, according to the Lipid Metabolites and Pathways Strategy (LIPID MAPS) consortium, lipids are defined in chemical terms as small hydrophobic or amphiphilic molecules, originate either entirely or in part from two distinct types of building blocks: ketoacyl and isoprene groups (Figure 3) (*Fahy et al. 2005*, *2009*, *2011*).

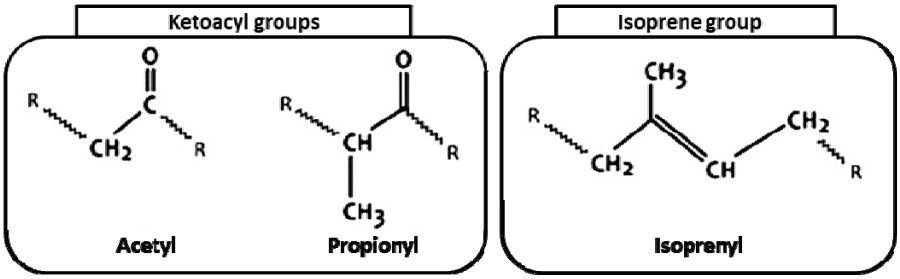

Figure 3. Structural formula of the three groups that comprise the so-called lipid building blocks.

Regarding lipid classification, there is no consensus but one of the most accepted classification system is the one developed in 2005 by the International Lipid Classification and Nomenclature Committee on the initiative of the LIPID MAPS Consortium. They established a comprehensive classification system for lipids based on well-defined chemical and biochemical principles and using a framework designed to be extensible, flexible, scalable, and compatible with modern informatics technology (*Fahy et al. 2005*, *2009*, *2011*; *Subramaniam et al. 2011*). The nomenclature adopted by the LIPID MAPS consortium carefully follows existing the International Union of Pure and Applied Chemists and the International Union of Biochemistry and Molecular

Biology (IUPAC–IUBMB) guidelines. Based on this classification system, lipids have been divided into eight categories: fatty acyls (FA); glycerolipids (GL); glycerophospholipids (GP); sphingolipids (SP); saccharolipids (SL) and polyketides (PK) (derived from condensation of ketoacyl subunits); sterol (ST); and prenol lipids (Pr) (derived from condensation of isoprene subunits). Each category is further divided into classes, subclasses, and, in the case of some subclasses of Pr species, 4th-level classes. Each lipid specie was assigned a unique 12- or 14-character identifier (LIPID MAPS ID or "LM ID") based on this classification scheme. Inside the website of the LIPIDMAPS consortium (www.lipidmaps.org, 2003), live statistics about the number of lipid structures registered can be found. In November of 2017, the database contained 40932 lipid structures of which 7206 were FA, GL category was composed by 7542, GP was the most abundant with 9629, 4357 were SP, 2828 were ST, 1251 were Pr and the sum of SL and PK was 8119. Below there is a brief description of the six main categories or families studied in this work, FA, GL, GP, SP, ST and Pr.

1.1.2.1.1. Fatty acyls

The FA category are a diverse group of molecules synthesized by chain elongation of an acetyl-CoA primer with malonyl-CoA (or methylmalonyl-CoA) groups and are characterized by a repeating series of methylene groups that impart hydrophobic character to this category of lipids (*Fahy et al. 2011*). Main subclass inside the FA category are fatty acids, a carboxylic acid with a variable length hydrocarbon chain. Fatty acids are the major building block of complex lipids; they also have important biological properties, fundamental to understanding structure and function of lipids. The hydrocarbon chain of the fatty acids may be either saturated (SFA) or unsaturated (UFA); unbranched or branched with one or more methyl substituents; as well as conjugated with other functional groups such as hydroxyl, hydroperoxy, oxo etc. In addition, they may adopted a cyclic configuration and/or be substituted with heteroatoms (*Gurr et al. 2002*). FA category not only contains fatty acids but several other functional variants such as alcohols, aldehydes, hydrocarbons, amines and esters (Figure 4). Inside the fatty ester class, other important biochemical compounds can be found such as FA thioester-CoA derivatives, FA thioester-acyl carrier protein (ACP) derivatives and FA carnitines (*Majerus and Vagelos 1967*; *Bach 1982*; *Riendeau and Meighen 1985*; *Reuter and Evans 2012*). Finally, inside FA category there are several subclasses of lipids derived from a common precursor. This is the case of octadecanoids derived from linoleic acid (LA); eicosanoids derives from arachidonic acid (AA) and docosanoids from docosahexaenoic acid. (*Smith and Murphy 2002*; *Mukherjee et al. 2007*).

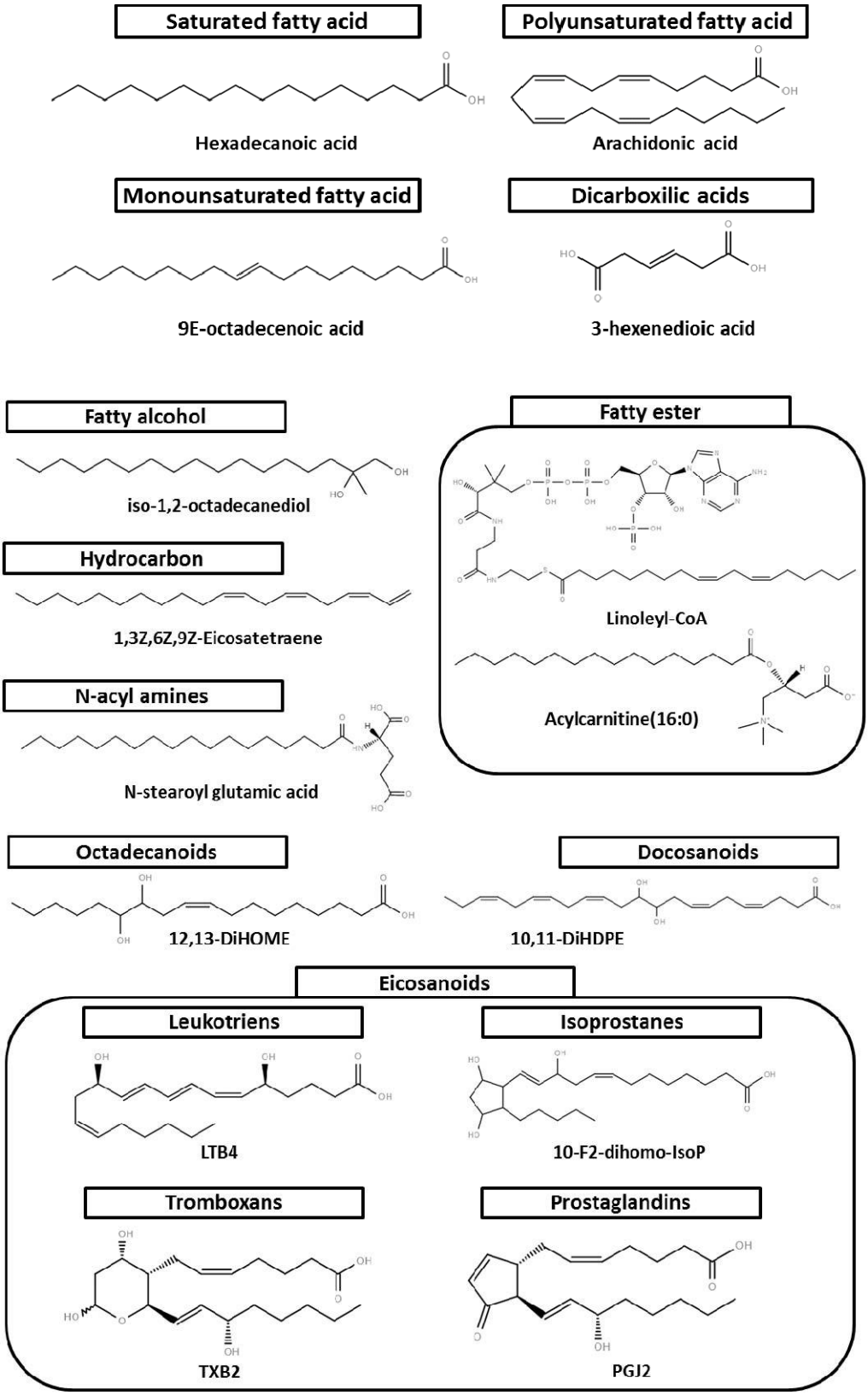

Figure 4. Structural formula of representative fatty acyl subclasses. In the upper part: saturated, monounsaturated, polyunsaturated and dicarboxylic species of fatty acids. In the middle, fatty alcohol, hydrocarbon, amines, fatty ester species, octadecanoids, docosanoids and in the bottom, eicosanoid species.

1.1.2.1.2. Glycerolipids

The GL category is composed by fatty acid esters of glycerol, or acylglycerols. The hydroxyl groups of the glycerol can be all of them esterified with fatty acids, triacylglycerol (TAG); only two of them, diacylglycerol (DAG); or just one, monoacylglycerol (MAG). Inside DAG and TAG subclasses, alkylglycerols can be found (Figure 5). These lipids contain one hydrocarbon chain linked to glycerol by an ether rather than an ester linkage (*Bell and Coleman 1980*; *Fahy et al. 2005*; *Watschinger and Werner 2013*). In most TAG, there are stereo-specific arrangements of fatty acids at the three positions. Animal depot fats have saturated fatty acids at position 1, short-chain and unsaturated fatty acids at position 2. Position 3 seems to have a more random population, although polyenoic acids tends to concentrate at position 3 in mammals (*Brockerhoff et al. 1966*).

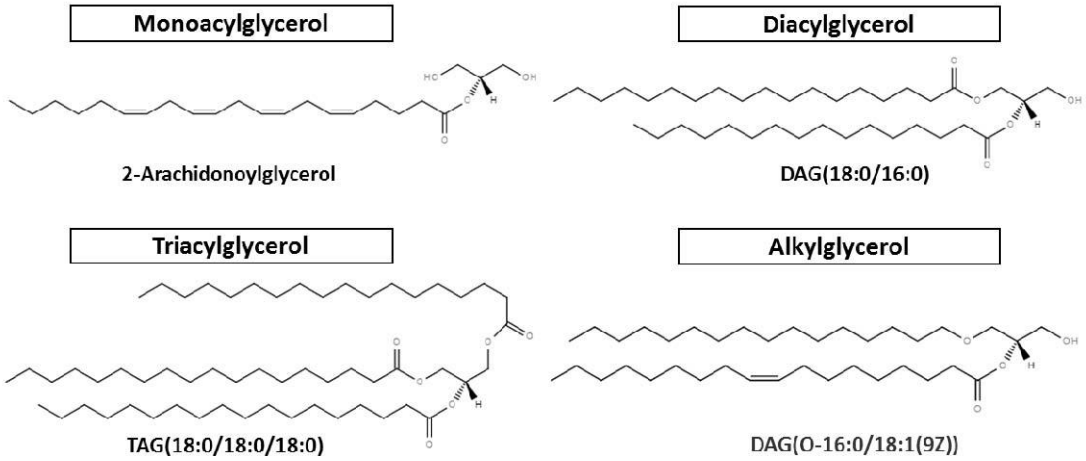

Figure 5. Structural formula of the main classes inside the glycerolipid category. Monoacylglycerol, diacylglycerol, triacylglycerol and one alkyl-acylglycerol as alkylglycerol example.

Regarding the biological functions of the GLs, MAG species are mainly signaling molecules. They play important functions regulating glucose-stimulated insulin secretion in the intestines, stimulating insulin secretion in the pancreas and regulating energy expenditure in brown adipose tissue by the activation of PPAR alpha and gamma proteins (*Shi and Cheng 2009*; *Hansen et al. 2012*; *Poursharifi et al. 2017*).

DAG species are minor components of membranes in mammals. Nevertheless they are very important molecules as they are key intermediates in the formation of many GLs, and their properties endow DAG species with specialized functions in the membrane, such as defining the membrane curvature, membrane fusion, cell-cell communication or protein recruitment (*Carrasco and Mérida 2007*; *Gómez-Fernández and Corbalán-García 2007*; *Almena and Mérida*

2011; *Ueda et al. 2014*). DAG species function also in many cellular processes as second messengers (*Eichmann and Lass 2015*). They can bind proteins and thus modulate their activity through a C1 domain. There are several reported proteins with this domain, for instance diacylglycerol kinase family, protein C kinase and Ras guanine-releasing protein among others; allowing DAGs to regulate cell proliferation, cytoskeletal remodeling, differentiation, immune response, cell migration, protein transport, insulin secretion and cell homeostasis (*Farese et al. 1991*; *Harden and Sondek 2006*; *Goto et al. 2008*; *Fukami et al. 2010*; *Antal and Newton 2014*).

TAGs are the main constituent of animal fats, major components of very low density lipoprotein (VLDL) and chylomicrons and play an important role in metabolism as energy sources and transporters of dietary fat (*Freeman et al. 2016*). The metabolizable energy, useful energy available to the body, depends mainly on the TAGs and the chain length of the constituent fatty acids. Useful metabolic energy is derived from TAGs mainly through b-oxidation of the constituent fatty acids. One mole of palmitic acid (16:0) yields 129 moles of ATP. When the energy supply from the diet exceeds the energy demands of the body, TAG molecules are deposited in adipose tissue. They have the advantage that they can be stored in anhydrous form and represent more energy for less bulk than the glycogen stored in the liver or muscle, which is heavily hydrated. The glycogen store, too, has little capacity to expand, whereas the adipose tissue is seemingly capable of enormous expansion (*Gurr et al. 2002*). There are two types of adipose tissue in the body, known as brown and white. White adipose tissue (WAT) is the more abundant and is the main tissue involved in the storage of body fat. Brown adipose tissue has a more specialized function in energy metabolism (*Bastard and Fève 2013*; *Ricquier 2013*). WAT is widely distributed throughout the body. In mammals, a large proportion is located just beneath the skin (subcutaneous adipose tissue, SAT). WAT is also located internally, being called visceral adipose tissue (VAT), and is composed of several adipose depots , and depending on the location it has its own characteristics and receives different names such as mesenteric adipose tissue, epididymal, inguinal, peritoneal and perirenal adipose tissue (*Lafontan 2013*). Besides acting as the main energy store for mammals, TAGs also functions as a reserve of bioactive lipids, such as eicosanoids and lipid-soluble vitamins, and provide structural components, including cholesterol and retinol, for membrane synthesis and repair. TAGs are accumulated in the cytoplasm of almost all type of cells, inside an intracellular organelle, called lipid droplets. This way, they are protected against lipotoxicity while they provide to the cell a rapid source of energy and essential metabolites (*Fujimoto and Parton 2011*; *Thiam et al. 2013*; *Rui 2014*; *Watt and Cheng 2017*).

1.1.2.1.3. Glycerophospholipids

GPs are the main and basic constituent of the cellular membranes and they can develop successfully this important physiological role due to their chemical structure and diversity. GP are composed of one glycerol backbone, one phosphate-head group attached to the third carbon of the glycerol and one or two fatty acids linked at the *sn-1* and *sn-2* positions by and acyl, alkyl or alkenyl bond (*Alberts et al. 2007*). When GP species only present one fatty acid they are called lysoglycerophospholipids (LGPs). In mammals, there are seven major classes inside de GL category determined by the polar head group and they are: phosphatidic acid (PA), phosphatidylcholine (PC) phosphatidylserine (PS), phosohatidylinositol (PI), phosphatidylglycerol (PG) and diphosphatidylglyerol or cardiolipin (CL). In Figure 6 the simplified structures of these classes are shown. Despite all GP classes contain a common glycerol backbone, the diversity of head groups, number and type of acyl chains, degree of unsaturation and type of bond can produce hundreds of different lipid species. This enormous structural diversity gives them a large variety of physical and chemical properties that will influence the properties of the membranes, including permeability, fluidity, curvature, presence of lipid rafts and the regulation of lipid-protein interactions (*Berg et al. 2002*; *Dowhan 2017*).

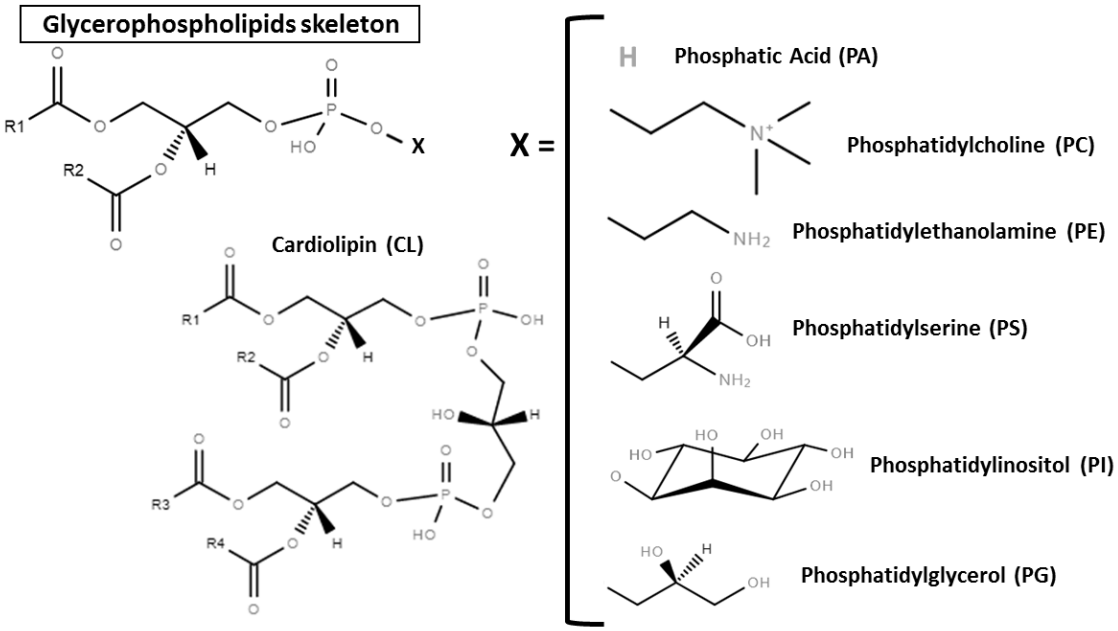

Figure 6. Simplified structures for the seven classes inside the GP category. In the upper left segment, it is shown the structure of the GPs skeleton. The R1 and R2 represent long-chain carboxylic acids connected via an ester or ether bond to the primary and secondary alcohol residues of the glycerol molecule. The X in the skeleton formula represent the different head-groups that can be joined by an ester bond to the skeleton originating the seven classes of GPs; PA, PC, PE, PS, PI, PG and CL.

Inside the GP category, besides the distinction of the seven groups classified by the polar head group, two large groups, LGP and proper GP species can be distinguished depending on the number of fatty acids. LGP are synthetized from their corresponding GPs by the action of phospholipases or acyltransferases and therefore they act as well as precursor of GP synthesis (*Gurr et al. 2002*; *Hishikawa et al. 2014*). These small molecules develop a wide range of functions as mediators through G-protein-coupled receptors specific for each LGP. This is possible thanks to the diversity provide by the nature of the phosphate head group, the positional distribution of the fatty acids on the glycerol moiety, the presence of ether or ester linkages to the glycerol backbone, and the chain-length and degree and position of saturation of the fatty acyl chains (*Makide et al. 2014*). Biological roles of LGP will depend on all the characteristics named above but almost all them, have a role in the regulation of cell proliferation, cell migration, eicosanoids metabolism, immune response and calcium ion mobilization (*van Corven et al. 1989*; *Ridley et al. 2003*; *Makide et al. 2009*; *Andradas et al. 2011*; *Sevastou et al. 2013*; *Grzelczyk and Gendaszewska-Darmach 2013*). On the other hand, there are some functions specific for each class. For example, LPA has regulatory functions in the reproductive systems of both, male and female; in brain development, vascular remodeling and neuropathic pain (*Blaho and Hla 2011*; *Sheng et al. 2015*; *Velasco et al. 2017*). LPC is the most abundant LGP with a relative high concentration in plasma being associated with albumin or in low-density lipoproteins (*Hasegawa et al. 2011*). LPC along with LPI are regulators of the nutrients uptake causing an increase in glucose-stimulated insulin secretion from pancreatic beta-cells (*Metz 1986*; *Chu et al. 2007*). The most characterized action of LPS is its role in inflammation and stimulation of immune cells, for instance triggering cell mast degranulation *(Frasch and Bratton 2012; Martin and Lagunoff 1979)*. Finally, little is known about the biological activity of lysophosphatidylglycerol (LPG) and lysophosphatidylethanolamine (LPE) in mammals, though it has been reported that LPG induces the phosphorylation of signaling molecules, such as the extracellular signal-regulated kinase (ERK) and LPE can act as a neurotrophic activator via activation of mitogen activated-protein kinase (MAPK) (*Nishina et al. 2006*; *Park et al. 2007*).

Concerning the seven groups of GP, the three main functions are i) structural components of membranes ii) as second messenger in signaling processes and iii) precursor for the biosynthesis of other lipid species (*Cevc et al. 1993*). More specifically, PA is the simplest GP and its main functions are signaling and intermediate in GL and GP synthesis. PA can be generated by several pathways; the one formed by 1-acyl-glycerol-3-phosphate, it is for GL biosynthesis while PA generated through dihydroxyacetone phosphate (DHAP) pathway, action of phospholipase D or

the acylation of LPA; it is meant to be for signaling purposes (*Shindou and Shimizu 2009*; *Kooijman and Burger 2009*; *Selvy et al. 2011*). Because it is a small anionic lipid, it contributes negative charge density to the membrane and its polar head is really close to the lipid bilayer, hence, PA molecules have been associated with fusion of membranes. Despite the interaction mechanism is still being under investigation there are reports that show an interaction of PA with kinases, phosphatases and G-proteins. PA seems to promote vesicle formation and it regulates trafficking events and transport within the cell (*Stace and Ktistakis 2006*; *Liu et al. 2013*).

PC is the most abundant GP in mammals and the major structural component in the membranes. Although PC has two charges, the net density of charge is neutral and it fits perfectly in the membranes (*Yeagle and Yeagle 2016*). Besides its key role in the membranes, PC is the main GP in plasma where acts as an important component of the lipoproteins and it is necessary to stabilize the surface of lipid droplets (*Vance 2008*; *Thiam et al. 2013*). In addition, PC species have different functions depending on their fatty acids; for example PC(16:0/16:0) is part of a surface-active layer of human lung that decreases the surface tension or PC(18:0/20:4) that acts as a regulator of the progression of the cell cycle (*Goss et al. 2013*; *Koeberle et al. 2013*). PC functions also depend on where they have been synthetized; PC species with SFA chains produced in the nucleus are responsible for the stabilization and regulation of the chromatin while PC species synthetized by enterocytes forms and hydrophobic mucus layer that protects the intestinal surface (*Albi and Magni 2004*; *Iqbal and Hussain 2009*).

PE is also one of the most frequent GP in the membranes and the PC/PE ratio is important for many cellular functions. As the rest of GP membranes constituents, PE characteristics will affect the membrane properties. For example, PE species form hydrogen bonds with neighboring polar groups, greatly influencing membrane structure (*Yeagle and Yeagle 2016*). On the other hand, the amine head group possesses a high chemical reactivity and by non-enzymatic modifications leads to hydroperoxidation products, which accelerate the peroxidation of membrane lipids and are believed to be important for generating oxidative stress but this will be discussed in more detail in the chapter lipidomics in aging (*Naudí et al. 2013a*). As a second messenger PE species are involved in autophagy and protein synthesis (*Ridgway 2016*).

PS is also component of cellular membranes, acts as a precursor for other phospholipids, but mostly is an essential cofactor that anchors to the membranes and activates large number of proteins among them ATPases, kinases, receptors, and the crucial signal transducing proteins,

protein kinase C (PKC) and adenylate cyclase. As a result, PS is involved in several processes, such as cell-cell recognition, membranes fusion or communication between cells (*Newton 1995*; *Vance and Steenbergen 2005*). PS is symmetrically distributed across the mammalian membranes being located almost exclusively in the membrane inner leaflet. Nevertheless, the action of flippases and scramblases can translocate PS to the outer leaflet. The exposure of PS on the outside surface of cells plays a key role in the removal of apoptotic cells and in the initiation of the blood clotting cascade (*Lentz 2003*; *Hankins et al. 2015*; *Bevers and Williamson 2016*).

PI is an anionic lipid that highly contributes to the surface negative charge density of the membranes. Despite its low concentration in membranes, it has several crucial roles in cell signaling and regulation and also as a precursor of the synthesis of potent biological signaling second messenger molecules, DAG, arachidonic acids derivatives and other metabolites (*D'Souza and Epand 2014*; *Irvine 2016*). The inositol chain of PI can be phosphorylated in three different positions. These are positions 3, 4 and 5 being the two lasts the most commonly phosphorylated. When both are phosphorylated the resulting compound is called PI 4,5-biphosphate (PIP2). These metabolites are called phosphatidylinositol phosphates or polyphosphoinositides (PIP) (*Hammond and Balla 2015*). Hence, thanks to the structural diversity, reversibility of the phosphorylation and different subcellular locations, PIs and its derivatives are key elements in cell signaling cascades and intracellular membrane trafficking. They are able to bind specific proteins through its polar head group, relocate integral membrane proteins or attract cytoskeletal components to the membrane. Amongst the proteins that bind to PIP are phospholipases, protein kinases, regulators of membrane trafficking, and cytoskeletal, scaffold and ion channel proteins (*Cullen et al. 2001*; *Bridges and Saltiel 2015*; *Cauvin and Echard 2015*; *Hille et al. 2015*).

PG is another anionic lipid found in mammalian membranes despite it is not a major structural component; it appears that the major membrane role for PG in animals is as a precursor for mitochondrial cardiolipin (CL) (*Gurr et al. 2002*). In addition, PG is the second most abundant lipid in lung surfactant and its concentration increases during fetal development (*Agassandian and Mallampalli 2013*). In mammalian cells, PG also activates a nuclear PKC while inhibiting some of the activities of platelet activating factor (*Lekka et al. 1993*; *Murray and Fields 1998*). Moreover, is also known to bind non-covalently to various membrane transporter and channel proteins (*Yeagle 2014*).

Finally, CL or 1,3-bis(sn-3'-phosphatidyl)-sn-glycerol, is the most unusual GP, structurally talking, and it is essential for normal electron transport and oxidative phosphorylation (*Schlame et al. 2000*). CL is found primarily in the mitochondrial inner membrane where aggregates are formed and stabilizes important electron transport protein complexes including cytochrome c oxidase, NADH dehydrogenase, ATP synthase, and various mitochondrial carrier proteins (*Ren et al. 2014*). By anchoring two types of kinase proteins along with the other carrier proteins, CL allows the transport of solutes between the intra and inter membrane spaced of mitochondria. Similarly to PS, although with another mechanism, CL is also implicated in apoptosis. During the mitophagy event, CL is externalized from the inner mitochondrial membrane to the surface of the mitochondria where interacts with several death-inducing proteins unchaining the apoptosis of the cell (*Haines 2009*). Other reported functions of CL are the promotion of protein folding as a molecular chaperone and acting as a cofactor for molecules translocation through the mitochondrial membranes (*Maguire et al. 2017*).

1.1.2.1.4. Sphingolipids

SPs are a complex category of compounds that share a common structural feature, a sphingoid base (also termed long chain base) composed of a hydrophobic moiety and a hydrophilic head group (*Gurr et al. 2002*). According to Fahy et al. 2005, SPs can be divided into several major classes (Figure 7). In mammalian tissues, it can be found among others the sphingoid bases and their simple derivatives (such as the sphingosine 1-phosphate), the sphingoid bases with an amide-linked fatty acid (ceramides, dihydroceramides and ceramide 1-phosphate), SPs conjugated with GPs called sphingomyelins (phosphosphingolipids) and glycosphingolipids. This last class is formed by SPs conjugated with one or more carbohydrates attached by a glycosidic bond (hexosylceramides, gangliosides or sulfatides, those that have a sulfate group).

Otherwise, fatty acids composition of the SPs influenced them considerable, especially but not only in relation to their physical properties and function in membranes. Fatty acids of SPs are very different from those of GPs, consisting of very-long-chain (up to C26) odd- and even-numbered saturated or monoenoic and often presented 2-R-hydroxy components. In some specialized tissues or cells, such as spermatozoa or epidermis, fatty acids of the SPs present even longer chains (C28 to C36) (*Sandhoff 2010*). Regarding SPs functions, lipid biosynthesis, signaling and structural lipids in membranes and lipoproteins are the main functions of the lipids in this category. Sphingoid bases are the characteristic or defining structural unit of the SPs, hence their primary function is to serve as a basic component of the SPs.

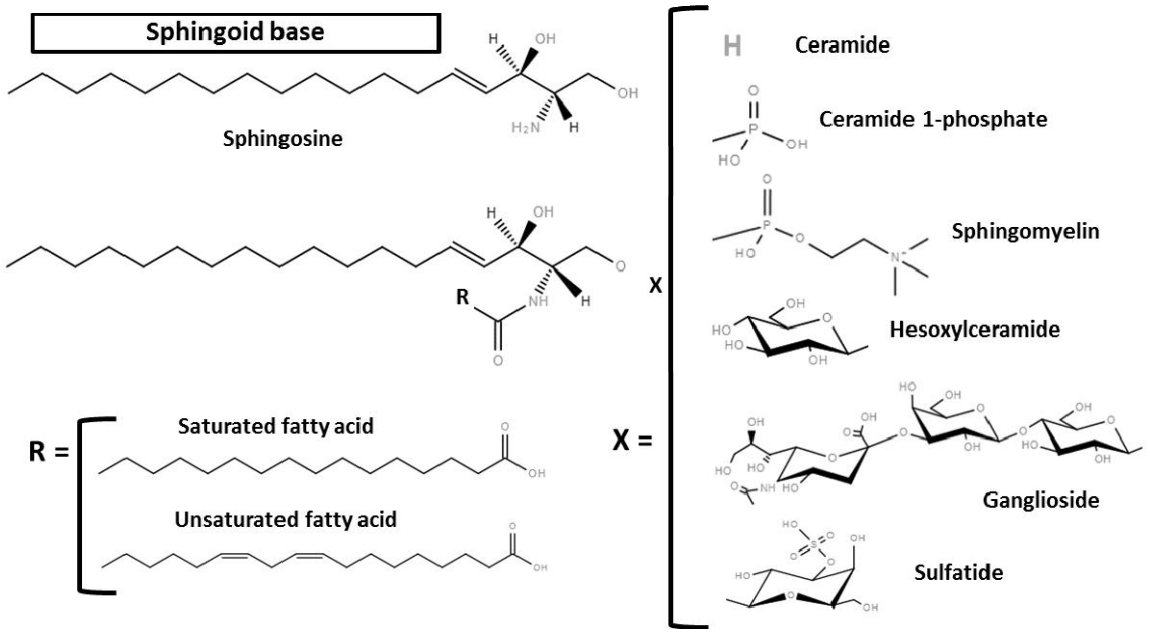

Figure 7. Simplified structural formulas of the main classes inside the sphingolipid category. In the upper left segment, it is shown the structure of the sphingosine (Sphingoid base) common for all SP. Down is the skeleton of the SP where R represent a fatty acid connected via amide bond. The X in the skeleton formula represent the different head groups that can be joined by an ester bond to the skeleton originating the main classes of SPs; ceramide, ceramide 1-phosphate, sphingomyelin, hexosylceramides, ganglioside and sulfatides examples are shown.

Free sphingosine and other long-chain bases function as mediators of many cellular events, for example by inhibiting the important enzyme protein kinase C. They have roles in regulating the actin cytoskeleton, endocytosis, the cell cycle and apoptosis (*Smith et al. 2000*).

Sphingosine-1-phosphate (Sph1P) is a potent messenger molecule that perhaps uniquely operates both intra- and inter-cellular. Extracellularly, acts as a ligand for specific receptors, G protein-coupled receptors located on the surface of the cell (called S1P1 to S1P5). Three of them are found in all tissues, whereas the other two are restricted to a few tissues. Each receptor when activated, triggers distinctive signaling pathways and cellular responses, important for the growth of new blood vessels, vascular maturation, cardiac development and immunity, and for directed cell movement (*Pyne and Pyne 2017*). In addition, Sph1P and its receptors regulate the biosynthesis of corticosteroid hormones and their function (*Lucki and Sewer 2008*). Intracellularly, it regulates calcium mobilization and cell growth in response to a variety of extracellular stimuli, and it has crucial roles in cell survival, cell migration and inflammation (*Hla 2004*).

Oppositely to Sph1P, which promote cellular division (mitosis), ceramides induces programmed cell death (apoptosis). As they have opposite functions, the balance between these lipids levels in cells is critical (*Obeid et al. 1993*). It should be noted that ceramides have different fatty acid and long-chain base compositions and they can be formed in different compartments or membranes of the cell by a variety of different mechanisms at different times. All these facts will influence their distinct functions. Ceramides are involved in cell signaling by mediating many cell-stress responses, regulating autophagy, cell senescence, cell differentiation, transformation and proliferation (*Venable et al. 1995*; *Young et al. 2013*; *Castro et al. 2014*). In addition, ceramides are minor components of membranes in general, their physical properties ensure that they are concentrated preferentially into lipid rafts and by their interactions with ion channels, ceramides influence the permeability of membranes. In general, ceramides tend to modify intracellular signaling pathways to slow anabolism and promote catabolism (*Merrill and Sandhoff 2005*).

Dihydroceramides present both fatty acids chains completely saturated unlike ceramides that also have at least the 4,5-double bond of the sphingosine. Hence, dihydroceramides functions differs from the ones carried out by the ceramides, thought they are as effective as ceramides in autophagy. However, they seem to be pro-survival under conditions of physiological stress. In addition, dihydroceramides are involved in the regulation of such diverse processes as production of reactive oxygen species in mitochondria (*Siddique et al. 2015*).

Ceramide 1-phosphate (Cer1P) and ceramides have antagonist functions and as what happened with Sph1P, balance in the cell between them is very important for the correct cell function (*Arana et al. 2010*). Cer1P is a key regulator of cell growth and survival, like Sph1P it is a potent inhibitor of apoptosis and it is an inducer of cell survival (*Chalfant and Spiegel 2005*). Moreover, Cer1P has important roles in inflammation with both pro- and anti-inflammatory effects and in vesicular trafficking due to it promotes fusion of the membranes (*Hinkovska-Galcheva et al. 2005*; *Gomez-Muñoz et al. 2016*).

Sphingomyelin (SM) consists of a ceramide unit conjugated with a phosphorylcholine. It is an ubiquitous component of animal cell membranes, where it is by far the most abundant SP. It can serve as a substitute for PC as a structural component of membranes. Apparently, PC and SM have many similarities however, there are great differences in the hydrogen bonding capacities and physical properties of the two lipids, for example, the unsaturation degree in each lipid is very different, and this fact gives them different packing properties in membranes (*Merrill and*

Sandhoff 2005). In addition, SM and cholesterol have a high affinity for each other, and they are usually located together in the lipid rafts of membranes, where SM concentration seems to control the cholesterol distribution, and on the surface of the lipoproteins (*Milhas et al. 2010*). Other important functions of SM species are eicosanoid biosynthesis as well as other SPs, regulation of the internalization of molecules through the plasma membrane and as the most abundant SP in the nucleus, has a role in chromatin assembly and dynamics as well as being an integral component of the nuclear matrix (*Lucki and Sewer 2008*; *Slotte 2013*).

Another important class inside the SPs category are glycosphingolipids. According to Fahy et al. 2005, they are classified on the basis of carbohydrate composition and below some of them will be discussed. Complex SPs are located mainly in the plasma membrane of mammalian cells where they have a structural function and also serve as adhesion sites for proteins from the extracellular medium (*Vance and Vance 2008*; *Hannun and Obeid 2008*).

Hexosylceramides (HexCer), or glycosylceramides, are neutral glycosphingolipids and in this class, there are three subclasses depending on the number of carbohydrate molecules attached and their nature. Monohexosylceramides (MHC) can be formed by the attachment of a glucose (glucosylceramide) or a galactose (galactosylceramide), they are also called cerebrosides. Dihexosylceramides (DHC) are mainly formed by the conjugation of the ceramide with a lactose molecule; hence, they are also called lactosylceramides (*Checa et al. 2015*). Finally, trihexosylceramides (THC) are composed by a lactose molecule and either a glucose or a galactose molecule. Among their functions, HexCer serve as a precursor for other glycosphingolipids synthesis, play an important role in cell signaling regulating several processes and helps to stabilize the membranes (*D'Angelo et al. 2013*). These lipids can form several hydrogen bonds by lateral interaction between the polar hydrogens of the sugar and the hydroxy and amide groups of the ceramide composing a dense network of hydrogen. They tend to be concentrated in the outer leaflet of the plasma membrane together with cholesterol and in some cases; they are also present in the lipid rafts (*Kasahara and Sanai 1999*). MHCs are involved in brain development and they are major constituents of lipids in the skin where they help to maintain the water permeability barrier of the skin (*Lingwood 2011*; *Breiden and Sandhoff 2014*). In addition, they are required for intracellular membrane transport, cell proliferation and survival, and for various functions in the immune system. Lactosylceramide forms lipid rafts on the plasma membrane of neutrophils and macrophages, which recognize, engulf and eliminate pathogens (*Merrill 2011*; *Kain et al. 2015*).

Gangliosides are acidic glycosphingolipids, they have several sugars and have at least one charged sugar residue, sialic acid. Gangliosides are further subdivided into series characterized by the number of sialic acid residues on the SP. GM series possess one sialic acid; GD, two residues of sialic acid; GT series has three residues and finally GQ series presents four sialic acid molecules (*Gurr et al. 2002*). They are anchored in membranes with their carbohydrate components extending out from the cell surface, where they can participate in intermolecular interactions by hydrogen bonding mainly. At the cell surface, they act as antigens or receptors by recognizing specific molecules (*Kolter 2012*). In addition, they modulate the charge density at the membrane surface, regulate the activities of the proteins within the plasma membrane and therefore play a role in important processes such as apoptosis or cell-cell interactions (*Russo et al. 2016*). However, gangliosides are known to be essential in brain function regarding neuronal growth, migration and maturation, integrity of axons and myelin, neuritogenesis, synaptogenesis, and myelination. These effects may be mediated by interactions of the negatively charged sialic acid residues of the gangliosides with calcium ions (*McJarrow et al. 2009*; *Aureli et al. 2014*; *Naito-Matsui et al. 2017*).

Finally, sulfatides are also acidic glycosphingolipids but they have a sulfate ester group attached to the carbohydrate moiety. Amongst their functions, they participate in protein trafficking, cell adhesion and aggregation, immune responses and signal transmission (*Honke 2013*). Many of these effects are a consequence of binding to specific proteins, which usually has a hydrophobic cavity that interacts with the ceramide component, being the hydrophilic moiety often exposed for further intermolecular associations (*Xiao et al. 2013*).

1.1.2.1.5. Sterol lipids

Sterol lipids (ST) category are major components of most of membranes in mammals, plants and fungi organism. The skeleton of the lipids of this category are four rigid sterol rings derivatives of cyclopentanoperhydrophenanthrene ring. Cholesterol (COH) or cholest-5-en-3β-ol is the most abundant member of this category in mammals (*Gurr et al. 2002*). According to the LIPIDMAPS consortium classification, ST category is subdivided primarily based on their biological function and number of carbons in the core skeleton. In mammals, beside COH and their closed derivatives, this category is comprised by cholesterol esters, steroid hormones, vitamin D, bile acids and bile alcohols (*Fahy et al. 2011*). In Figure 8 there are represented some structural formulas of a few ST species of each class.

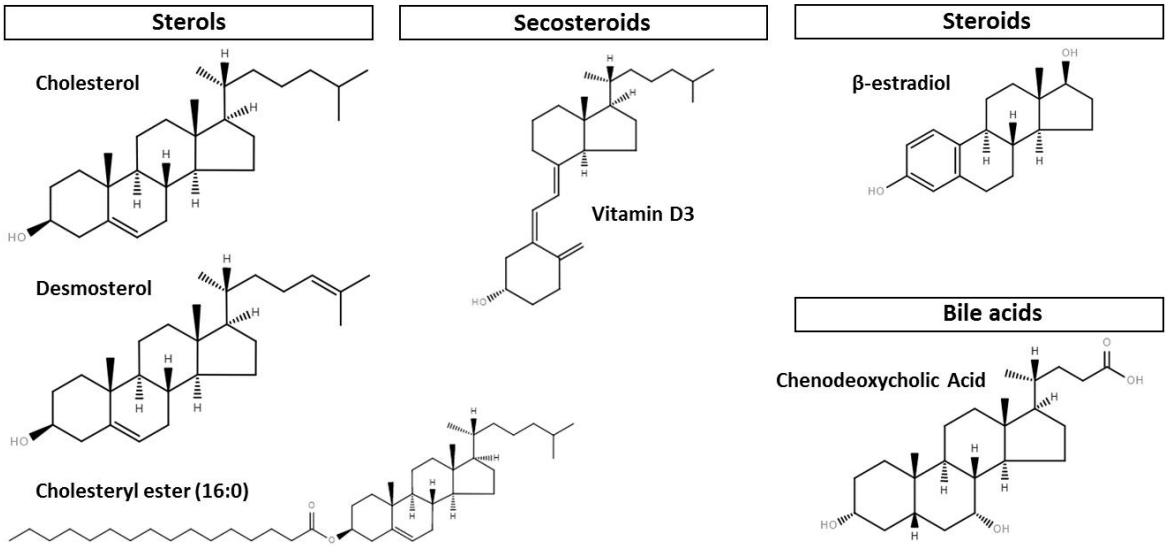

Figure 8. Structural formulas of representative sterol lipid subclasses in mammals. Species from sterols, secosteroids, steroid hormones and bile acids subclasses are represented.

COH has two main roles in mammalian cells, as a structural component of plasma membranes and some organelles, and as a precursor for other essential lipid species. Regarding its role in membranes, COH is able to modulate the fluidity of membranes by interacting with their complex lipid components (*Vance and Vance 2008*). Moreover, it regulates lateral organization of membranes and their free volume distribution, allowing correct protein-COH interactions that may regulate the activities of many membrane proteins. COH is linked covalently hedgehog proteins, which, have a major role in signaling during the differentiation of cells in the embryonic development (*Bürglin 2008*). Other membrane proteins also bind strongly to COH through a conserved region called sterol-sensing domain, which appears to function as a regulatory domain involved in linking vesicle trafficking and protein localization with such varied processes as COH homeostasis, cell signaling and cytokinesis (*Kuwabara and Labouesse 2002*). In addition, COH, along with other SP species, are main components of the lipid rafts regulating coordinately membranes function and composition to satisfy all the requirements of the cell (*Ohvo-Rekilä¤ et al. 2002*).

COH catabolism generates several important lipid species, such as cholesteryl esters or oxysterols. Esterification of COH in its hydroxyl group with a fatty acid leads to the formation of cholesteryl esters (CE). These lipid species are less polar than free COH and they are stored in the lipid droplets or in lipoprotein particles in plasma (*Korber et al. 2017*). On the other hand, oxysterols are oxygenated derivatives of COH or its precursors, which are generated by the addition of hydroxyl, epoxyl or keto groups (*Björkhem 2013*). Oxysterols functions are act as

precursors of other ST species and as paracrine and autocrine agents for immune cells. 7-ketoCOH and 7-hydroxyCOH are cytotoxic and thus they are good biomarkers for oxidative stress. Oxysterols play an important role in embryonic development by regulating the activity of hedgehog proteins and they are as well regulators of COH biosynthesis by modulating the action of proteins like Liver X receptor (LXR) or sterol regulatory element binding protein (SREBP) (*Griffiths et al. 2016*). Oxysterols are present in lipoproteins and biological membranes and despite their low abundance perform an important role. For instance, some oxysterol species are required along with COH to form lipid rafts in the plasma membranes (*Kulig et al. 2016*).

Steroid hormones are synthesized from COH and oxysterols and according to their biological roles they are classified in three groups: sex steroids, corticosteroids and neurosteroids. Amongst sex steroids there are estrogens and progesterone, which are synthesized primarily in the ovary and placenta during pregnancy, and testosterone mainly in the testes. On the other hand, corticosteroids, such as cortisol or aldosterone, are synthesized in the adrenal glands. Finally, neurosteroids are synthesized in the central and peripheral nervous systems. Functions of the steroid hormones are several and essential in physiology or physiopathology of the organisms, playing an important role in aging, which will be discuss in the next section. They are key regulators in homeostasis, glucose metabolism, the reproductive system, central nervous system, immune system, among others (*Katsu and Iguchi 2016*; *Ogino et al. 2016*; *Tsutsui and Haraguchi 2016*).

Vitamin D and their derivatives are also products of COH catabolism and they are essential for the regulation of calcium and phosphorus levels and have many other functions, including induction of cell differentiation, inhibition of cell growth, immunomodulation, and control of other hormonal systems (*Ohyama and Shinki 2016*).

Bile acids (BAs) are amphipathic molecules derived from COH catabolism with the steroid backbone, divided in “primary” BAs, which are synthesized in parenchymal cells of the liver; and “secondary” BAs, which are generated by dehydroxylation, oxidation of hydroxyls to oxo groups and epimerization, modifications carried out by intestinal bacterial flora. An alternative minor biosynthetic pathway of BAs, which takes place in the inner membrane of the mitochondria, utilizes oxysterols as precursor instead of COH. BAs can be conjugated with taurine, glycine, sulfate or glucuronic acid in the peroxisomes (*Hofmann and Hagey 2014*). The major function of BAs is the absorption of dietary lipids in the intestines during digestion. They act as detergents or emulsifying agents mainly for fatty acids and MAGs. They also play an important role in COH

homeostasis by preventing the precipitation of this molecule in the bile (*Lefebvre et al. 2009*). Furthermore, BAs act as nutrient signaling molecules, via interactions with several receptors and thereby regulating the expression of key genes in sterol, TG and carbohydrate metabolisms (*Nguyen and Bouscarel 2008*; *Zhou and Hylemon 2014*). For instance, they can regulate de TG biosynthesis in the liver and production of VLDL, which leads to a decrease in plasma TG levels (*Watanabe et al. 2004*). They control their synthesis and circulation in the liver by a negative feedback mechanism through the farnesoid X receptor (FXR). In addition, BAs are involved in other biological processes such as apoptosis and cell survival, they influence in calcium mobilization, in the cyclic AMP synthesis and in the activation of the kinase PKC (*Maruyama et al. 2002*; *Amaral et al. 2009*).

1.1.2.1.6. Prenol lipids

Pr are synthesized from the five carbon precursors isopentenyl diphosphate and dimethylallyl diphosphate and though this category is formed by several subclasses; below there are briefly described those with major functions in mammals, retinoids and quinones (*Fahy et al. 2011*).

Retinoids are exclusively found in mammals but their biosynthetic precursors are carotenoids, plant metabolites ingested in the diet. Retinal, retinoic acid and retinol are the first metabolites of this subclass synthetized in the liver or intestines. Retinol (Figure 9) is also called vitamin A, a well known compound because of its key role in vision function (*Kiser et al. 2013*). Retinol can be esterified and retinol esters are stored in lipid droplets mainly in the liver and in specialized cells in the eye but also in other tissues. Retinol esters and primarily retinyl palmitate, in the lipid droplets, are the main storage form of vitamin A (*Chelstowska et al. 2016*). Membranes also have a relatively small proportion of the cellular retinoids in tissues. Aside from their main role in vision sharpness, they are known to act as antioxidant agents because they are efficient quenchers of singlet oxygen and scavengers of other reactive oxygen species (*O'Byrne and Blaner 2013*). Moreover, retinoids perform other functions in signaling and modulation of gene transcription by acting as ligand of retinol binding proteins (*Noy 2015*). They control the expression of a large number of genes and are therefore involved in several processes such as cell proliferation and differentiation, embryogenesis, lipid metabolism in liver, skeletal muscle and adipose tissue and in the correct performance of the immune and reproductive systems (*Bonet et al. 2012*; *Al Tanoury et al. 2013*). Inside the quinones subclass, ubiquinones better known as Coenzime Q (CoQ) can be found. These compounds have a nucleus formed by 2,3‑dimethoxy-5-methylbenzoquinone and a side chain of nine to ten isoprenoid units in

mammals (*Wang and Hekimi 2016*). They are redox active lipids present in most eukaryote organelles located in the membranes bilayers. It can exist in three different forms in terms of oxidation. The first one is its oxidized form, ubiquinone (UQ), then its partially reduced form, ubisemiquinone radical (UQ-) and the reduced form ubiquinol (UQH2) (*Stefely and Pagliarini 2017*).

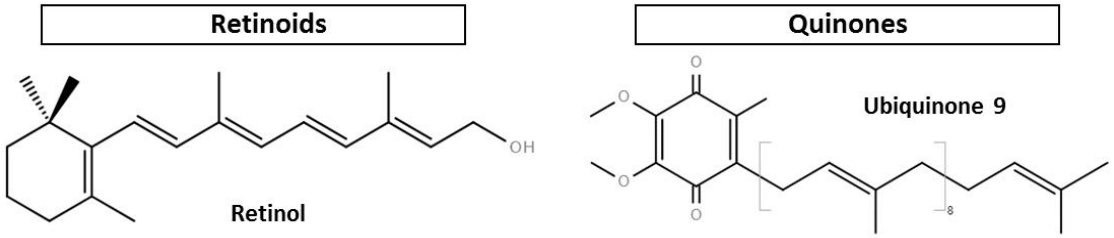

Figure 9. Structural formulas of representative prenol lipid subclasses in mammals. Retinol and ubiquinone 9 are represented as example of retinoids and quinones subclasses respectively.

Due to its capacity to undergo reversibly between the three forms, it is essential in the mitochondrial electron transfer for ATP production. Briefly, UQ role is to transfer electrons from Complex I and Complex II of the electron transport chain to Complex III while transferring protons to the inter membrane space thus generating a proton motive force leads to the pass of protons throughout the ATP synthase (or Complex V) generating ATP via oxidative phosphorylation (*Turunen et al. 2004*). In this process, UQ goes from its oxidized form to the reduced form. UQH2 is an endogenous antioxidant that prevents lipid peroxidation in biological membranes and in serum LDL proteins. Ubiquinol also protects mitochondrial membrane proteins and DNA against oxidative damage (*Frei et al. 1990*). Besides its role in the electron transport chain and oxidative phosphorylation, UQ is a regulator of mitochondrial permeability and within this organelle; it is a critical cofactor for pyrimidine nucleotide biosynthesis and for mitochondrial uncoupling proteins function (*Jones 1980*; *Fontaine et al. 1998*; *Klingenberg et al. 2000*). In addition, UQ is an electron acceptor for fatty acids oxidation (*Watmough and Frerman 2010*).

1.1.2.2. Analytical challenges of lipidomics

The great diversity of the physicochemical and structural properties of the species that comprise the lipidome poses a challenging scenario for lipidomics methods. An important annotation is that, despite the advances in mass spectrometry and bioinformatics, the choice of the sample extraction and the liquid chromatography (LC) separation methods are the two steps that will

provide the degree of the lipidome coverage. A single extraction procedure will unvaryingly generate a bias toward certain lipid species at the expense of others and therefore the combination of multiple extraction and separation procedures is essential to maximize coverage of both lipid classes, those more hydrophilic and the more hydrophobic. In this sense, several lipid extraction and LC procedures have been published recently increasing the changes for maximizing the number of species detected in a single analysis. In Figure 10 there is a summary of the lipid classes that can be detected with the most used extraction methods in lipidomics analysis (*Tumanov and Kamphorst 2017*). Besides from the solvents, there are other characteristics in the extraction protocols that increase the possibilities for maximized the lipid species detected.

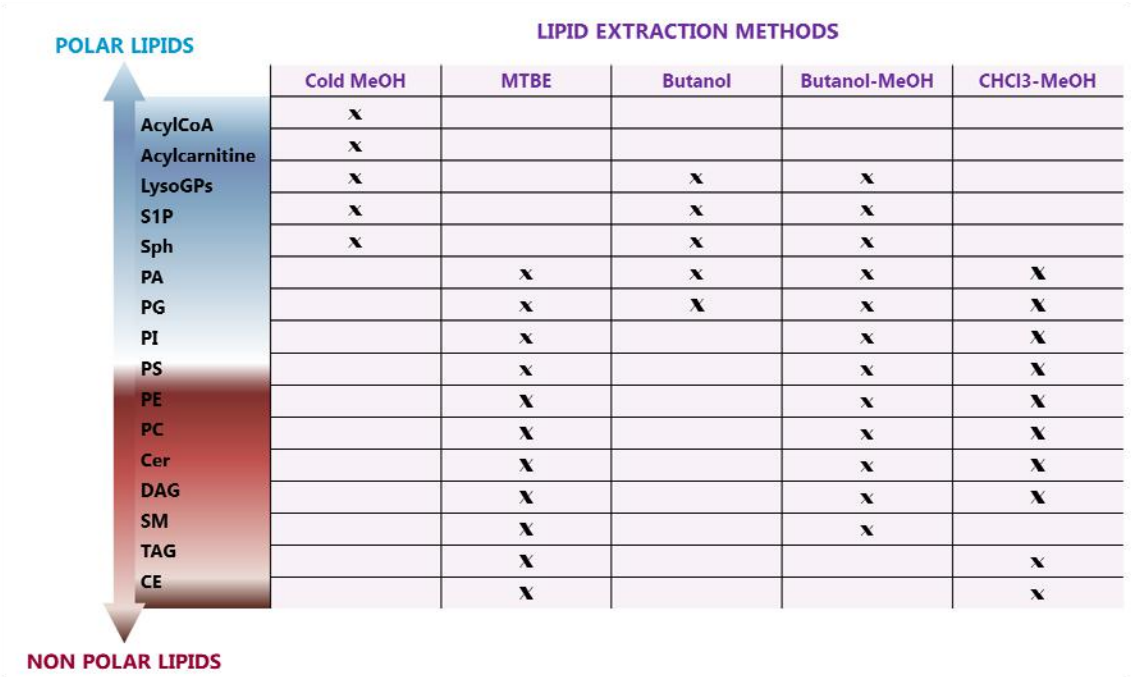

Figure 10. Commonly used lipid extraction methods and the lipid classes they cover with better intensity in the analysis. Detection of the lipid classes will be always depending on the LC separation methods being possible to increase or decrease the lipid coverage range. Adapted from Tumanov and Kamphorst 2017**.**

Regarding the liquid chromatography separation, several protocols for lipidomics have been published about two types of LC, hydrophilic interaction liquid chromatography (HILIC) and the reverse phase liquid chromatography (RPLC). HILIC was design for the retention and separation of polar-ionic compounds and therefore it is particularly suitable for separating LGP regioisomers (Buszewski and Noga 2012). Nevertheless, RPLC is the most popular separation method for lipidomic analysis. In the RPLC analysis a C8/C18 column it is used and depending on the composition of the mobile phases and the gradient a set of lipid will be detected at the expense

of others. GPs, SM, Cer, CE, DAG and TAG will be detected under a combination of acetonitrile–water (60:40) and isopropanol–acetonitrile (90:10) as mobile phases, while more polar species can be detected with a methanol-water gradient (Castro-Perez et al. 2010; Cajka and Fiehn 2014). Inside mass spectrometry-based lipidomics, alternatively to LC-MS, there is another strategy called shotgun lipidomics. In this approach the lipid extracts are directly infuse into the mass spectrometer which significantly reduce the time course of a sample (*Han et al. 2012*). Therefore, shotgun lipidomic analysis it is a useful tool for high-throughput and routine analysis of major lipid species, although as a counter point the identification of isobaric species as well as low abundant species are the main disadvantages of this lipidomic strategy (*Schuhmann et al. 2012*).

Finally, the choice of an extraction method or LC separation protocol will have to be made according to the purpose of the experimental design. Meanwhile, the continuity in the improvements of lipid extraction protocols and liquid chromatography conditions guarantee a better comprehensive characterization of lipids in the biological systems.

1.2 Lipidomics in aging

The origin and early evolution of life is closely linked to lipids (*Segré et al. 2001*; *Paleos 2015*), and their inherent self-organization ability to form membranes (*Tanford 1978*). In fact, all organisms/cells from the three domains of life (archaea, bacteria, and eukaryotes) have lipid membranes (Lombard et al. 2012). The unique trait of lipids to generate membranes was later during evolution extended to new functional properties such as cell signaling and energy storage (*Hulbert et al. 2014*). The evolution of early organisms toward complexity was also associated with an enlargement in the structural and functional diversity of lipid species. As it has been discussed in the previous chapter, the result is the generation of thousands of different lipids, which require cells to invest approximately 5% of their genes for lipid synthesis (*Sud et al. 2007*). Contrasting the case of genes and proteins, which are primarily composed of linear combinations of 4 nucleic acids and 20 amino acids, respectively, lipid structures are more complex due to the number of different biochemical transformations, which occur during their biosynthesis. This diversity is also extended to cellular membrane from a compositional point of view. Thus, the lipid profile varies within the lateral plane of the membrane, between the two leaflets of the lipid bilayer, between territories of the membrane, between organelles, between organs, and between animal species *(Vereb et al. 2003; Van Meer et al. 2008; Klose et al. 2013; Naudí et al. 2013; Jain et al. 2014; Naudí et al. 2017)*. To this diversity in spatial distribution must be added the temporal trait. Thus, the lipid profile varies in time according to a circadian rhythmicity, as well as during the vital cycle of an organism, for instance, during aging (*Naudí et al. 2015*; *Aviram et al. 2016*; *Jové et al. 2017*).

1.2.1. Lipidomics in longevity and aging

Aging causes numerous deleterious changes at every level of the biological organization, reducing the maximum functional capacities and homeostasis, and increasing the likelihood of suffering degenerative processes, leading to death in every organism. All these changes have probably originated in a small number of basic causes, such as oxidative stress, which continuously operate throughout life and determine the rate of aging, which is specific to the cell type, tissues and species (*Cabré et al. 2017a*).

The association between healthy aging or longevity and lipid profiles and metabolism has been reported throughout the last decade and results from lipidomic profiling studies have sought to associate lipid levels and its composition with a certain phenotype of healthy aging (*Pamplona*

2008; *Jové et al. 2013b*, *2017*; *Gonzalez-Covarrubias 2013*; *Hulbert et al. 2014*; *Schroeder and Brunet 2015*). In this way, the unsaturation degree of fatty acyl chains plays an important role in longevity due to the susceptibility of polyunsaturated fatty acyls chains (PUFA) to be oxidized (*Pamplona et al. 1998*; *Jové et al. 2013b*). Oxidative stress is a natural consequence of aerobic life and the production of reactive oxygen species (ROS) is an inevitable effect of the metabolism of molecular oxygen in the mitochondria. Although ROS are molecular messengers and have numerous roles in cell signaling their accumulation or limited scavenging by antioxidants, contribute to the deterioration of proteins, DNA, and lipids (*Halliwell and Gutteridge 2015*). Since organic regions contain more free radicals than aqueous ones, mitochondrial membranes bilayers are the primary targets of oxidative damage (*Pamplona 2008*). PUFA are particularly susceptible to this attack because the hydrogen atoms attached to the methylene group located between two double bonds have the lowest bond energies of any other hydrogen in the fatty acyl chain. Therefore, it is relatively easy for the radicals to remove them and that is the reason why PUFA are more prone to oxidative damage than saturated and monounsaturated fatty acyl chains (SFA and MUFA, respectively) (*Hulbert et al. 2007*; *Pamplona 2008*; *Naudí et al. 2013a*, *b*). Free radicals, then, will leave a carbon atom with an unpaired electron by pulling off the hydrogen atoms that were attached to him. This carbon-center radical can be combined with an oxygen molecule in the membrane, generating a lipid peroxide radical, which is highly reactive. Lipid peroxides are able to attack membrane proteins and other PUFA chains initiating a cascade of lipid peroxidation reactions. Lipid peroxides are more hydrophilic and because of this, they migrate to the surface of the membrane, disrupting its structure and altering its fluidity. Other end-products of lipid peroxidation are generated called reactive carbonyl species (RCS) with much longer half-life than ROS and with the ability of migrate through either membranes or cytosolic media and thereby, RCS generate damaging effects far from the production site (*Pamplona 2008*). As a result, a higher MUFA-to-PUFA ratio is associated with lower lipid peroxidation, oxidative damage, and maximum lifespan (*Pamplona 2008*). Variations in the membrane lipid composition directly affects longevity and lower membrane unsaturation and larger lifespan has been established for membranes of different tissues and animal species (*Pamplona et al. 2000*; *Portero-Otín et al. 2001*; *Naudí et al. 2013b*). In addition of lowering the levels of PUFA, there are other cellular defense mechanisms against oxidative damage, such as antioxidants and removal/repair systems. Ubiquinone and ether phospholipids, like plasmalogens, act as ROS scavengers being able to stop the autocatalytic process of lipid peroxidation (*Engelmann 2004*; *Wang and Hekimi 2016*).

As in longevity, the membrane fatty acid composition shows differences in the aging process. Hulbert, Pamplona and collaborators, published a complete summary of the association between the lipid composition with advancing age in different tissues and species. The trend of the many studies summarized in this review is an increase in either PUFA content or PI of membranes with age, an increase in both in vitro and in vivo membrane lipid peroxidation with age, as well as age-related changes in physicochemical membrane properties (*Hulbert et al. 2007*). Studies with rodents show that liver, heart, kidney, testis presents either an increase, or no change, in PUFA content and/or PI, while the brain shows a decrease with age in the rat. However, likewise the other tissues, the brain reveal high levels of lipid peroxidation and increase in the membrane microviscosity, which it translates into a decrease in the fluidity of the membrane reported by several studies (*Hulbert et al. 2007*). The possible explanations for the membrane fluidity changes observed could be as a result of the modification of the fatty acid chain composition and/or as a change in the cholesterol content of the membrane and therefore, the reported increase in PI and PUFA in the membrane composition it is responsible for the age-related membrane rigidity (*Pamplona et al. 2002a*). Although a higher content of PUFAs should increase the membrane fluidity because PUFAs presents lower melting points than SFAs, their susceptibility to free radical attack along with the increased oxidative stress with advancing age lead to higher rates of lipid peroxidation production, as it has been reported in different tissues of insects, rodents and humans (*Hulbert et al. 2007*). Age-related changes in the membrane are an increase in lipid peroxidation along with higher lipoxidative damage, to both proteins and DNA and lipid peroxidation products and peroxidized lipids are expected causes in generating the membrane rigidity associated with age as well as the loss of membrane functioning that correlates with the modification of its physical state (*Pamplona et al. 2002a*).

Since a few years ago, all the studies in the bibliography discussing the lipid metabolism in aging and longevity were focused on the fatty acid composition and the oxidative stress state. Although fat has been historically considered detrimental to health and lifespan, emerging lipidomic technologies have provide the opportunities to probe that lipids can be beneficial in the aging process as it have been reported in the lipid profiles of long-lived humans and model organisms and genetic studies of lipid metabolism (*Tomás-Loba et al. 2013*; *Jové et al. 2014*, *2017*). Most of the metabolomic and lipidomic studies have been performed in order to study the lipid metabolism and the aging process have been performed in plasma or serum from rodents and humans (*Houtkooper et al. 2011*; *Yu et al. 2012*; *Gonzalez-Covarrubias et al. 2013*; *Tomás-Loba et al. 2013*; *Lee et al. 2014*; *Cheng et al. 2015*; *Jové et al. 2017*). The common trait in

all of them is the agreement in the existence of a metabolic or lipidomic signature associated with the aging process. Lipidomic analysis in serum or plasma reveal an association in lipid metabolism with the aging process concerning mainly SP and GP species. Also, it has been reported sexual dimorphisms in regard to the metabolome in aging and longevity, being most of the lipid species associated only with female longevity and revealing important gender-related differences (*Gonzalez-Covarrubias et al. 2013*; *Jové et al. 2017*). Females live longer than males in many species, including humans and differences in regulatory lipid metabolism pathways due to their different in energy request during their reproductive years have been reported. (*Viña et al. 2011*; *Gonzalez-Covarrubias et al. 2013*; *Jové et al. 2017*). The lipidomic studies in serum and/or plasma represent a valuable tool to study global changes in the lipid metabolism, however if the goal is to focus on the association or implication of age-related changes in the lipid metabolism of a given type of tissue the number of published studies decrease significantly. Metabolomic and lipidomic studies in rodents have reported an increased in PUFA content in the skeletal muscle along with a decreased in bile acid and dysregulation of GP, SP and GL metabolism with advancing age (*Houtkooper et al. 2011*; *Garvey et al. 2014*). In liver, metabolomic study propose fatty acids and GP species as the best metabolites to predict age in an animal model (*Houtkooper et al. 2011*). The brain metabolome study of male rats across the lifespan revealed a decrease in bile acids whereas acylcarnitines and several SP and GP species are increase with advancing age (*Zheng et al. 2016*). The metabolomic analysis of this study performed in rats also reported a decrease in the PUFA content of the brain of the rodents in concordance with previous results published (*Hulbert et al. 2007*; *Zheng et al. 2016*).

Nowadays, the information available about lipid metabolism and the process of aging is still scarce and the emergence of lipidomics upsurge as a possible solution to define and to understand the changes of the lipidome in the aging process.

1.2.1.1. Lipidomics in centenarians

Centenarians are the model of healthy and successful aging. In this line, the study of lipid profile in humans with exceptional longevity helps us to better understand the aging process. The studies done in centenarians and their offspring showed that among phospholipids, alkylphosphatidylcholine species (PC(O-)), especially PC (O-34:3) and PC (O-34:1), have been positively associated with longevity, in contrast to the PE(38:6) (*Gonzalez-Covarrubias et al. 2013*). On the other hand, particle size of the lipoprotein has also been associate with longevity and aging. Centenarians and their offspring have significantly larger HDL and LDL particle sizes.

Moreover, HDL are main carriers of ether PCs, which are associated with a healthy aging profile while low density lipoproteins, main carriers of SM and Cer species, have a main role in cardiovascular disorders (*Barzilai et al. 2003*). Interestingly, low glycosphingolipids levels seem to be central for healthy aging. Cer(d39:0), Ganglioside GM3 (d40:1), GlcCer(d40:0) and GlcCer(d36:2) are some of the SP species found to be decrease in centenarians (*Jové et al. 2017*). Further, higher levels of certain SM species such as SM(d18:1/18:2) and SM(d18:1/17:0) has seen to be positive associated with healthy aging in women (*Gonzalez-Covarrubias et al. 2013*). As it can be seen, lipids of the same category may have opposite associations for the same process and the study of the individual lipid species can help us to unravel the molecular characterization of the human lipidome. Some of these studies also describe a more oxidative-resistant lipidomic signature associated with extreme longevity that it translates into a low double bond index in their fatty acids being in concordance with the results published in animal longevity studies (*Jové et al. 2013b*, *2017*).

1.2.2. Lipids in aging tissue by tissue

In this section, it has been reviewed the state of the art of lipid metabolism studies in each aged tissue without any age-related pathology, meaning the information is only about the lipid studies of healthy aged tissues, paying special attention to those tissues that comprise our study. In that sense, there is a lack of lipidomic studies in almost every tissue regarding the aging process. So, aging affects tissues and their morphology and physiologic functions causing a progressive deterioration and age-related changes in lipid metabolism that seem to be tissue-specific (*Ma et al. 2015*).

In the **skeletal muscle** the gradual loss of mass and functionality, known as sarcopenia, is one of the more consistent hallmarks of aging. Regarding lipid metabolism in the skeletal muscle during aging there is a redistribution of lipids and changes in their concentration (*Lang et al. 2010*). Lipids can be contained within adipocytes as well as deposited within muscle fiber, known as extramyocellular and intramyocellular lipids, respectively. It has been reported that the aging process in humans leads to an increase frequency of adipocytes within muscle tissue and therefore in extramyocellular lipids. On the other hand, there is also an increase in intramyocellular lipids due to an increment of the number and size of lipid droplets because of the reduced oxidative capacity of muscle fibers with aging (*Crane et al. 2010*; *Gueugneau et al. 2015*). In addition of the changes in energy store, specific lipid species such as Cer1P or ganglioside GM3 are involve in the regulation of skeletal muscle growth and/or differentiation

and dysregulation of these lipids are associated hyperlipidemia or loss of skeletal muscle mass (*Lipina and Hundal 2017*).

For cardiovascular system, different age-related changes have been establish in humans and animal models such as endothelial dysfunction and vascular stiffening which increases the pulse wave velocity and in turn increases the systolic blood pressure (*Heiss et al. 2017*). On the other hand, mechanical forces, such as stretch and shear stress, regulate the redox balance in the vascular wall producing ROS and lipid hydroperoxides that will act as second messengers and also are kept in check by antioxidant defenses (*Lehoux 2006*). This delicate redox balance is altered in the elderly because of antioxidant capacity is weakened during aging (*Ji et al. 1991*). Moreover, stiff arteries promotes the oxidative stress in the circulation promoting as well oxidation of bystander lipids and proteins causing collateral damage in other tissues (*Mitchell 2008*). Focusing on the heart, similar to that seen in humans, aging in rodents is characterized by left ventricular hypertrophy, diastolic and systolic dysfunction, cardiomyocyte loss, increased fibrosis and electrophysiology deregulation that leads to arrhythmias (*Walker et al. 2006*; *Rossi et al. 2008*; *Fannin et al. 2014*). Most of the age-related changes suffered by the heart are explained by the lipotoxicity effect (*Drosatos 2016*). The **heart** has both the greatest caloric needs and the most robust oxidation of fatty acids (*Goldberg et al. 2012*). Cardiac uptake and oxidation are perfectly balanced but with advancing age, lipids tends to accumulate potentially leading to cardiac lipotoxicity maybe because of a disruption of mitochondrial dynamics and autophagy (*Schulze 2009*; *Abdalla et al. 2011*; *Zhao et al. 2014*). The underlying molecular mechanisms could be both or either increased lipid uptake or impaired mitochondrial oxidative function but nowadays further studies need to be done in order to clarify what is happening in an aging heart.

Age-related changes in the vascular system, have been linked to other organ structure and function specially brain and kidneys, which are high-flow, low-impedance organs that are, as a result, particularly susceptible to cardiac abnormalities caused by an increase aortic stiffness (*Mitchell 2008*). In addition to vascular changes, renal aging is associated with alterations in its morphology and with a decline in renal function. The **kidney** is one of the organs with higher susceptibility to age-dependent tissue damage and male rats most frequently die of renal failure (*O'Sullivan et al. 2017*). Regarding its morphology alterations, the average kidney weight progressively decreases with age, affecting mainly the renal cortex. As well, there is a decline in total nephron size and number likewise a global increased glomerulosclerosis, tubular atrophy and interstitial fibrosis (*Zhou et al. 2008*). These changes were associated with age-related

increase in lipid accumulation of TAG and cholesterol content. This lipid accumulation could be due to an age-related increase in renal expression of SREBP-1 and SREBP-2 (*Jiang et al. 2005*). As it was discussed before in the cardiovascular system, lipid accumulation potentially leads to lipid peroxidation and with advancing age, there is an increase in renal ROS production along with a decrease in the expression of antioxidant enzymes (*Martin et al. 2002*; *Csiszar et al. 2007*; *Uzun et al. 2013*). In this sense, levels of F2-Isoprostanes (F2-IsoPs) are found to be increased in the kidney of old rats (*Ward et al. 2005*). Regarding its function decline, with advancing age, glomerular filtration rate diminishes as well as the renal tubular function; therefore, the ability of the kidney to both maximally concentrate and dilute the urine diminishes and the handling of sodium and potassium is also affected (*Abdel-Rahman and Okusa 2014*; *O'Sullivan et al. 2017*). Lipid metabolism has an important role in the age-related decline in renal function through the role of AA and its metabolites (*Dunn 1987*). A decrease in AA and its metabolites, both prostaglandins, epoxy eicosatrienoic acid (EET) and dihydroxy eicosatrienoic acid (HETE), generates an imbalance between vasodilatory and vasoconstrictive events affecting the renal function in the aging kidneys (*Omata et al. 1992*; *Hornych 2004*; *Drenjančević et al. 2016*).

Regarding how aging affects the **liver**, it has been reported a decline in organ volume as well as a reduction in total hepatic blood flow (*Wynne et al. 1989*). On the other hand, scientific consensus is not reached about the effects of aging on hepatocytes and other cell types in the hepatic tissue such as Kupffer cells (*Schmucker 2005*). Despite possible morphological alterations with advancing age, liver function tests have failed to identify significant age-related deficits with the exception of diminished bile acid secretion and increased biliary cholesterol (*Tuchweber B et al. 1987*; *Krøll 2012*). Several studies, in humans and rodents, have reported a decrease in bile flow, bile salt secretion and composition, coupled with the increase in both cholesterol and phospholipids secretion with age in rodents but the cause or mechanism by which bile acid production is decline remains unknown (*Schmucker et al. 1985*; *Einarsson et al. 1985*; *Tietz et al. 1992*). In addition to deregulation in bile acids, the hepatic mitochondrial lipid composition has been reported to be significantly altered in aged rats, in which the total cholesterol increases but the phospholipids decrease, specially cardiolipin levels (*Vorbeck et al. 1982*; *Paradies and Ruggiero 1991*). Besides that, alterations were also found in the pattern of fatty acids with an increase in levels of LA and elaidolinoleic acid and a decrease in eicosatrienoic acid and eicosapentanoic acid (*Engler et al. 1998*). In addition, it has been reported that liver in old rodents present higher levels of F2-IsoP, an oxidative stress biomarker, suggesting an increase in lipid peroxidation as well in the hepatic tissue (*Ward et al. 2005*).

As in humans, rodents aging leads to **white adipose tissue** dysfunction, subcutaneous fat loss and an increase in visceral and ectopic fat (*Tchkonia et al. 2010*). Thus, fat redistribution with aging occurs across species. A decrease in the ratio of functioning subcutaneous to visceral fat, as well as an imbalance between *de novo* lipogenesis and fatty acid oxidation are associated with an increase in lipotoxicity (*Lelliott and Vidal-Puig 2004*; *Kuk et al. 2009*). These substantial changes are accompanied by alterations in WAT metabolic function leading to insulin and fatty acid responsiveness (*Kirkland and Dax 1984*). Regarding fatty acid synthesis, SAT presented lower ratios of synthesis than visceral fat (*Benjamin et al. 1961*; *Huffman and Barzilai 2010*). Fatty acid profiles for both types of WAT were composed by a decrease in SFA with an increase in MUFA and PUFA. Nevertheless, there is no consensus on the levels of specific lipid species which may be due to the variability between diets, strains of animals or animal models and studies in humans (*de Heredia et al. 2008*). **Brown adipose tissue**, likewise WAT, is reduced with advancing age and studies in rodents showed a preadipocyte dysfunction which contributes to thermal dysregulation and energy imbalance (*Gabaldón et al. 1998*; *McDonald and Horwitz 1999*; *Tchkonia et al. 2010*) but little is known about lipid metabolism changes with advancing aged in this type of adipose tissue.

For other tissues, that have not been analyzed in this thesis project, age-related changes without pathologies associated have been described however information about the role of lipid metabolism in these changes is scarce. Thus, **skin** aging have been linked to an increase in lipid peroxidation along with a decrease in lipid content and changes in fatty acids and sterol ester composition (*Nazzaro-Porro M et al. 1979*; *Waller and Maibach 2006*; *Krutmann et al. 2017*). The **gastrointestinal tract** is affected by age and a decrease in the absorption of nutrients have been reported, including the lipid uptake (*Holt and Balint 1993*; *Salles 2007*). However, studies about lipidomic changes have not been performed. Age related changes in the **pancreas** involve a reduction in the pancreatic volume and alteration in enzymatic and exocrine functions (*Chantarojanasiri et al. 2015*). This changes are accompanied by alterations in lipid composition of the GP of the mitochondrial membrane, a decrease in ubiquinone levels and in other ST species (*Honjo et al. 1968*; *Kalén et al. 1989*). **Spleen** suffers as well the effects of aging and one of the alterations reported in the bibliography is a loss of the microarchitecture integrity of T-cell and B-cell (*Aw et al. 2016*). Turner and Mabbott (2017) suggested this alteration could be related with low blood levels of Sph1P; due to the capacity of Sph1P in B-cell mobilization. Concerning the respiratory system, there are many age-associated changes including a decrease in the volume of the thoracic cavity, reduced lung volumes, and alterations in the muscles that aid

respiration (*Lowery et al. 2013*). Therefore, aging affects the mechanical properties of the lungs and one possible reason is the increase in lipid peroxidation products, seeing in rodents, and because of the changes in the GL composition of the alveolar tissue in humans (*Bellmunt et al. 1995*; *Eggers et al. 2017*). Finally, several studies have been done about age-related changes in lipid metabolism of the **nervous system**, especially in the brain. However, for a better understanding, each one of its regions should be studied as an entity due to the lipid content differs between them. If this condition is a requirement, the number of studies decreases. Studies in human have revealed a decrease in phospholipids in different brain regions such as gray matter, white matter, nucleus caudate, hippocampus, pons, cerebellum, medulla oblongata in the elderly (*Söderberg et al. 1990*). In the hippocampus it has been reported a decrease with advancing age of minor fractions of phospholipids containing adrenic and AA (*Hancock et al. 2015*). Finally, age-related changes in frontal cortex include low levels in PUFA series n-6 content with age, particularly affecting adrenic and arachidonic acid, and the maintenance or minor changes in SFA, MUFA and docosahexaenoic acid (*Cabré et al. 2017b*).

Therefore, the complex relationship between aging and lipid metabolism still raises many questions and additional lipidomics analysis in order to investigate the signaling pathways and tissue localization of lipid species in females and males will reveal many new roles for lipids in the regulation of longevity and deepen our understanding of the lipidomics of aging field.

1.3 Lipid metabolism in anti-aging nutritional interventions

Aging is multifactorial process and depends on genetics and environmental factors. Successful aging relies upon a nutritionally complete diet and an adequate exercise to counteract some of the physiologic changes related to age. The purpose of nutritional interventions is to shift the metabolic profile of an organism into a healthier direction (*Nelson and Franzi 1989*). In this sense, nutritional intervention models have shown that it is possible to modulate the aging process and the onset and ratio of age-related diseases. In fact, dietary restrictions have even probed to reduce oxidative stress, improve the antioxidant defense system, and extend both median and maximum life spans in several animal models (*Pamplona 2008*).

1.3.1. Dietary restrictions and aging

Dietary restriction seems to be able to preserve the mitochondrial function in the aging process through a decrease in ROS production and molecular oxidative damage (*Sanz et al. 2005*, *2006d*; *Pamplona and Barja 2007*; *Caro et al. 2008b*). Studies performed about the effects of dietary restriction in rodents, non-human primates and human beings showed a delay in the aging process. Low caloric diets, protein and methionine restriction diets and intermittent fasting delay the physiologic processes of aging and extend the average and maximum life expectancy in rodents up to a 40%, as well as in non-humans primates (*Pamplona and Barja 2006*; *Colman et al. 2009*; *Redman and Ravussin 2011*).

1.3.1.1. Caloric restriction

Since the work of McCay et al. in 1935, much interest has been shown in caloric restriction's ability to improve health and to extend lifespan. Caloric restriction (CR) is the reduction of caloric intake, typically by 20 - 40% of *ad libitum* consumption, while maintaining adequate nutrient intake (*Cantó and Auwerx 2009*). This non genetic experimental intervention has been the most investigated because its ability of decreasing the aging rate and extend the maximum lifespan in different species such as yeast, rotifers, arachnids, flies, nematodes, fish, rodents and primates (*Piper et al. 2005*; *Mair and Dillin 2008*; *Colman et al. 2009*). CR has additional beneficial effects, reducing age-related diseases such as cancer, obesity, diabetes, sarcopenia, autoimmune diseases, cardiovascular and neurodegenerative diseases in both rodents and nonhuman primates (*Weindruch et al. 1988*; *Mattson 2002*; *Weindruch 2003*; *Jang et al. 2012*). With respect to physiological effects, CR courses with a significant reduction of body fat and mass, which supports a healthy cardiovascular system and reduces incidents of myocardial infarction. In

addition to cardio protection, a greater tolerance to stress is induced in the liver and in the brain, the elevation of neurotrophic factors supports the maintenance of complex neuronal circuits required for memory retention and cognition *(Martin et al. 2006)*.

In Macaco rhesus monkeys, it has been observed that a 30% CR considerably reduces the mortality related to age (from 13 to 37%), neoplasms, cardiovascular diseases, diabetes and age-related cerebral atrophy (*Colman et al. 2009*; *Mattison et al. 2012*, *2017*). CR in the Macaco rhesus monkeys showed a correlation between preservation of the volume and the microstructure of the brain with a lower iron accumulation, over and above less circulating pro inflammatory cytokines and an improvement in sensitivity to insulin *(Kastman et al. 2010; Willette et al. 2012 and 2013)*. Taken together these data confirm that the beneficial effect of CR observed in other species for a healthy aging are as well conserved in monkeys and suggest that CR mechanisms are likely translatable to human health. In fact, CR in humans seems to have beneficial effects similar to those observed in these animal models. Data from a series of studies conducted in members of the Calorie Restriction Society showed similarities respect to the metabolic and signaling of anti-aging effects of CR in rodents, providing them protection against the loss of learning ability and memory, obesity, insulin resistance, hypertension, Inflammation and atherosclerosis (*Fontana et al. 2004*, *2006*; *Meyer et al. 2006*). Other short-term studies in humans showed a decrease in fasting insulin levels, body temperature and DNA damage as well as a decrease in risk factors for arteriosclerosis, diabetes, cardiovascular disease, cancer and neurodegenerative diseases (*Heilbronn et al. 2006*; *Larson-Meyer et al. 2006*; *Redman et al. 2007*).

Although CR and its effects have been are under study for many years, the mechanisms responsible for an increase in longevity remain unknown. As evidence shows, feeding limitation extends life expectancy along the evolutionary scale, from yeasts to primates. Longevity seems to be determined by a specific metabolic regulation through a complex set of responses -from autonomous and non-autonomous cells- still far from being clarified. Among the proposed hypotheses, the most relevant were the decrease in the mitochondrial production of ROS *(Barja 1993; Gredilla and Barja 2005; Pamplona and Barja 2006)* and changes in signaling pathways: Insulin / IGF-1, mTOR and sirtuins (*Mair and Dillin 2008*; *Selman et al. 2008*; *Harrison et al. 2009*).

For all that, several researchers have deepened in how CR affects lipid metabolism and studies in rodents have reported that CR can decrease the susceptibility to peroxidative damage by modifying the fatty acid composition in lymphoid cells, muscle and in liver mitochondria and

microsomal membranes of rats (*Laganiere and Yu 1987*; *Laganiere and Fernandes 1991*; *Cefalu et al. 2000*). These changes have been reported as well in the fatty acid composition of GP from liver, kidneys, heart and skeletal muscle after 1 month of CR (*Faulks et al. 2006*). Additional studies in old rats support the effects of CR not only fatty acid composition but also in GP species in brain, liver and the decrease in the peroxidability index of kidney, liver and heart mitochondria membranes and proteins (*Tacconi et al. 1991*; *Jeon et al. 2001*; *Pamplona et al. 2002b*, *c*; *Ward et al. 2005*). Moreover, it has been found that CR diets as low as 8.5 and 25% result in a decreased PI of membrane lipids and lipoxidative damage to proteins (*Gómez et al. 2007*). The chain length and degree of saturation of fatty acids from circulating TAG, CE, GP and nonesterified free fatty acid species are affected by moderate CR or by the combination effect of both diet and age, especially for the CE species. Along with these results, age and CR both modify the ratio of AA to LA (20:4n6/18:2n-6), which suggest differences in the inflammatory state caused by moderate CR (*Miller et al. 2017*). Mild CR in young mice Male C57BL/6 N but no in young male NZO/HIBomDife mice decreased hepatic levels of TAG and cholesterol. Skeletal muscle and liver from this last group of mice show a no significant tendency in DAG species being lower in CR animals while ceramides levels of skeletal muscle and liver do not suffer any change with CR (*Baumeier et al. 2015*; *Park et al. 2017a*). The remaining questions about the effects of CR on lipid metabolism led to the performance of metabolomic studies. A NMR-based metabolomic analysis of plasma samples from male C57BL/6 mice showed that short-term CR produce lower levels of circulation lipid species, which they attribute to a decrease in lipid biosynthesis, whilst a mass spectrometry based analysis revealed a metabolomic and lipidomic signature in liver due to a 30% CR (*Selman et al. 2006*; *Jové et al. 2014*). Furthermore, CR increases PE and MUFA hepatic species whilst TAG, PUFA and lipoxidation products decrease, suggesting that CR produces a metabolic reprogramming that involves an up-regulation of β-oxidation and lower levels products of oxidative damage in the liver of adult mice under CR (*Jové et al. 2014*). Finally, a mass spectrometry based metabolomic analysis of serum samples from old mice under chronic CR showed not only that CR alters the metabolomic pattern in old mice compared to age-matched control group but also that CR effect on the metabolome it is as well different from young control mice. Thus, CR does not result in complete protection from the aging-associated metabolic state although CR restore the serum levels of several metabolites towards a young phenotype, being among them LysoPC, SM and cholesterol derivatives (*De Guzman et al. 2013*). CR in nonhuman primates has been reported to be able to modify the lipid metabolism into a healthier lipid profile. Two different studies report changes in lipoproteins levels, one of them show that CR animals have low-density lipoproteins (LDL) with lower

molecular weight and without TAG or GP species associated while the other study reported an increase in HDL2b along with a decreased of plasma TAG (*Verdery et al. 1997*; *Edwards et al. 1998*). Rezzi and collaborators published a metabolomic analysis of plasma samples of rhesus monkeys under CR and they reported a metabolic shift due to long-term CR that comprise an increase in PC species and HDL along with a decrease in TAG levels (*Rezzi et al. 2009*). A more recent lipidomic study performed in liver of adult male rhesus monkeys under 30% CR for 2 years reveal GP, Cer and TAG lipid species significantly different between animals under CR and the control group. CR increase the hepatic GP levels and unsaturated TAG, whereas the TAG with SFA species levels are lower with CR (*Rhoads et al. 2018*).

Finally, a short-term CR study in humans revealed a decrease in ectopic fat including intrahepatic and intramyocellular lipids (*Larson-Meyer et al. 2006*). Lipid metabolism also was reported to be influence by acute CR humans and a metabolomic signature is associated with CR. The reported changes were an increase in long-chain acylcarnitines, 3-hydroxy fatty acids, fatty acid dicarboxylates and SM while most of the GP detected and Sph are decrease in acute CR. Interestingly, the plasmalogen PEs, but not the plasmalogen PCs, decrease on CR proposing a specific role for each subclass (*Collet et al. 2017*). The biological significance of these changes in lipid composition is currently unclear but overall these studies suggest a key role for lipid metabolic integrity in health and aging.

1.3.1.2. Protein restriction and Methionine

After many years thinking CR effect, responsible for extend longevity, was given exclusively by the amount of ingested calories, several studies began to question it (*Iwasaki et al. 1988*; *Orentreich et al. 1993*; *Richie et al. 1994*; *Mair et al. 2005*; *López-Torres and Barja 2008*; *Sun et al. 2009*; *Piper et al. 2011*). The results of these investigations showed that part of the CR effects extending longevity was due to a decrease in certain components of the diet (*Pamplona and Barja 2006*). It was reported that a 40% isocaloric protein restriction (PR) induces the CR effects on mitochondrial ROS production and oxidative damage in rodents and these effects were not replicate when decreasing other macronutrients (*Miller and Payne 1968*; *Shimokawa et al. 1996*; *Sanz et al. 2004*, *2006b*, *c*; *Ayala et al. 2007*). This fact pointing perhaps to a particular role for protein or amino acid restriction as responsible for the beneficial PR effects, decreasing ROS production and extending longevity. In detail, it has been shown that the 80% restriction of methionine (RMet), without an energy restriction, increases longevity in both rats and mice. This effect happens even when the intervention begins at an advanced age (12 months of age), with

similar results to those obtained by a PR (extending longevity around 18%). (*Orentreich et al. 1993*; *Richie et al. 1994*; *Sun et al. 2009*).

Methionine is an essential amino acid in diet and has a key role in proteins structure as well as in cellular metabolism. Methionine is one of the four most common sulfur compounds along with cysteine, homocysteine and taurine *(Lehninger et al. 2005)*. Its structure it is characterized by one methyl group covalently bound to one sulfur atom, being the most hydrophobic amino acid, which explains why more than two thirds of methionine residues in globular proteins are present in the internal hydrophobic core. The rest of methionine residues are in the surface of the proteins and in membrane-spanning protein domains, methionine is often found interacting with the lipid bilayer (Brosnan and Brosnan, 2006). Besides its structural role, methionine plays a key role in protein synthesis, acting as the initiating amino acid in eukaryotic cells, and as a precursor molecule donor of methyl group through its metabolite S-adenosylmethionine (SAM), being essential for several cellular processes that involved biological methylation, including phospholipid and carnitines biosynthesis (*Drabkin and RajBhandary 1998*; *Stipanuk 2004*). Methionine metabolism along with the folate cycle are part of the one-carbon metabolism represented in Figure 11, whose role cellular physiology is to function as an integrator of nutrient status being an essential couple of pathways to lipid, protein and nucleotide metabolism as well as a key regulator of the redox status and epigenetics (*Locasale 2013a*). Due to their importance in the regulation of the redox system, isocaloric RMet of 80% and 40%, applied to young rats for 7 weeks, showed a decrease in mitochondrial ROS production, mainly in complex I, the escape of free radicals and complex I amount. An 80% RMet decreased the mitochondrial DNA damage and levels of specific markers of oxidative, glicoxidative and lipoxidative modifications in mitochondrial proteins of rat heart and liver. Same effects were seen with a 7-weeks 40% RMet in rat liver, kidney and brain *(Sanchez-Roman et al. 2011; Caro et al. 2008 and 2009; Naudí et al. 2007; A. Sanz et al. 2006)*. Besides lengthening the average and maximum longevity, 80% RMet is able to reduce the incidence of degenerative diseases associated with age and decrease glucose levels in blood, insulin, IGF-1, TAGs, cholesterol and leptin (*Perrone et al. 2013*). Likewise, RMet attenuates age-related changes in the immune system and decreases mitochondrial oxidative stress levels and the incidence of developing cataracts. Furthermore, there are evidences showing that RMet can be an important strategy to inhibit the growth of certain tumors (*Sanchez-Roman and Barja 2013*). There are other evidences suggesting that methionine or its metabolites may be involved in aging and longevity and supporting the beneficial effects of the RMet diet.

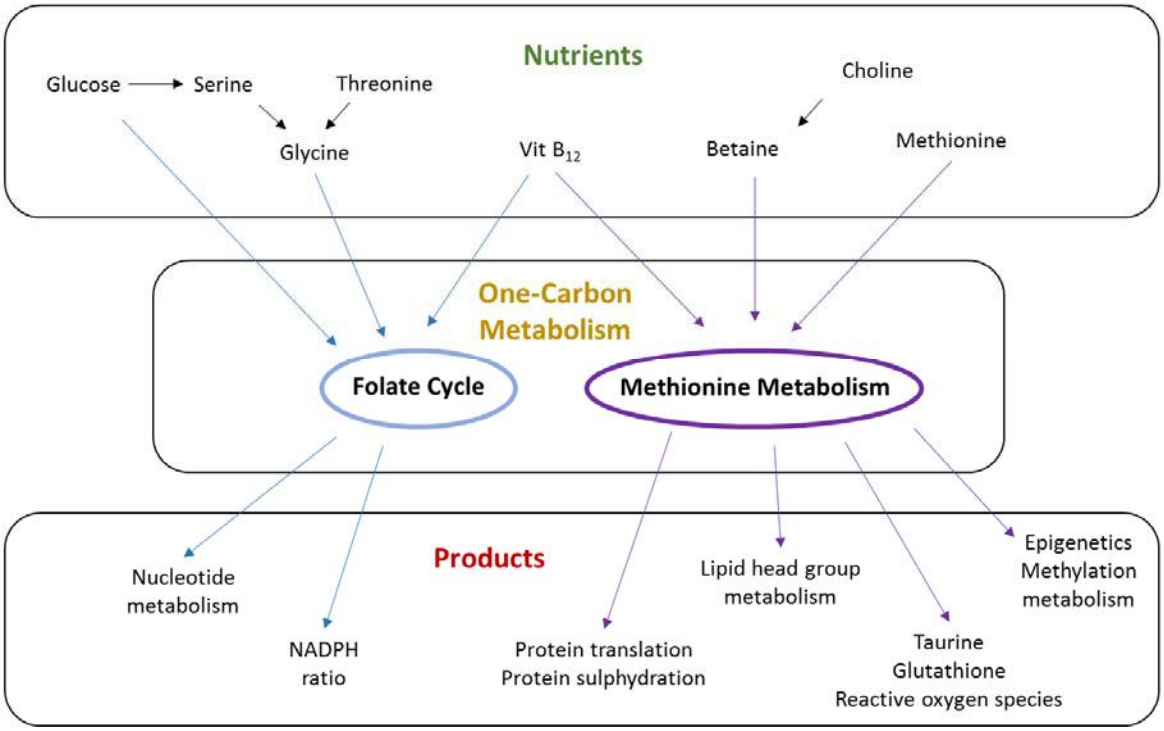

Figure 11. One-carbon metabolism scheme. One-carbon metabolism can be divided in two main independent pathways, folate cycle and methionine cycle. As inputs of the metabolism, nutrient sources involving amino acids are either imported or synthesized *de novo* and enter one carbon metabolism. As outputs, the products of all the nutrients processed through these metabolic cycles, including nucleotides, proteins, lipids, reducing power, and substrates for methylation reactions.

Excessive intake of methionine in the diet have been proved harmful to the vital organs and increased oxidative stress in tissues *(Gomez et al. 2009 and 2011)*. In fact, studies focus at heart and liver showed how methionine supplementation dysregulated lipid and one-carbon metabolism pathways, increased inflammatory cytokines and altered the expression of cardiovascular disease-related genes and caused molecular alterations triggering the development of nonalcoholic fatty liver disease *(Aissa et al. 2014 and 2017)*.

1.3.1.2.1. Methionine restriction and lipid metabolism

RMet diet of 80% not only improves biomarkers of metabolic health and increases longevity in rodents but also produces a highly integrated series of physiological and biochemical responses including remodeling lipid metabolism into a healthier lipid profile (*Anthony et al. 2013*). RMet increases energy expenditure and induces weight loss along with a reduction of fat deposition, especially of visceral and ectopic depots (*Orentreich et al. 1993*; *Zimmerman et al. 2003*; *Malloy et al. 2006*). RMet reduces plasma and hepatic TAGs and cholesterol levels generating as well as a reduction of leptin plasma levels while adiponectin plasma levels are increased (*Malloy et al.*

2006; *Perrone et al. 2010*, *2012*, *Hasek et al. 2010*, *2013*; *Lees et al. 2014*). Although, it is still unclear whether the reductions in hepatic and circulating lipids are due to RMet effects on energy balance, a direct effect in the liver or a combination of both mechanisms. However, it is known that RMet-induced changes in hepatic lipid metabolism are independent of weight loss and remodeling of WAT (*Stone et al. 2015*).

Several studies in adult and young rodents showed that an 80% RMet induces significant changes in the lipid-related gene expression in visceral and subcutaneous types of WAT. RMet increases the expression of genes related to lipid synthesis, to the transport of fatty acid from the cytosol to the mitochondrial matrix and fatty acid oxidation such as sterol receptor element binding protein 1 (SREBP1C), fatty acid synthase (FAS), acetyl-CoA carboxylase-2 (ACC-2), stearoyl-CoA desaturase-1 (SCD-1) in both types of WAT depots (*Perrone et al. 2010*; *Hasek et al. 2013*; *Ghosh et al. 2017*). RMet also produced changes in lipogenic gene expression in both liver and skeletal muscle. In the hepatic tissue of young and adult rats SREBP1, ACC2 and SCD-1 are significantly downregulated by RMet while increases peroxisome proliferator activated receptor alpha (PPARα) and adipose triglyceride lipase (ATGL) hepatic mRNA levels (*Perrone et al. 2010*, *2012*; *Hasek et al. 2013*). In skeletal muscle of 6-weeks rats, 3 month RMet induces PPARδ expression significantly as well as the levels of coactivators and nuclear receptors target genes associated with the transformation of glycolytic (type II) to lipid oxidizing (type I) myofibers *(Perrone et al. 2010 and 2012)*. Studies on 10 and 12-months old mice reproduce the gene expression pattern of RMet in WAT and liver of young mice, and they go beyond by checking gene expression with its corresponding protein expression (*Lees et al. 2014*, *2017*).

These changes in the expression of genes and key proteins involved in the lipid metabolism are translate into changes that RMet induce in the fatty acid composition of different tissues. Mitochondria from heart and liver of male Wistar rats present a decrease of highly unsaturated fatty acids 20:4n-6 and 22:6n-3, which are substituted for the much less unsaturated 18:2n-6, 18:1n-9, and 18:0, leading to a lower lipid peroxidation and lipoxidation-dependent damage to macromolecules (*Sanz et al. 2006a*). Studies in brain, spinal cord and liver support the fact that RMet results in changes in the fatty acid composition leading to a decrease of both double bond index and peroxidizability index conferring higher resistance to oxidative damage (*Jové et al. 2013a*). Nevertheless, the changes in the fatty acid composition in WAT by RMet show an increase in both PUFA and MUFA species including 22:5n-6, 22:6n-3, 16:1n-7 and 18:1n-9, which suggest a tissue-specific RMet effect on lipid metabolism (*Perrone et al. 2012*).

The remaining questions about the effects of RMet on lipid metabolism led to the performance of metabolomic studies. One of these metabolomic studies corroborates previous results reporting a decrease in cholesterol, medium-chain and long-chain fatty acids content in both serum and liver of young rats after 3 month RMet. Hepatic changes by RMet include significantly lower levels of glycerol, glycerol-3-phosphate and PC species while in WAT RMet increases the levels of the hydroxylated linoleates 13-HODE and 9-HODE. RMet affects as well bile acid metabolism being the levels of glycocholate and glycodeoxycholate increase in serum and liver. However, consistent with the low levels of available taurine, these tissues had significantly lower levels of taurine-conjugated bile acids (*Perrone et al. 2012*). Primary bile acid biosynthesis pathway upregulation by RMet takes place as well in young mice along with changes in long-chain fatty acids, PUFAs in both WAT and liver whereas the metabolomic changes in skeletal muscle due to RMet affects to a reduce number of metabolites including a decrease in hypotaurine as it was reported in a recent metabolomic study (*Ghosh et al. 2017*). Further lipidomic studies have revealed that RMet induces marked changes in the lipidomes of brain, spinal cord and liver from mice defining a nervous system-specific lipidomic profile of RMet due to at least 50% of the lipids changed are common in the brain and spinal cord but not in the liver. Among the differential lipid species are GP, SP and ubiquinone reflecting changes in the membranes, signaling and redox homeostasis (Jové et al. 2013).

These changes in lipid metabolism by RMet in rats and mice were also reported in humans with metabolic syndrome. A short term (16 weeks) methionine restriction was applied to those subjects and as a result RMet increased fat oxidation and reduced the hepatic lipid content (*Plaisance et al. 2011*).

To sum up, RMet affects the lipid metabolism and there is still a lack of lipidomic studies about the effects of RMet in specific tissues during the aging process. Moreover, most of the studies already published about the modifications of the lipid metabolism in this nutritional intervention has been performed in young rodents, which precludes the evaluation of the possible RMet effects towards a protection from the aging-associated lipidomic profile. Therefore, studies in old animals represent a better approach in order to assess the changes of the lipidome with advancing age and how RMet affects the lipid metabolism in this universal process.

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HIPOTHESIS AND OBJECTIVES

2. HYPOTHESIS AND OBJETIVES

2.1 Hypothesis

The aging process causes numerous deleterious changes at every level of the biological organization, reducing the maximum functional capacities and homeostasis, and increasing the likelihood of suffering degenerative processes, leading to death. All these changes have been probably originated in a small number of basic causes, such as oxidative stress, which continuously operate throughout life and determine the rate of aging, which is specific to the cell type, tissue and species. Moreover, the role of metabolites, especially lipids, in each specie or tissue, during the aging process still unclear.

Metabolomics and the branch lipidomics are two relatively new “omics” that allow to study the terminal downstream products of the genome, serving as direct signatures of biochemical activity and being, therefore, easier to correlate with the phenotype than genes or proteins. Metabolomics and lipidomics studies in aging are limited in the literature and most of them are only focus on the plasma or serum compounds, being an uncover need the study of metabolites and lipids in the rest of tissues affected by the aging process.

On the other hand, it is well known that nutritional interventions such as dietary restriction (caloric, protein or methionine restriction) are able to extent longevity and retard the effects of the aging process. In addition, dietary restriction influences in the lipid metabolism, reduces adiposity and produces a shift to a healthier lipid profile. However, the study of the role of the lipid metabolism in dietary restrictions has been ascribed mainly to plasma or serum, adipose tissue and liver. Moreover, most of the published studies have been performed in young or adult animals rather than old animals, and the possibility of reverting age-related changes by dietary restriction in the elderly, as well as the assessment of lipidome remodeling, must still be studied in order to obtain definitive conclusions.

2.2 Objectives

In order to elucidate the hypothesis the study was divided in three objectives:

2.2.1. Objective 1: Study of the metabolites and lipids concentration and distribution in adults animal model

The objective is the study of the metabolome and lipidome in the skeletal muscle, white adipose tissue, liver, heart and kidney of healthy adult male Wistar rats. This study will allow to describe a metabolomic and lipidomic profile for each tissue and evaluate differences among them. In order to achieve this goal, untargeted metabolomics as well as untargeted and targeted lipidomics were performed for each tissue.

2.2.2. Objective 2: Effect of aging in the metabolome and lipidome profiles of an animal model

The objective is to evaluate the effect of the aging process in the metabolome and lipidome of healthy male Wistar rats. In order to achieve this goal, differences in the metabolomic and lipidomic profiles of each tissue analyzed (skeletal muscle, white adipose tissue, liver, heart and kidney) of adult and aged male rats will be discussed.

2.2.3. Objective 3: Effect of the methionine restriction diet in the metabolome and lipidome profiles of an aged animal model

The objective is to evaluate the effect of the methionine restriction in the metabolome and lipidome of the aged tissues analyzed. In order to achieve this goal, differences in the metabolomic and lipidomic profiles of each tissue analyzed (skeletal muscle, white adipose tissue, liver, heart and kidney) of adult and aged control animals along with aged male rats with 7 weeks methionine restriction will be discussed.

MATERIALS AND METHODS

3. MATERIALS AND METHODS

3.1 Animals and experimental design

For this study, thirty males Wistar rats from Iffa-Creddo (Lyon, France) were used. All the animals were caged individually and maintained in a 12:12 (light:dark) cycle at 22±2 ºC and 50 ± 10% of relative humidity.

Ten of these animals had 8 months old with a body weight of 468.9±37.8 grams, this group of animals were the adults control group (from now on, Adults). One the other hand we had twenty rats of 26 months old and a body weight of 595.4±69.9 grams. Ten rats of this last group were the old control groups (from now on, Old) and the rest of them were the Restricted in Methionine group (from now onwards, RMet Old).

All procedures with animals have followed the protocols approved by the Institutional Committee of Care and Use of Animals (Comitè Institucional de Cura i Ús d'Animals).

3.2 Diets

In order to study the effect of the methionine restriction in the process of aging, prepared diets in the Metabolic Physiopathology Laboratory have been used. These semi-purified diets were prepared following the criteria of diet AIN 93 from the United States Department of Agriculture (*Reeves et al. 1993*) but modifying the amino acids composition. In Table 3 the composition of both types of diets is shown.

The control animals (Adults and Old) were fed a diet based on AIN-93G composition. This diet has been modified only reducing its content in an 80% of L-methionine for the experimental group restricted in this amino acid. The calorie composition is the same in both diets since the decrease in methionine was compensated by a little increase in the rest of the components of the diet. This increase was in direct proportion to their abundance in the diet. At the end, the ingested amount per day of all dietary components was virtually identical in controls and experimental animals except for methionine. Intake was monitored daily and every day all the control animals received the same amount of food that the restricted animals in methionine had ingested on average the previous week following a pair feeding criteria. The reason of this pair feeding was because previous evidence shown that rodents subjected to methionine restriction tend to eat a little less than control ones (*Caro et al. 2009*; *Sanchez-Roman et al. 2012*).

This procedure ensures that all experimental groups consumed the same amount of calories, and helps to minimize the potential effect of a possible caloric restriction (*Martin et al. 2010*).

Table 3. Composition of the diets ingested by the three experimental groups in the dietary intervention with an 80% of methionine restriction (Data from *Cabré 2015*).

Components (g/100g)	Control Diet	80% RMet Diet
L-Arginine	1.12	1.13
L-Lysine	1.44	1.45
L-Histidine	0.33	0.33
L-Leucine	1.11	1.12
L-Isoleucine	0.82	0.83
L-Valine	0.82	0.83
L-Threonine	0.82	0.83
L-Tryptophan	0.18	0.18
L-Methionine	0.86	0.17
L-Acid Glutamic	2.70	2.72
L-Phenylalanine	1.16	1.17
L-Glycine	2.33	2.35
Dextrin	5.00	5.04
Cornstarch	43.61	43.91
Saccharose	20.00	20.14
Cellulose	5.00	5.04
Choline bitartrate	0.20	0.20
AIN 93 Vitamin MIX	1.00	1.01
AIN 93 Mineral MIX	3.50	3.52
Corn oil	8.00	8.06

Nutritional intervention was carried out for seven weeks because previous works in nutritional interventions had shown that this short-term calorie restriction was enough to see physiological changes such as a reduction in free radical production (*Gredilla et al. 2001*). After 7 weeks, the animals were sacrificed by cervical dislocation. Blood was collected in heparinized tubs for subsequent plasma collection and samples were stored at -20^{o}C. After that liver, heart, kidney, two types of skeletal muscle (gluteus and soleus) and two types of WAT (visceral and subcutaneous) were extracted, frozen immediately in liquid nitrogen and stored at -80^{o}C. Renal cortex was the part of the kidney processed and in this work it is named indistinctly as kidney or renal cortex.

3.3 Sample Processing

3.3.1. Sample homogenization

The homogenization solution used contains 180 mM of potassium chloride (KCl), 5 mM of 3-(N.morpholino)propanesulfonic acid (MOPS), 2 mM of ethylendiamine-tetraacetic acid (EDTA), 1 mM of dethyltriamine-penta acetic acid (DTPAC) and 1 µM of 2,6-Di-tert-butyl-4-methylphenol (BHT) adjusted to pH 7,4. This solution prevents the effect of metal chelators and lipid oxidation due to sample processing. For Immunodetection by Western Blot, a commercial mix of proteases inhibitors (#80-6501-23 Amersham Bioscience, Madrid, Spain) and phosphates inhibitors (1 mM of sodium orthovanadate and 1 mM of sodium of fluoride) were added. For homogenization 50-150 mg of tissue were weighted and homogenized with an Ultra-Turrax (3420000 IKA, Germany), followed by centrifugation for 1 min at 750 x g and 4ºC in order to remove tissue debris. The supernatants obtained were used for the different analysis and experiments.

3.3.2. Protein quantification

In order to determine the amount of protein, two types of methods were used depending on the final analysis or experiment. For immunodetection by Western Blot, protein was quantified by Bradford's method (Bradford, 1976). Protein concentration of each sample has been analyzed by interpolation of the data obtained from the corresponding concentrations in the standard curve, performed with known concentrations (rang 0-250 µg/µL) of bovine serum albumin (BSA). The Bradford reagent (Protein Assay #500-0006 Bio-Rad, Munich, Germany) was added to every sample and BSA standards and then agitated. After 10 minutes of incubation at room temperature, the absorbance was determined by spectrophotrometry with a microplate reader (Multiskan ascent 354, Thermo Labsystem) at a wavelength of 595 nm in a 96 well plate. For the targeted lipidomic analysis, protein was quantified by Bicinchoninic acid protein assay (Smith 1985). Protein concentration of each sample has been analyzed by interpolation of the data obtained from the corresponding concentrations in the standard curve, performed with known concentrations (range 0-2000 µg/mL) of albumin. The BCA reagents previously mixed (Pierce BCA Protein Assay Kit #23225 Thermo Scientific, Massachusetts, USA) were added to every sample and albumin standards and then agitated. After 30 minutes of incubation at 37ºC, the plate was cooled to room temperature and then the absorbance was determined by spectrophotometry with a microplate reader (BioRAD Benchmark Plate Reader) at a wavelength of 562 nm in a 96 well plate.

3.4 Metabolomic analysis

3.4.1. Sample processing

For metabolites extraction we have followed the method published by Jové et al. in 2014. Samples were stored at -80ºC and methanol was the organic solvent used for the extraction. Briefly, to 50 mg of tissue 20 volumes of cold methanol were added with 1 µg/mL of phenylalanine isotopic labeled with ^{13}C, as an internal standard and 1 µM of BHT as antioxidant (Figure 12). Then, samples were homogenized at 4ºC with and Ultra-Turrax (3420000 IKA, Germany) and incubated at -20ºC for one hour. Later, samples were centrifuged at 12,000 x g at 4ºC for 3 minutes achieving the precipitation of all the protein. Finally, the supernatant was filtered through UltraFree Eppendorfs with a pores size of 0,22 µm (UFC3LTK00, Millipore, Bredford, MA, EUA) and 200 µL were pipette in Agilent vials with glass inserts for further analysis.

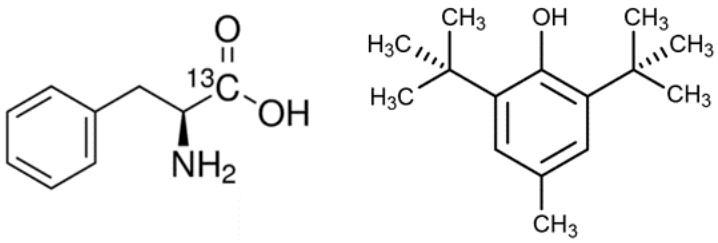

Figure 12. Chemical structure of phenylalanine isotopic labeled with ^{13}C on the left and BHT on the right.

3.4.2. Untargeted metabolomic

3.4.2.1. Equipment

The analysis was performed through liquid chromatography coupled to a hybrid mass spectrometer with electrospray ionization and a quadrupole time of flight type (LC-ESI-QTOF-MS/MS). The equipment for the liquid chromatography phase was an ultra-high performance liquid chromatograph model 1290 coupled to ESI-Q-TOF MS/MS model 6520 both from Agilent Technologies (Barcelona, Spain).

3.4.2.2. Analysis conditions

For the metabolomic analysis, 2 µL of the methanol extract was injected in a C18 reversed-phase column (Zorbax SB-Aq 1,8 µm x 2,1 x 50 mm; Agilent Technologies, Barcelona, Spain) heated at

60ºC and coupled to a precolumn (Zorbax SB-C8 Rapid Resolution Cartridge 3,5 µm x 2,1 x 30 mm; Agilent Technologies, Barcelona, Spain). Flux was constant at 0,6 mL/min and the composition of the mobile phases were water with 0,2% acetic acid for the mobile phase A and methanol with 0,2% acetic acid as mobile phase B. The gradient used in the UHPLC was at the beginning 2% of phase B, then gradient of phase B reached 98% at minute 13 and it remained constant for 6 minutes. At the end the system was balanced for 5 minutes at 2% of mobile phase B (*Jové et al. 2014*). Data was collected in positive electrospray ionization mode TOF operated in full-scan mode at 100 to 3000 m/z in an extended dynamic range (2 GHz), using N_2 as nebulizer gas with flux at 5 L/min and 350°C of temperature. The capillary voltage was 3500 V with a scan rate of 1 scan/s. At the same time, the electrospray has another independent nebulizer with flux at 10 L/min where the reference compounds are continuously injected in order to calibrate mass. In positive mode these compounds have an exact mass of 121,050873 and 922,009798. For the negative mode, the exact mass of these compounds are 119,036320 and 966,000725.

3.4.2.3. Data analysis

The MassHunter Data Analysis Software (Agilent Technologies, Barcelona, Spain) was used to collect the results and the MassHunter Qualitative Analysis Software (Agilent Technologies, Barcelona, Spain) to obtain the molecular features of the samples, representing different, co-migrating ionic species of a given molecular entity using the Molecular Feature Extractor (MFE) algorithm (Agilent Technologies, Barcelona, Spain)(*Jové et al. 2013b*). Briefly, the MFE algorithm uses the accuracy of the mass measurements to group related ions (basing on charge-state envelope, isotopic distribution and/or the presence of different adducts and dimers/trimers) assigning multiple species (ions) to a single compound referred to as a feature. Finally, the MassHunter Mass Profiler Professional Software (Agilent Technologies, Barcelona, Spain) was used to perform a non-targeted metabolomic analysis over the extracted features. Only those features with a minimum abundance of 5000 counts and 2 ions as a minimum were selected. After that, molecular features of the samples were aligned using a retention time window of 0,1% ± 0,25 minutes and 30,0 ppm ± 2,0 mDa. Finally, to avoid background, only common features (found in at least 50% of the samples of the same condition) were taken into account to correct for the individual bias. The feature defined by exact mass and retention time were searched against the METLIN database (accuracy < 30 ppm) (*Zhu et al. 2013*). The identities obtained were compared to retention time of the authentic standards added and confirmed by MS/MS by checking the MS/MS spectrums in the same METLIN database.

3.5 Lipidomic analysis

3.5.1. Untargeted lipidomic analysis

3.5.1.1. Preparation of Lipid Standards

Lipid standards consisting of isotopically labeled lipids (Table 4) were used for external standardization (i.e., lipid family assignment) and internal standardization (i.e., for adjustment of potential inter- and intra-assay variances). Stock solutions were prepared by dissolving lipid standards in methyl tert-butyl ether (MTBE) at a concentration of 1mg/mL, and working solutions were diluted to 2.5 µg/mL in methyl tert-butyl ether.

3.5.1.2. Lipid Extraction

Lipidomic analysis was based on a previously validated method published by Pizarro et al. 2013. Samples were stored at -80ºC and MTBE was the organic solvent used for the extraction. Briefly, to 50 mg of tissue we added 20 volumes of cold homogenization buffer (composition is described in section 3.3.1) and samples were homogenized at 4ºC with and Ultra-Turrax (3420000 IKA, Germany). In order to precipitate plasma protein fraction of this homogenized, 10 µL were mixed with 5 µL of miliQ water and 20 µL of ice-cold methanol. After the addition, samples were vigorously shaken by vortex for 2 minutes and then, 250 µL of MTBE (containing internal lipid standards) were added. Samples were immersed in a water bath (ATU Ultrasonidos, Valencia, Spain) with an ultrasound frequency and power of 40kHz and 100W, respectively, at 10°C for 30 minutes. Then, 25 µL of miliQ water were added to the mixture, and organic phase was separated by centrifugation (1,400g) at 10°C for 10min. Lipid extracts, contained in the upper phase, were collected and subjected to mass spectrometry. A pool of all lipid extracts was prepared and used as quality controls.

3.5.1.3. Equipment

The analysis was performed through liquid chromatography coupled to a hybrid mass spectrometer with electrospray ionization and a quadrupole time of flight type (LC-ESI-QTOF-MS/MS). The equipment for the liquid chromatography phase was an ultra-high performance liquid chromatograph model 1290 coupled to ESI-Q-TOF MS/MS model 6520 both from Agilent Technologies (Barcelona, Spain).

3.5.1.4. Analysis conditions

Lipid extracts were analyzed following the method published by (*Castro-Perez et al. 2010*). Sample compartment of the UHPLC was refrigerated at 4°C and for each sample, 10µl of lipid extract was applied onto 1,8 µm particle 100 × 2,1mm id Waters Acquity HSS T3 column (Waters, Mildord, MA) heated to 55°C. The flow rate was 400 µL/min with solvent A composed of 10mM ammonium acetate in acetonitrile-water (40:60, v/v) and solvent B composed of 10mM ammonium acetate in acetonitrile-isopropanol (10:90, v/v). The gradient started at 40% of mobile phase B and reached 100% B in 10 minutes and held for 2 minutes. Finally, the system was switched back to 60% of mobile phase B and was equilibrated for 3minutes. Duplicate runs of the samples were performed to collect positive and negative electrospray ionized lipid species in a TOF mode, operated in full-scan mode at 100 to 3000 m/z in an extended dynamic range (2 GHz), using N2 as nebulizer gas (5L/min, 350°C). The capillary voltage was set at 3500V with a scan rate of 1 scan/s. Continuous infusion using a double spray with masses 121.050873, 922.009798 (positive ion mode) and 119.036320, 966.000725 (negative ion mode) was used for in-run calibration of the mass spectrometer.

Table 4. Class representative and extraction internal standards added to the samples in untargeted lipidomics.

Compound	Reference
1,3(d5)-dihexadecanoyl-glycerol	110537, Avanti Polar Lipids
1,3(d5)-dihexadecanoyl-2-octadecanoyl-glycerol	110543, Avanti Polar Lipids
1-hexadecanoyl(d31)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphate	110920, Avanti Polar Lipids
1-hexadecanoyl(d31)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphocholine	110918, Avanti Polar Lipids
1-hexadecanoyl(d31)-2-(9Z-octadecenoyl)-sn-glycero-3-phosphoethanolamine	110921, Avanti Polar Lipids
1-hexadecanoyl-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-(1'-rac-glycerol-1',1',2',3',3'-d5)	110899, Avanti Polar Lipids
1-hexadecanoyl(d31)-2-(9Z-octadecenoyl)-sn-glycero-3-phospho-myo-inositol	110923, Avanti Polar Lipids
1-hexadecanoyl(d31)-2-(9Z-octadecenoyl)-sn-glycero-3-[phospho-L-serine]	110922, Avanti Polar Lipids
26:0-d4 Lyso PC	860389, Avanti Polar Lipids
18:1 Chol (D7) ester	111015, Avanti Polar Lipids
cholest-5-en-3ß-ol (d7)	LM-4100, Avanti Polar Lipids
D-erythro-sphingosine-d7	860657, Avanti Polar Lipids
D-erythro-sphingosine-d7-1-phosphate	860659, Avanti Polar Lipids
N-palmitoyl-d31-D-erythro-sphingosine	868516, Avanti Polar Lipids
N-palmitoyl-d31-D-erythro-sphingosylphosphorylcholine	868584, Avanti Polar Lipids
Octadecanoic acid-2,2-d2	19905-58-9, Sigma Aldrich

3.5.1.5. Data analysis

The MassHunter Data Analysis Software (Agilent Technologies, Barcelona, Spain) was used to collect the results and the MassHunter Qualitative Analysis Software (Agilent Technologies, Barcelona, Spain) to obtain the molecular features of the samples, representing different, co-migrating ionic species of a given molecular entity using the Molecular Feature Extractor (MFE) algorithm (Agilent Technologies, Barcelona, Spain)(*Jové et al. 2013b*). Briefly, the MFE algorithm uses the accuracy of the mass measurements to group related ions (basing on charge-state envelope, isotopic distribution and/or the presence of different adducts and dimers/trimers) assigning multiple species (ions) to a single compound referred to as a feature. Finally, the MassHunter Mass Profiler Professional Software (Agilent Technologies, Barcelona, Spain) was used to perform a non-targeted lipidomic analysis over the extracted features. Only those features with a minimum abundance of 5000 counts and 2 ions as a minimum were selected. After that, the molecular characteristics in the samples were aligned using a retention time window of 0,1% ± 0,25 minutes and 20,0 ppm ± 2,0 mDa. Finally, to avoid background, only common features (found in at least 50% of the samples of the same condition) were taken into account to correct for individual bias. The features defined by exact mass and retention time were searched against the LIPID MAPS database (accuracy < 20 ppm)(*Fahy et al. 2007*). The identities obtained were compared to retention time of the authentic standards added. Finally, identities were confirmed by MS/MS by checking the MS/MS spectrums using LipidBlast software(*Kind et al. 2013*) and LipidMatch, a R-based tool for lipid identification (*Koelmel et al. 2016*).

3.5.2. Targeted lipidomic analysis

3.5.2.1. Preparation of lipid standards

Lipid standards were used for external standardization (i.e., lipid family assignment) and internal standardization (i.e., for adjustment of potential inter- and intra-assay variances). All of the standard solutions used in the targeted lipidomic analysis are listed in Table 5. Stock solutions were prepared by dissolving lipid standards in chloroform:methanol (1:1,v/v), and working solutions were at 100 pmol in chloroform:methanol as well except for cholesterol that was 10000 pmol, CE 1000 pmol and SM and DAG that were at 200 pmol. Finally, for the dhCer and HexCer the working solutions were at 50 pmol.

Table 5. Class representative and extraction internal standards added to the samples in targeted lipidomics.

Compound	Reference
N-heptadecanoyl-D-erythro-sphingosine (Cer(d18:1/17:0))	860517, Avanti Polar Lipids
Cholesteryl-2,2,3,4,4,6-d6 Octadecanoate (CE(18:0))	D-5823, CDN Isotopes
N-octanoyl-D-erythro-sphinganine (dhCer(d18:0/8:0))	860626, Avanti Polar Lipids
1-tridecanoyl-2-hydroxy-sn-glycero-3-phosphocholine (LPC(13:0))	855476, Avanti Polar Lipids
1,2-ditridecanoyl-sn-glycero-3-phosphocholine (PC(13:0/13:0))	850340, Avanti Polar Lipids
1,2-diheptadecanoyl-sn-glycero-3-phosphoethanolamine (PE(17:0/17:0))	830756, Avanti Polar Lipids
1-myristoyl-2-hydroxy-sn-glycero-3-phosphoethanolamine (LPE(14:0))	856735, Avanti Polar Lipids
1,2-diheptadecanoyl-sn-glycero-3-phospho-(1'-rac-glycerol) (PG(17:0/17:0))	830456, Avanti Polar Lipids
1,2-diheptadecanoyl-sn-glycero-3-phospho-L-serine (PS(17:0/17:0))	840028, Avanti Polar Lipids
1-tridecanoyl-2-hydroxy-sn-glycero-3-phospho-(1'-myo-inositol) (LPI(13:0))	850101, Avanti Polar Lipids
N-(dodecanoyl)-sphing-4-enine-1-phosphocholine (SM(d18:1/12:0))	LM-2312, Avanti Polar Lipids
D-erythro-sphingosine (C17 base) (Sph(d17:1))	860640, Avanti Polar Lipids
Glyceryl triheptadecanoate (TAG(17:0/17:0/17:0))	T2151, Sigma Aldrich
1,2-dipentadecanoyl-sn-glycerol (DAG(15:0/15:0))	P7285, Sigma Aldrich
Cholest-5-en-3ß-ol(d7) (COH)	LM-4100, Avanti Polar Lipids
D-glucosyl-ß-1,1'-N-palmitoyl-D-erythro-sphingosine (GlcCer(d18:1/16:0)	860539, Avanti Polar Lipids
D-lactosyl-ß-1,1' N-palmitoyl-D-erythro-sphingosine (LacCer(d18:1/16:0)	860576, Avanti Polar Lipids
Trihexosylceramide 17:0 (LacGlcCer(d18:1/17:0)	860646, Avanti Polar Lipids

3.5.2.2. Lipid Extraction

Samples were stored at -80^{o}C and a single phase chloroform:methanol was used for the extraction lipid extraction (*Alshehry et al. 2015*) adapted for tissues. Briefly, to 50 mg of tissue we added 10 volumes of cold phosphate buffered saline solution (pH 7.47) and samples were homogenized at 4^{o}C with an Ultra-Turrax (3420000 IKA, Germany). Then, samples were sonicated for 30 minutes. For protein quantification, each sonicated tissue homogenate was diluted at 1:25 (240 µl mQ water + 10 µl homogenate) and the BCA protein assay was performed as previously described before in this chapter. After that, stocks of tissue homogenates were prepared containing 5.0 mg protein/ml homogenate except for the WAT where no protein quantification was performed. To 10 µL of the stock tissue homogenates, 200 µL of chloroform/methanol (2:1, v/v) were added together with 10 µL of internal standards in chloroform/methanol (1:1, v/v). The mixture was mixed for 10 min on a rotary mixer, sonicated in a water bath (18 °C–24 °C) for 30 min, left to stand on the bench for 20 min and then centrifuged at 16,000 × g for 10 min and 20 °C. The supernatant was transferred to a 96-well plate and dried under a stream of nitrogen gas at 40 °C. Samples were reconstituted with 50 µL

H2O-saturated 1-butanol and sonicated for 10 min. Then, 50 µL of 10 mM ammonium formate in methanol was added. The extract was centrifuged at 1,700 × g, for 5 min and 20 °C). Finally, the supernatant was transferred into a 0.2 mL glass insert with Teflon insert cap for analysis by LC ESI-MS/MS. Technical quality controls (ISTD mix solution) were injected every 10 samples as well as lipid extraction quality controls (plasma samples with ISTD mix solution) every 15 samples.

3.5.2.3. Equipment

The analysis was performed through liquid chromatography coupled to a mass spectrometer. The equipment for the liquid chromatography phase was an ultra-high performance liquid chromatograph model 1290 coupled to electrospray ionization on a triple quadrupole mass spectrometer (LC ESI-QQQ MS/MS) model 6490 both from Agilent Technologies (Melbourne, Australia).

3.5.2.4. Analysis conditions

Lipid extracts were analyzed following the method published by (*Tham et al. 2018*). Samples were thawed at room temperature for 1 hour and then sonicated for 15 minutes. From every sample, 1µl of lipid extract was applied onto ZORBAX eclipse plus C18 column, 2.1x100mm 1.8µm, (Agilent Technologies, Melbourne, Australia) heated to 60°C. The flow rate was 400 µL/min with solvent A composed of 10mM ammonium formate in acetonitrile-water-isopropanol (50:30:20,v/v) and solvent B composed of 10mM ammonium formate in acetonitrile-water-isopropanol (9:1:90, v/v). The gradient started at 10% of mobile phase B and reached 100% B in 11 minutes and held for 1 minutes. Finally, the system was switched back to 10% of mobile phase B and was equilibrated for 3minutes (see Table 6 for further details).

Table 6. Chromatographic gradient and flow used in the targeted lipidomic analysis.

Time (min)	Mobil phase A (%)	Mobil phase B (%)	Flow (ml/min)
0.00	90.00	10.00	0.40
2.70	55.00	45.00	0.40
2.80	47.00	53.00	0.40
9.00	35.00	65.00	0.40
9.10	11.00	89.00	0.40
11.00	8.00	92.00	0.40
11.10	0.00	100.00	0.40
11.90	0.00	100.00	0.40
12.00	90.00	10.00	0.40
15.00	90.00	10.00	0.40

Data was collected in the multiple reaction monitoring scan type and the capillary voltage was set at 3500V. Positive polarity of electrospray ionization was set using N_2 at 20 psi as nebulizer gas (17L/min, 150°C) and the sheath gas parameters were flow at 10L/min and temperature at 200°C.

For every target compound there was a lipid standard of reference. In Table 7, shows the list of standards and the main characteristics as the transition detected, retention time, time segment and collision energy. Transition is the m/z values measured for this compound. The format of the Transition string depends on ScanType. In the MRM scan, the transition string has the format "SelectedMZ -> MZ", where SelectedMZ is the precursor ion and MZ is the product ion. Retention time (RT) defines, in units of minutes, the chromatographic retention time at which the chromatographic peak for this target compound is associated. Time Segment (TS) is the index of the acquisition time segment that was used to acquire the signal for this compound. Collision Energy (CE) represents the amount of collision-induced dissociation (CID) occurring in the triple quadrupole collision cell. CID is a mechanism to fragment molecular ions in the gas phase. The molecular ions are accelerated by this electrical potential to high kinetic energy in the vacuum of a mass spectrometer and to collide in the higher pressure collision cell with neutral gas molecules (nitrogen). In the collision, some of the kinetic energy is converted into internal energy which results in bond breakage and the fragmentation of the molecular ion into smaller fragments.

For all the standard lipid species the cell accelerator voltage was 5 volts, except for the Sph(d17:1) that was 4 volts. The acceleration of the ions from the source into the rest of the mass spectrometer known as fragmentor was 380 volts, the window of the retention time was 10% and the accuracy mass 20%. The conditions for tandem mass spectrometry quantification of the 652 lipid species detected by the targeted lipidomic analysis are specified in Table S1 of the annex. Technical quality control coefficient variation (CV) was 7.6% across measured lipids suggesting a good technical reproducibility.

3.5.2.5. Data analysis

The MassHunter Data Analysis Software (Agilent Technologies, Melbourne, Australia) was used to collect the results and the software MassHunter Quantitative Analysis (Agilent Technologies, Melbourne, Australia) was used to quantify every lipid specie in the sample. Concentrations were obtained first in pmol/ml and then normalize to milligrams of protein.

Table 7. Conditions for tandem mass spectrometry quantification of major lipid species internal standards in targeted lipidomic analysis.

Internal Standard	Lipid Class	Nº of species	Transition	RT	TS	CE
CE(18:0) (d_6)	Cholesteryl ester (CE)	45	676.7 -> 375.3	11.99	1	10
Cer(d18:1/17:0)	Ceramide (Cer)	50	552.5 -> 264.3	8.43	1	29
COH-d7 (161)	Free cholesterol (COH)	1	376.4 -> 161.2	6.27	1	23
DAG(15:0/15:0/0:0)	Diacylglycerol (DAG)	20	558.5 -> 299.2	8.83	1	21
dhCer(d18:1/8:0)	Dihydroceramide (dhCer)	11	428.4 -> 284.3	4.65	1	30
LPC(13:0)	Lysophosphatidylcholine (LPC) Lysoalkylphosphatidylcholine (LPC-O) Lysoalkenylphophatidylcholine (LPC-P) Acylcarnitines (AC)	91	454.3 -> 184.1	1.59	1	21
LPE(14:0)	Lysophosphatidylethanolamine (PE) Lysoalkylphosphatidylethanolamine (LPE-O) Lysoalkenylphophatidylethanolamine (LPE-P)	18	426.3 -> 285.2	1.99	1	17
SM(d18:1/12:0)	Sphingomyelin (SM)	44	647.5 -> 184.1	4.50	2	25
TAG(17:0/17:0/17:0)	Triacylglycerol (TAG)	47	866.8 -> 579.5	11.63	3	21
LPI(13:0)	Lysophosphatidylinositol (LPI)	8	548.3 -> 271.3	1.23	1	17
Sulfatide(d18:1:/12:0)	Sulfoglycosphingolipids (Sulfatides)	6	724.8 -> 264.3	4.10	3	56
Hex1Cer(d18:1/16:0) (d_3)	Monohexocylceramide (MHC)	14	703.6 -> 264.3	6.36	1	33
Hex2Cer(d18:1/16:0) (d_3)	Dihexosylceramide (DHC)	10	865.6 -> 264.3	5.85	1	53
Hex3Cer(d18:1/17:0)	Trihexosylceramide (THC)	15	1038.7 -> 264.3	5.99	1	57
PC(13:0/13:0)	Phosphatidylcholine (PC) Alkylphosphatidylcholine (PC-O) Alkenylphosphatidylcholine (PC-P)	116	650.5 -> 184.1	4.56	1	21
PE(17:0/17:0)	Phosphatidylethanolamine (PE) Alkylphosphatidylethanolamine (PE-O) Alkenylphosphatidylethanolamine (PE-P) Phosphatidylinositol (PI)	133	720.6 -> 579.5	8.29	2	17
PG(17:0/17:0)	Phosphatidylglycerol (PG)	4	768.6 -> 579.5	6.89	2	21
PS(17:0/17:0)	Phosphatidylserine (PS)	11	764.5 -> 579.5	6.78	2	25
Sph(d17:1)	Sphingoid bases (Sph)	8	286.3 -> 268.3	2.06	3	8

RT: retention time (minutes) TS: time segment (arb. unit) CE: collision energy (volts)

3.6 Immunodetection by western blot

The Immunodetection by western blot technique was used to study the expression of proteins involved in lipogenesis and bile acid metabolism in hepatic tissue. These proteins were SREBP1c, FXR and SHP.

3.6.1. Sample processing

From the protein quantification of the homogenized samples (see section 3.3), concentrations have been equalized (35-80 µg/µL) and normalized with the solution containing 62.5mM of 2-Amino-2-(hydroxymethyl)-1,3-propanediol hydrochloride (Tris-HCl) pH 6.8, 2% (w/v) of sodium dodecyl sulfate (SDS), 10% (v/v) of glycerol, 20%(v/v) of β-mercaptoethanol and 0.02% (w/v) of bromophenol blue. For the protein denaturalization samples were heated at 95 ^{o}C for 3 minutes in a dry bath (Termobloc Selecta, Barcelona, Spain).

3.6.2. Electrophoresis

For protein separation of the samples according to their molecular weight, acrylamide gels with SDS detergent were used. The anionic detergent SDS solubilizes and denaturalizes the proteins in the sample. Over and above, SDS allows the proteins to separate according to their molecular weight once the gel with the samples are subjected to an electric field. Proteins will migrate from the anode to the cathode more or less fast depending on their size.

The acrylamide gels used for the separation were of different percentage of acrylamide/bisacrylamide depending on the molecular weight of the proteins to be separated, this percentage ranged from 10% to 15% with a thickness of 1.0 mm. Stacking gels to deposit the samples were 5% of acrylamide/bisacrylamide. Both, separating and stacking gels, polymerize after the addition of the catalyzers ammonium persulfate (PSA) at 10% and N,N,N',N'-tetramethylethylenediamine (TEMED) at 0.03%. As a control and identification measure, 2.5 µL of a molecular weight marker was used (Precision Plus Protein™ Dual Color Standards, #1610374 from BioRad, Spain). The electrophoretic separation was performed in electrophoresis cells from BioRad (Mini-PROTEAN II, #165-2940) filled with a buffer solution made of 25mM of TRIS, 192 mM of glycerol, 0,1% (p/v) of SDS and applying a constant amperage of 15 mA/gel.

3.6.3. Electroblotting

After electrophoretic protein separation, proteins are transferred to a PVDF membrane (Immobilion-P, #IPVH00010, Millipore, Bedford, MA, USA) previously activated by incubation with 99.9% methanol for 5 minutes and equilibrated with transfer buffer made of 25 mM of TRIS, 192 mM glycerol and 20% (v/v) of methanol. The separating gel is in touch with the PVDF membrane inside a sandwich system (from the anode to the cathode) for a wet transfer in a Mini Trans-Blot Transfer Cell from BioRad (Munich, Germany). The voltage applied was constant at 100V for 90 minutes.

3.6.4. Membrane blocking

Once the proteins have been transferred to the PVDF membrane, next step is blocking the membrane. This step serves to avoid false positives in those places of the membrane where there is not protein coupled. Two types of blocking solutions have been used depending on whether the proteins were phosphorylated or not. For phosphorylated proteins we used bovine serum albumin (BSA) 5% with TBS-T 0.1% (Tris 2 M, sodium chloride 2.5 M and Tween-20 0.01%) and for non-phosphorylated proteins we used I-Block (Tropix® I-Block, ThermoFisher Scientific, Barcelona, Spain) with phosphate buffered-saline 10 mM and Tween-20 0,01% . After the blocking step, membranes were washed for 5 minutes with TBS-T 0.05% (Tris 2 M, sodium chloride 2.5 M and Tween-20 0.05%) in order to remove the excess of blocking solution.

3.6.5. Immunodetection

Membranes were incubated with the primary antibody in TBS-T 0.05% or in BSA 5% with TBS-T 0.01% overnight at 4 ^{o}C and mild shaking. All the primary antibodies used in this work are summarized in Table 8. After the incubation with the primary antibody, three washes of 5 minutes were performed with TBS-T 0.05% solution and the membranes were incubated with the appropriate secondary antibody linked to peroxidase (Table 9). In every Immunodetection the secondary antibody is been dissolved in the same solution of incubation which lasts one hour and it was performed in mild shaking. After this incubation, the membranes were washed three times for 5 minutes each wash with TBS-T 0.05% and two more washes with TBS and strong shaking for 5 minutes each wash.

Table 8.Experimental conditions of the primary antibodies used in the Immunodetection.

Antibodies	Description	Reference	M.W (kDa)[1]	%[2]	µg[3]	Dilution[4]	Secondary antibody[5]
FXR	Farnesoid X Receptor	ab73299-Abcam	70	10	35	1:1000	Anti-rabbit
SHP	Small Heterodimer Partner	Sc-30169-Sta Cruz Biotech	28	15	35	1:200	Anti-rabbit
SREBP1	Sterol Regulatory Element Binding Protein1	ab-3259-Abcam	70	10	35	1:1000	Anti-mouse

[1]Molecular weight of the protein [2]% of acrylamide of the separating gel [3]Ammount of protein in µg [4]Dilution used of the primary antibody [5]Secondary antibody used

Table 9. Experimental conditions of the secondary antibodies used in the Immunodetection.

Antibodies	Description	Reference	Dilution
Anti-mouse	ECL Anti Mouse IgG, Horseradish Peroxidase-linked Species-Specific Whole Antibody (from sheep)	NA931 GE-Healthcare	1:30000
Anti-rabbit	Anti-rabbit IgG, H&L, Horseradish Peroxidase-linked species (from goat)	31460 Pierce	1:50000

3.6.6. Chemiluminescent detection and data analysis

For the exposure, PVDF membranes were incubated at room temperature for 5 minutes with the chemiluminescent substrate (Luminol™ Western Chemiluminiscent HRP from Millipore Corporation, Billerica, MA, USA). The luminescence emission was detected with a ChemiDoc™ MP imaging System from BioRad (Munich, Germany) and it was analyzed with the software called Image Lab v4.0 (BioRad, Hércules, CA, USA). The amount of luminescence is directly proportional to the amount of protein in the membrane. In every Immunodetection by western blott the signal obtained was relativized with a loading control applied to the same membrane after washing. This loading control was Commassie Blue staining of the PVDF membrane.

3.7 Statistical analysis

Different statistics have been used in this work; we will explain them clustering them in two groups depending on the experimental method or technique performed. In the next sections, we will break down these statistical methods used in each one.

In every analysis, the minimum level of statistical significance was a p value equal to 0.05. The significance level was represented in every graph as indicated: * if p value is lower than 0.05; ** if p value is lower than 0.01 and *** if p value is lower than 0.001.

3.7.1. Metabolism and lipids in the experimental groups

The results obtained in the untargeted metabolomic and lipidomic analysis as well as in the targeted lipidomic analysis have been treated first applying unsupervised multivariate analysis such as principal component analysis or a hierarchical clustering using *Pearson* distance and *Wards* clustering algorithm. Both analyses were performed thanks to the free online platform MetaboAnalyst (*Xia and Wishart 2016*). These two types of multivariate analyses were an initial overview of data set about group classification and trends between samples in the different experimental groups. Partial Least Squares Discriminant Analysis (*PLS-DA*), a supervised analysis, was used to discriminate better the experimental groups and to find out features as markers that had significant discriminatory power between groups. An analysis of variance (ANOVA) of one-way with a Post Hoc, specifically *Tukey's* multiple comparison test, was performed in order to identify those features significantly different in each group using MassHunter Mass Profiler Professional Software (Agilent Technologies, Barcelona, Spain), MetaboAnalyst free online platform and SPSS statistics 17.0 (Inc. Chicago, IL, USA).

3.7.2. Protein expression in the experimental groups

In order to evaluate the possible differences between the protein expressions of the individuals in the experimental groups a One-way ANOVA with a Post Hoc, specifically *Tukey's* multiple comparison test, was performed with the software GraphPad Prism v5.0 (GraphPad, La Jolla, CA, USA). The graphical representation of the western blott analysis was also performed with this software.

RESULTS

4. RESULTS

4.1 Study of the metabolites and lipid species distribution in adults male rats

In order to achieve the objectives set out before, in this study it has been evaluated the metabolic and lipid profiles of healthy adult male Wistar rats without any kind of dietary restriction. Tissues evaluated were heart, liver, kidney (renal cortex), two types of WAT –visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT)- and two types of skeletal muscle –gluteus (as a representation of glycolytic fibers of skeletal muscle) and soleus (as a representation of oxidative fibers of skeletal muscle)-. Techniques chosen for this purpose were untargeted metabolomic and both types of lipidomic analysis. First, an untargeted lipidomic analysis was performed and after that, a more specific targeted lipidomic analysis was performed for each tissue. Lipidomic analysis was carried out for every type of tissue but both types of WATs were removed from the metabolomic analysis due to their highly hydrophobic nature. Below are represented the results obtained.

4.1.1. Clustering mammalian tissues based on their metabolome and lipidome

In order to study the distribution of metabolites across tissues an untargeted approach with a LC-QTOF MS/MS was used. The tissues selected for this study were heart, liver, kidney (represented by renal cortex), gluteus (as a representation of glycolytic fibers of skeletal muscle) and soleus(as a representation of oxidative fibers of skeletal muscle) from male Wistar rats. As a results, 7475 compounds were detected and after data filtering 1885 metabolites. The distribution of metabolites can be visualized in a heat map representation created for the whole amount of detected metabolites using a hierarchical ward clustering algorithm with Pearson as a distance measure (Figure 13A). The same unsupervised multivariate statistical analysis was performed but instead with the whole metabolome with the top hundred statistical significant lipid species with lower p-value obtained by one-way analysis of variance (ANOVA) amongst the analyzed tissues (Figure 13B). In both of them, perfect division of the samples can be seen according to their origin. First, samples were divided in two big groups looking at their metabolic profiles. On one hand, heart, liver, and kidney while on the other hand were both types of skeletal muscle. Then, inside each group, liver, kidney and heart were perfectly separated by

their metabolome profiles while the two types of skeletal muscle were separated only by in the heat map representing the top hundred metabolites with lower p-values (Figure 13B).

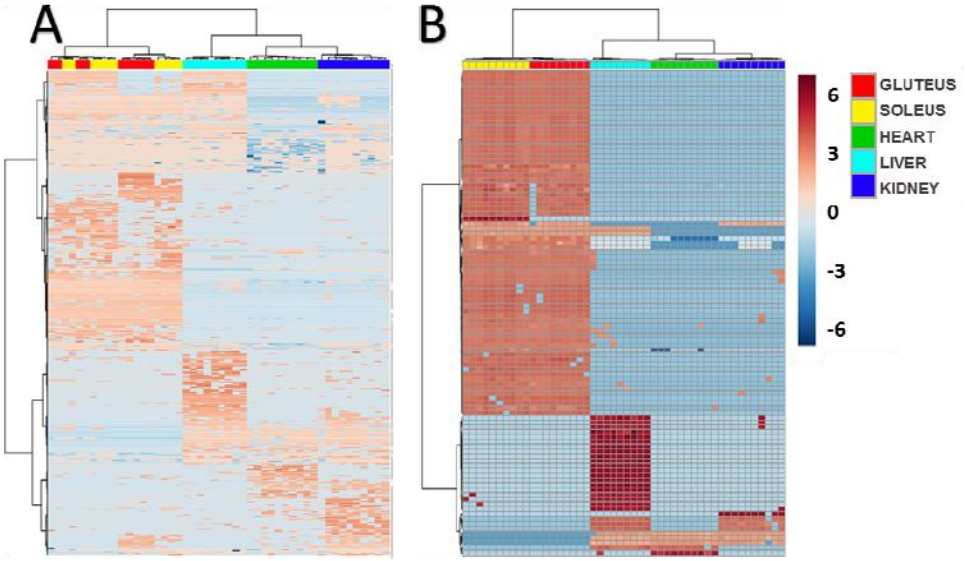

Figure 13. Metabolites distribution in mammalian tissues. A) Heat map representation of 1885 molecular features found in all organs and tissues. B) Heat map using 100 most statistical significant compounds (one-way ANOVA). Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median. The scale from -6 (blue) to 6 (red) represents this normalized abundance in arbitrary units. Analysis was performed in positive ESI polarity.

Inside multivariate statistics, an unsupervised principal component analysis (PCA) was performed and results are shown in Figure 14. The PCA of Figure 14A shows how metabolites distribution was completely tissue-specific and a 48.9% of the variability across samples can be explained by their metabolomes. Each type of tissue is clustered separately from the rest excep for both types of skeletal muscles. Gluteus and soleus were clustered together suggesting common metabolites profiles and fewer differences between their metabolomes. Performing the same analysis, PCA, without both type of skeletal muscle, metabolome of each tissue continues being specific and the division between liver and the other two tissues –cardiac and renal- was then more pronounced (Figure 14B). A non-parametrical t-test for equal variances and with Benjamini Hochberg correction was carried out for different groups. First, between gluteus and soleus and from the 1885 metabolites detected in the untargeted analysis, only two of them were statistically different between both types of skeletal muscle being the metabolic variability between them of 0.1%. Therefore, gluteus and soleus were studied together as skeletal muscle and the metabolic profile of the skeletal muscle differed from the other tissues in a 69.9% of the detected metabolites.

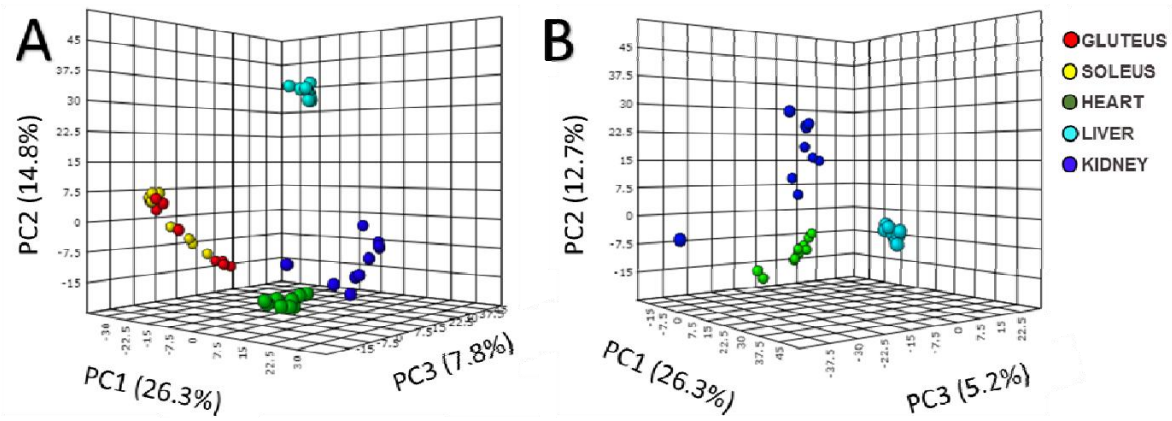

Figure 14. Multivariate statistics with an unsupervised PCA reveal a specific metabolic profile for each tissue. A) Representation of the five different types tissues analyzed in positive ionization. B) Representation of the metabolomic profiles of heart (green), liver (cyan) and kidney (blue) in positive ionization.

Then, in order to find metabolites common amongst tissues or specifics a t-test was performed comparing the metabolome of each tissue versus the average of the other tissues analyzed. Hence, 1312 compounds were statistically different between the skeletal muscle and the other analyzed tissues (heart, kidney and liver) in the untargeted metabolomics and 820 metabolites were present only in the skeletal muscle or the concentration was significantly higher. From these 820 metabolites up regulated in the skeletal muscle, fifty five of them were identified. All of the non-identified compounds obtained by untargeted metabolomics are in Table S2 of annex and identified compounds are listed in Table 10. Amongst the identified metabolites, nucleotides involved in the purine metabolism were found. However, most of the compounds identified belong to the fatty acyl category being involved in fatty acid metabolism including elongation in the mitochondria or UFA biosynthesis. Moreover, a great amount of signaling molecules were identified such as MAGs, eicosanoids involved in the arachidonic metabolism or steroid hormones. The identified GPs were members of the LGPs subclass composed of glycerol, phosphatidic acid, choline or ethanolamine. Additionally, ether lipid metabolism was enhanced in the skeletal muscle for both types of bonds, alkyl and alkenyl, in LGPs formed of phosphatidic acid or choline.

Regarding cardiac tissue, when a non-parametric t-test was performed, 723 compounds were statistically different between the cardiac tissue and the rest of tissues analyzed (skeletal muscle, kidney and liver) in the untargeted metabolomics. From the 723 statistically different metabolites, 159 were present only in the cardiac tissue or the concentration was significantly higher, nineteen of them have been identified and are listed in Table 11.

Table 10. Skeletal muscle characteristic metabolites in adult animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI(+). Up-regulated metabolites were chosen for the identification.

Classification	Compound	Product ion	m/z	RT	Log FC	p(Corr)
Purine Base	Adenine	M+H+	136.0641	1.32	10.21	6.16E-07
Purine nucleotides	Inosine 5'-monophosphate	M+H+	349.0579	0.65	13.95	1.12E-10
	cyclic ADP ribose	M+H+	542.0666	0.82	4.42	3.38E-02
Eicosanoids	10-F2-dihomo-IsoP	M+H+	397.2952	10.46	6.87	6.85E-03
	15-HETE	M+H+	321.2455	11.26	6.87	4.84E-03
	15S-HETrE	M+H+	323.264	11.65	7.15	2.36E-04
	Leukotriene D4 methyl ester	M+H+	511.2913	5.87	13.59	3.50E-10
Fatty acyl CoA	N-stearoyl tyrosine	M+H+	448.3498	9.74	7.04	1.11E-02
	3-Hydroxyisovaleryl-CoA	M+H+	868.1776	11.44	5.97	2.86E-03
	Hexanoyl-CoA	M+H+	866.1896	11.45	6.85	1.21E-04
Fatty acyl carnitines	trans-Hexadec-2-enoyl carnitine	M+H+	398.3286	9.44	13.71	1.01E-07
	Stearoylcarnitine	M+H+	429.8064	10.63	10.95	8.68E-08
	Elaidic carnitine	M+H+	426.3631	10.14	8.12	1.87E-03
	Hexanoyl carnitine	M+H+	260.1875	2.89	16.21	6.82E-25
	Myristoyl carnitine	M+H+	372.3172	9.17	17.23	5.77E-19
	Palmitoyl carnitine	M+H+	400.3483	9.95	6.66	1.55E-02
	Isobutyryl carnitine	M+H+	232.1571	1.17	6.26	7.12E-03
	Linoleyl carnitine	M+H+	424.3429	9.73	7.00	2.55E-03
	Arachidyl carnitine	M+H+	456.4085	11.12	5.41	4.64E-02
	Clupanodonyl carnitine	M+H+	474.3622	9.99	11.44	3.47E-09
	Decanoyl-L-carnitine	M+H+	316.2534	6.85	9.14	5.96E-07
MAG	MAG(14:0)	M+H+	303.2513	10.46	2.23	1.66E-02
	MAG(16:0)	M+H+	331.2848	11.12	5.03	1.16E-02
	MAG(18:0)	M+H+	359.3164	11.65	7.18	3.95E-03
	MAG(18:1)	M+H+	357.3006	11.27	4.51	1.33E-02
	MAG(18:2)	M+H+	355.2877	10.92	6.42	1.83E-02
	MAG(20:0)	M+H+	387.3559	12.06	10.29	5.95E-07
	MAG(22:0)	M+H+	415.3681	12.41	8.88	4.47E-06
	MAG(24:1)	M+H+	441.3858	12.75	7.54	1.21E-04
LGP	LPG(12:0)	M+H+	429.2297	8.81	15.33	9.62E-12
	LPA(20:0)	M+H+	467.3244	5.69	6.82	2.58E-05
	LPC(18:0)	M+H+	524.3725	11.54	7.08	2.15E-02
	LPC(22:6)	M+H+	568.3431	10.46	8.60	1.06E-03
	LPE(22:5)	M+H+	528.3119	10.46	8.50	4.79E-04
LGP(P-)	LPA(P-20:0)	M+H+	451.3298	5.08	11.26	9.35E-11
	LPC(P-15:0)	M+H+	466.325	10.97	7.32	4.02E-04
	LPC(P-16:0)	M+H+	480.3369	11.03	5.41	1.64E-02
LGP(O-)	LPA(O-20:0)	M+H+	453.3442	5.88	1.37	5.82E-13
	LPC(O-16:0)	M+H+	482.3695	10.47	7.51	2.58E-05

Sphingoid bases	SM(d18:1/0:0)	M+H+	465.8351	11.17	7.57	2.58E-05
Steroids	Tetrahydrocorticosterone	M+H+	351.2549	7.32	5.65	1.23E-04
Isoprenoids	All-Trans-3,4-Didehydro-Retinoic acid	M+H+	299.1937	8.42	5.62	4.79E-04

Table 11. Cardiac tissue characteristic metabolites in adult animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity. Up-regulated metabolites were chosen for the identification.

Classification	Compound	Product ion	m/z	RT	Log FC	p(Corr)
Alkylamines	Phenylethanolamine	M+H+	120.0803	0.83	9.46	1.50E-02
Aminoacids	L-Valine	M+H+	118.0826	0.43	9.85	7.92E-03
	L-Isoleucine	M+H+	249.1526	0.42	6.55	2.88E-02
Monosaccharides	D-Ribulose 5-phosphate	M+H+	442.0385	0.89	11.33	1.13E-08
Purine	Hypoxanthine	M+H+	137.0472	0.7	11.6	6.41E-03
Purine nucleoside	5'-Methylthioadenosine	M+H+	298.097	3.01	7.49	1.56E-02
	Guanosine	M+H+	284.0949	0.8	9.73	2.47E-04
Purine nucleotide	ADP-ribose	M+H+	560.0861	0.76	14.79	1.01E-08
Branched fatty acids	Dimethyl-docosanoic acid	M+H+	369.3752	12.83	6.94	4.95E-02
Eicosanoids	Leukotriene C4	M+H+	626.2979	5.89	8.79	3.38E-04
Fatty amides	N-oleoyl tyrosine	M+H+	446.3247	6.88	7.98	1.62E-02
Hydroxy fatty acids	(S)-3-Hydroxybutyric acid	M+H+	105.0565	7.44	8.26	3.80E-06
Octadecanoids	dihydroxy stearic acid	M+H+	317.2676	11.83	9.11	5.02E-06
	13(S)-HODE methyl ester	M+H+	311.2557	10.99	6.9	4.25E-02
Thia-fatty acids	2-Oxo-4-methylthiobutanoic acid	M+H+	149.0252	9.48	14.76	1.47E-04
LGP	LPE(22:4)	M+H+	530.3299	10.78	5.76	4.93E-02
LGP(O-)	LPC(O-19:0)	M+H+	524.4005	11.5	10.94	7.53E-06
Bile acids	Lithocholic acid	M+H+	377.3061	11.65	10.21	4.11E-06
Polypeptide Hormone	Angiotensin I	M+H+	1296.6624	11.49	10.07	5.73E-08

All of the non-identified compounds obtained by untargeted metabolomics are in Table S3 of annex. Amongst the identified compounds, there were metabolites of the purine metabolism, pentose phosphate pathway and amino acids. Some fatty acyls members were also present including hydroxy, branched and thiol groups fatty acids. LGP category members identified were LPE(22:4) and one ether lipid with an alkyl bond. Finally, signaling molecules such as eicosanoids, lithocholic acid and angiotensin I were found to be in higher concentrations in the heart compared to other tissues.

In order to find characteristic metabolites of the hepatic tissue respect to the other tissues analyzed, a non-parametric t-test was performed comparing the hepatic metabolome versus the average of the other tisssues. Results showed 593 compounds were statistically different between liver and the rest of tissues analyzed (skeletal muscle, kidney and heart) in the untargeted metabolomics. From the 593 statistically different metabolites, 480 were present only in the hepatic tissue or the concentration was significantly higher, forty five of them have been identified and are listed in Table 12. All of the non-identified compounds obtained by untargeted metabolomics are in Table S4 of annex.

Table 12. Hepatic tissue characteristic metabolites in adult animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity. Up-regulated metabolites were chosen for the identification.

Classification	Compound	Mass	RT	Log FC	p (Corr)
Amino acids	L-Isoleucine	248.1456	0.42	6.70	2.94E-02
	L-Leucine	131.0944	0.55	17.32	8.44E-10
	L-Proline	313.1352	0.86	10.13	3.36E-04
Deoxyribonucleosides	S-Adenosylhomocysteine	384.1229	1.12	6.65	3.88E-02
Peptide	Glutathione	307.0833	0.51	11.74	3.58E-03
Purine base	Xanthine	152.0327	0.8	8.22	3.50E-02
Purine nucleosides	Adenosine	249.0869	2.05	15.40	7.94E-07
	ADP	427.0291	0.85	7.63	9.93E-04
	Inosine	574.1173	0.81	9.41	3.24E-05
	Xanthosine	284.0758	1.07	17.23	5.29E-18
Purine nucleotides	Deoxy GMP	347.0627	0.51	11.78	2.92E-03
Pyrimidine nucleotides	CDP-Colina	488.1063	0.48	15.02	7.07E-13
	UDP-N-acetyl-D-galactosamine	607.08	0.85	13.34	2.11E-06
	UMP	324.0378	0.58	13.87	3.57E-11
Amino fatty acids	2,3-Diaminopropionic acid	104.0555	7.42	9.52	4.20E-03
Dicarboxylic acids	Methylglutaric acid	146.0577	5.97	13.54	2.04E-06
Fatty acyl CoA	4-Pentenoyl-CoA	849.1495	11.44	7.05	1.56E-02

	Farnesoyl-CoA	985.2544	13.78	8.21	4.88E-05
	Malonyl CoA	852.1161	11.44	8.42	2.20E-03
Hydroperoxy fatty acids	15(S)-HpEDE	340.2583	10.31	7.46	4.78E-02
Oxo fatty acids	3-oxo-nonadecanoic acid	312.2712	10.51	8.59	1.11E-04
Protectins	10S,17S-DiHDoHE	360.233	9.94	7.39	4.26E-02
Straight chain fatty acids	Arachidic Acid	626.5278	13.1	13.48	3.69E-05
Glycerophosphates	Glycerol 2-phosphate	172.0128	0.44	8.06	5.02E-04
LGPs	LPC(14:0)	467.307	10.06	12.43	1.51E-14
	LPC(18:0)	523.3655	11.54	10.18	1.28E-02
	LPC(18:1)	521.3472	10.87	8.72	1.35E-02
	LPC(18:3)	517.3206	10.84	9.51	1.65E-04
	LPC(20:4)	543.3334	10.57	8.66	3.69E-02
	LPC(22:6)	567.3322	10.61	11.46	1.55E-08
	LPE(18:0)	481.3197	11.19	15.51	6.28E-06
	LPE(18:1)	479.3016	10.71	9.52	9.72E-03
	LPE(18:2)	477.2868	10.34	12.59	7.99E-05
	LPE(20:0)	509.3421	11.2	7.93	9.15E-05
	LPE(20:4)	501.2886	10.36	12.14	1.07E-03
	LPE(20:5)	499.2748	10.3	6.79	1.02E-04
	LPE(22:6)	525.2858	10.37	6.59	2.61E-02
	LPG(19:0)	526.34	11.09	8.59	2.60E-02
	LPS(16:0)	497.2844	9.44	9.58	2.63E-08
	LPS(16:1)	495.2723	8.47	13.33	1.65E-14
Sphingoid base	Sphinganine (Spa)	301.298	9.39	12.97	1.51E-14
Bile acid	6-Ethylchenodeoxycholic acid	420.3225	12.32	7.68	1.10E-03
	Glycocholic Acid	465.31	8.88	18.13	9.78E-06
	Sulfoglycolithocholate	513.2764	8.47	15.40	4.29E-21
	Taurocholic acid	553.2412	9.44	9.60	2.63E-08

Amongst the identified compounds, several nucleosides and nucleotides involved in the purine and pyrimidine metabolism as well as amino acids involved in their biosynthesis, degradation and aminoacyl tRNA metabolism. Other metabolic pathways of the hepatic tissue were glutathione, pyruvate, SFA and UFA metabolism. GPs and SPs metabolism was also enhanced in the liver as well as primary bile acids and taurine metabolism.

As representation of the kidney, renal cortex samples were processed in the untargeted metabolomic analysis and a non parametric t-test was performed in order to find characteristic metabolites of this tissue. Results showed 540 compounds were statistically different between

renal cortex and the rest of tissues analyzed (skeletal muscle, heart and liver) in the untargeted metabolomics. From the 540 statistically different metabolites, 280 were present only in the renal cortex or the concentration was significantly higher, twenty seven of them have been identified and are listed in Table 13. All of the non-identified compounds obtained by untargeted metabolomics are in Table S5 of annex. Amongst the identified metabolites, nucleosides and nucleotides of the purine and pyrimidine metabolism were found as well as amino acids or monosaccharides with a carboxyl group. Additionally, in Table 13 can be seen different subclasses of fatty acids and derivatives and LGPs with both SFA and UFA. LGPs found were conjugated with choline and ethanolamine mostly.

Table 13. Renal cortex characteristic metabolites in adult animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity. Up-regulated metabolites were chosen for the identification.

Classification	Compound	Mass	RT	Log FC	p (Corr)
Alkylamines	Phenylethanolamine	120.0803	0.83	12.67	6.51E-04
Amino acids	L-Phenylalanine	166.0854	0.83	8.73	1.61E-02
Deoxyribonucleosides	S-Adenosyl homocysteine	385.1299	1.12	9.68	1.38E-03
Peptides	Gamma-glutamylglutamic acid	277.1003	0.47	11.2	2.08E-10
Purine nucleosides	Adenosine	250.0939	2.05	10.78	4.69E-03
Purine nucleotides	Adenosine monophosphate	348.0697	0.51	9.07	3.71E-02
	Cyclic ADP ribose (cADPR)	542.0667	0.57	7.24	1.54E-04
Pyrimidine nucleotides	UDP-N-acetyl-D-galactosamine	608.087	0.85	10.12	2.48E-03
Sugar acids	Threonic Acid	137.0428	0.83	14.1	6.79E-04
Amino fatty acids	Diaminobutyric acid	119.0834	8.37	8.19	1.71E-02
Eicosanoids	Leukotriene C4	626.2979	5.89	5.75	3.94E-02
Fatty amides	N-oleoyl tyrosine	446.3247	6.88	8.91	8.49E-03
Fatty acyl CoA	Arachidonoyl-CoA	1054.3532	13.98	8.59	4.86E-03
Hydroperoxy fatty acids	15(S)-HpEDE	341.2653	10.31	9.69	9.34E-03
Protectins	10(S),17(S)-DiHDoHE	361.24	9.94	7.72	3.63E-02
Straight chain fatty acids	Nonanoic acid	298.2759	8.66	11.96	2.08E-10
Unsaturated fatty acids	5,8-Tetradecadienoic acid	225.1899	7.64	7.28	2.79E-02
LGP	LPC(16:0)	496.3411	10.69	8.83	1.62E-02
	LPC(18:0)	524.3625	11.1	15.91	1.88E-08
	LPC(20:4)	544.3404	10.57	10.77	8.90E-03
	LPE(16:0)	454.3017	10.43	9.19	2.29E-03
	LPE(18:0)	482.3267	11.19	12.68	1.34E-03
	LPE(18:1)	480.3079	10.63	13.52	5.08E-14
	LPE(20:4)	502.2956	10.36	10.21	1.38E-02
	LPS(22:1)	580.3626	11.34	15.48	6.07E-12
LGP(P-)	LPE(P-16:0)	438.3001	10.88	9.97	4.68E-06

4.1.2. Lipidomic profiles of mammalian tissues

In order to study the distribution of lipids across tissues an untargeted approach in a LC-QTOF mass spectrometer was used. The samples selected for this study were the same of the untargeted metabolomic analysis (Gluteus, soleus, heart, kidney and liver) plus two different types of WAT; VAT and SAT. After data filtering, the number of lipid species detected was 1264 (970 in positive and 294 in negative ionization mode) where multivariate statistics were applied. Distribution of the detected lipids in both polarities showed differences between the tissues analyzed (Figure 15). Both heat maps, performed with the analysis in positive and negative ionization, showed a distribution of the lipid species detected where it can be appreciated a first division between both types of WAT and the rest of the tissues analyzed. At the same time, in this second group, both types of skeletal muscle are separated from heart, kidney and liver. Finally, these three tissues are perfectly separated from each other. Hence, metabolomic and lipidomic profiles for these samples showed the same pattern and results of the untargeted lipidomic analysis showed a lipidomic profile specific for each type of tissue. In the PCA representations of every type of sample analyzed (Figure 16A and B) most of the tissues were well separated based on their lipidome and those tissues with similar functions or common developmental origin were clustered together.

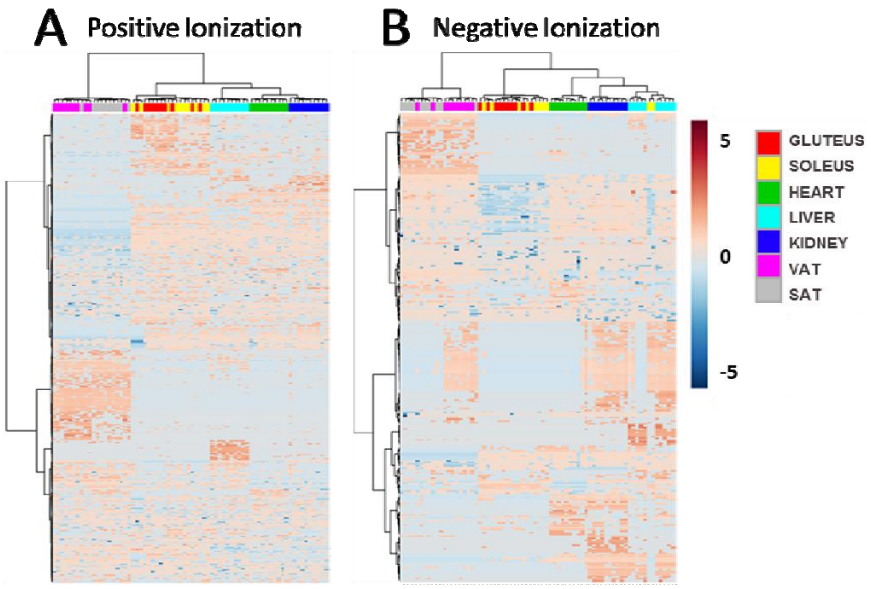

Figure 15. Lipid distribution in mammalian tissues. A) Heat map representation of 970 molecular features found in all organs and tissue samples in positive ionization B) Heat map representation of 294 molecular features found in all organs and tissue samples in negative ionization. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -5 (blue) to 5 (red) represents this normalized abundance in arbitrary units.

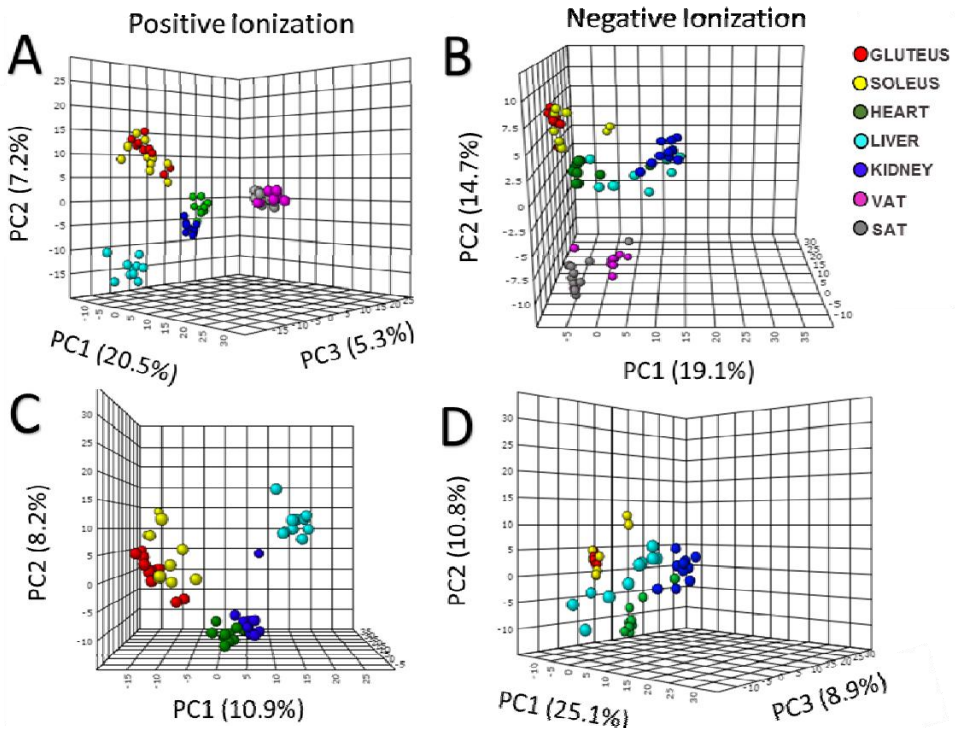

Figure 16. Multivariate statistics with an unsupervised PCA revealed a specific lipidomic profile for each tissue. A,B) Representation of the six different types of tissues in positive and negative ionization polarities. C,D) Representation of the lipidomic profiles of every tissues except for both type of adipose tissues in positive and negative ionization polarities.

On this wise, first division between samples separated both types of WAT from the rest of the tissues. Furthermore, as the lipidomic profile of WAT was completely different of the rest samples, a second PCA approach without WAT was performed (Figure 16C-D). The lipidome detected from positive and negative polarities clustered separately for every type of sample. Gluteus and soleus were together and in hierarchical clustering analysis represented by a heat map they appeared evenly mixed (Figure 15), being that their lipid profile/composition was very similar. The tissue most closely clustering with skeletal muscle was, as expected, cardiac muscle. However, PCA results from lipids detected with positive polarity showed that kidney and heart were closely clustered relative to hepatic tissue. This situation change for those lipids detected with negative polarity or in the global analysis with the hierarchical clustering algorithm, where kidney and liver were closely aligned. In the previous multivariate analysis, differences between both types of WAT or both types of skeletal muscle seem minimal (Figure 15 and Figure 16). Nevertheless, each type of tissue have a specific lipid profile when the multivariate analysis is performed for each class separately (Figure 17). The first PCA showed a clear separation between soleus and gluteus (Figure 17A). Difference between those two types of skeletal muscle is the predominance of the type of fibers. Soleus presents mainly fibers type I and fibers type II

are more abundant in gluteus. Therefore, soleus metabolism is mainly a slow oxidative metabolism while in gluteus a fast glycolytic metabolism is favored. Differences in the metabolism of each type of skeletal muscle are translated to differences in the lipid profile of each tissue. Regarding both types of WAT, the untargeted lipidomic analysis showed differences between VAT and SAT. Results of the multivariate analysis are shown in Figure 17B and C. Both PCA and clustering analysis showed that clearly, both types of WAT had a different lipid composition.

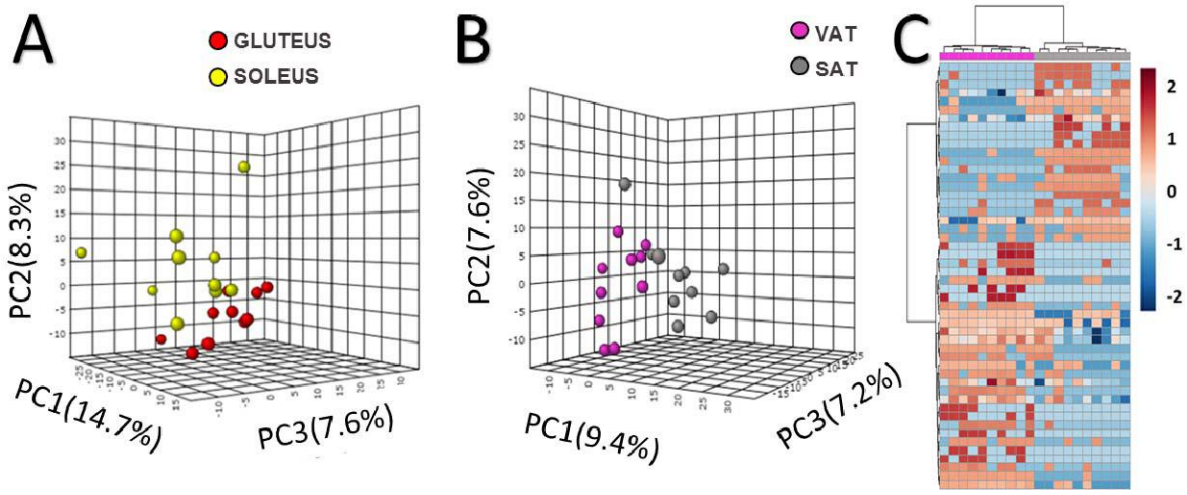

Figure 17. Lipidomic specific profiles of different types of skeletal muscle and WAT. A) Multivariate statistics with an unsupervised PCA revealed differences between both types of skeletal muscle -soleus and gluteus-. B) PCA representing both types of WAT -VAT and SAT-. C) Heat map representations of hierarchical clustering analyses using 50 most statistical significant lipids species (unpaired t-test) of 970 entities found in both types of WAT. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units. All data was obtained by untargeted lipidomic analysis with positive ESI polarity.

4.1.3. Assessing lipids across mammalian tissues

After assessing the lipidome characteristics in each tissue using an untargeted analysis, a more specific approach was performed using a targeted analysis. As it has been previously described in the Materials and Methods chapter, 652 lipid species were detected, 14 were acylcarnitines of the FA category; 46 were cholesterol derivatives of the category of ST and 157 were SP including Cer, gangliosides, SM and sulfatides. Of the GL category 67 lipids were detected, 20 of them DAGs and the rest of them TAGs, mostly with UFA chains. Most of the lipids were part of the GP category; concretely 367 lipid species were detected; 124 with ethanolamine (being 73 ether lipids, 14 of them with an alkyl ether bond and 59 plasmalogens); 193 with choline (being 62 ether lipids, 32 of them plasmalogens as well and 32 plasmanyl species); 11 with serine; 35 with inositol and only 4 lipid species conjugated with another molecule of glycerol. The only lipid detected in the Pr category was ubiquinone. Concentration of each lipid species was represented in nmol/g of tissue and the values of the concentration of all the species detected inside each lipid category is represented in Table 14. To first obtain a high-level view of lipid tissue distribution, the concentration of the main eight categories according to LIPIDMAPS were

represented for every mammalian tissue analyzed
(

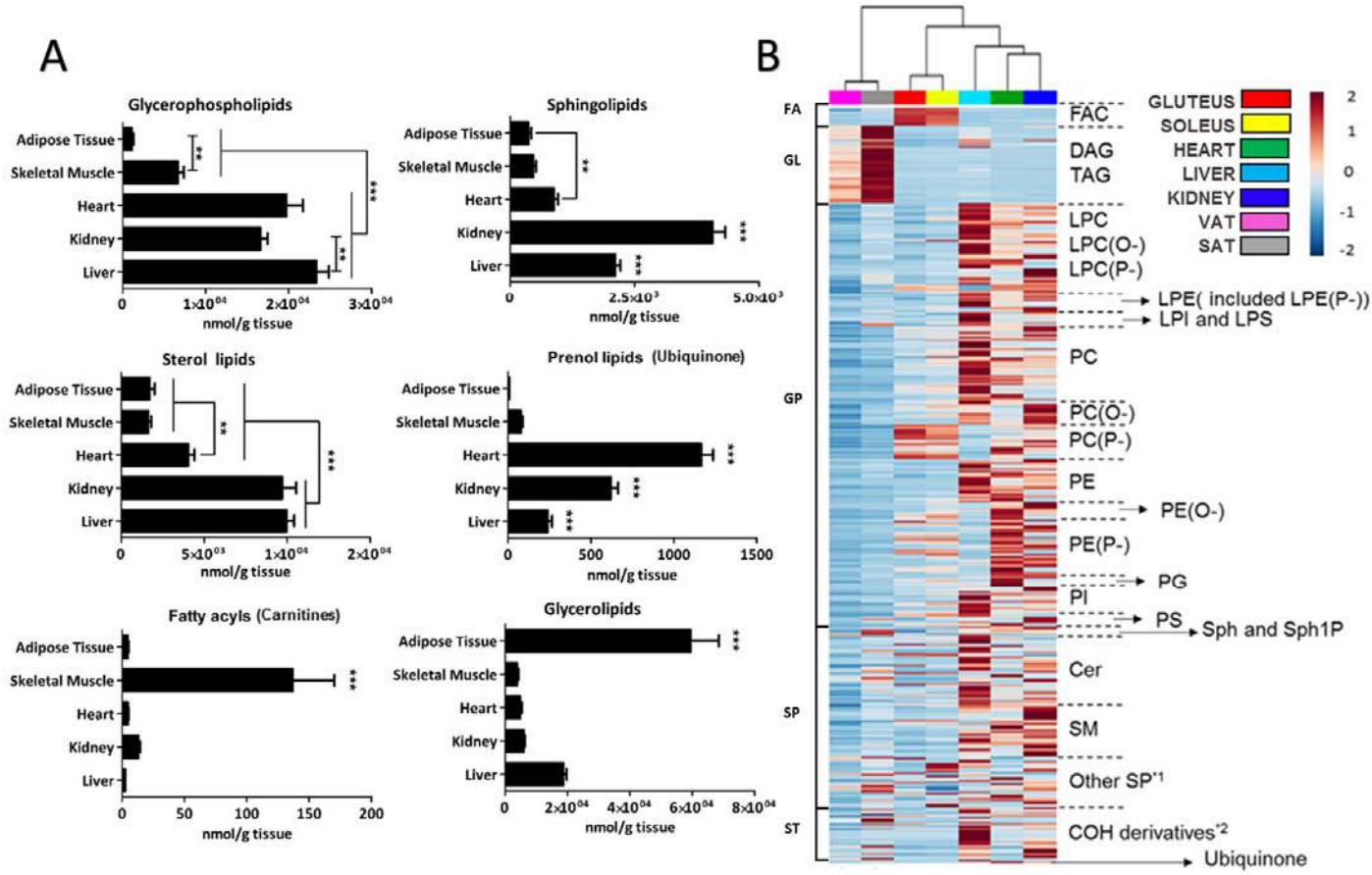

Figure 18A). In every category, there were significant differences amongst the tissues analyzed. Inside the FA category, represented only by fatty acylcarnitine species, were present at higher concentrations in skeletal muscle compared with the other tissues. In the GL category, both types of WAT presented statistically higher concentrations. In the GP category, there were two groups statistically differentiated, adipose and skeletal muscle on one hand and on the other heart, liver and renal cortex. On top, inside this two differentiated groups there were statistical differences in the total GP concentration between adipose and skeletal muscle as well as between liver and kidney. SP category showed a higher concentration in the renal cortex followed by the hepatic tissue being the total concentration of SP species in these two tissue statistically different from the other. Additionally, the concentration of SP in the cardiac tissue was statistically different compared to both types of WAT. The ST species were more concentrated in kidney and liver compared to the other tissues. In turn, the concentration in heart was significantly higher compared to skeletal muscle and WAT. Ubiquinone, the only lipid detected in PR category, was more concentrated in heart, liver and kidney rather than skeletal muscle or WAT. Further, in order to have a more graphical view a heat map clustering analysis, where both WAT and skeletal muscles were treated as different tissues, was applied

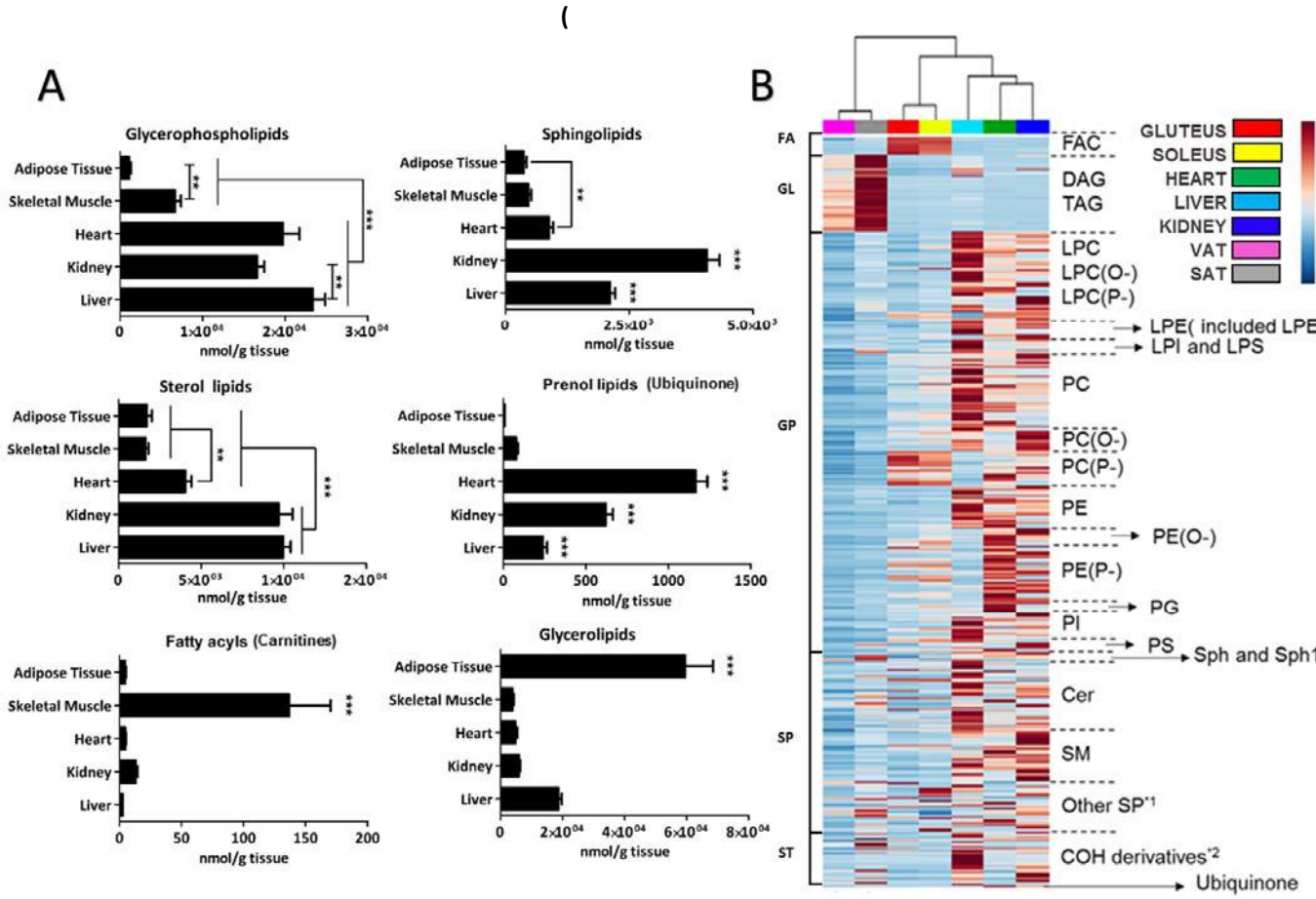

Figure 18B). Both lipidomic analysis, targeted and untargeted, showed the same separation pattern of the tissues based on their lipid profiles. First division across tissues is due to the presence of both types of WAT and their content in GL species, followed by skeletal muscle rich in FAC and plasmalogens. The third division comprised the two last groups, one with hepatic tissue and the other one comprised heart and kidney.

4.1.3.1. Fatty acyls and glycerolipids across mammalian tissues

As it has been said, the 14 species of fatty acylcarnitines (FAC) that represent the FA category were present at higher concentration in skeletal muscle compared with the other tissues. FAC total concentration in the different tissues is found in Figure 19A. Between gluteus and soleus there were no differences in the total concentration or in any of the individuals acylcarnitines detected (Table S7).

Table 14. Lipid concentration in nmol/g of tissue organized according LIPIDMAPS classification and analyzed by targeted lipidomics.

Lipid Class	Nº of species	Liver	Kidney	Heart	Gluteus	Soleus	VAT	SAT
Fatty acyls								
FAC	14	2.30 ± 0.18 $^{d***;c*}$	13.21 ± 1.04 $^{d***;c*}$	4.66 ± 0.64 $^{d***;c*}$	151.78 ± 45.99 $^{b,e,f,g***;a**}$	119.34 ± 29.46 ^{a,b,e,f,g*}	2.88 ± 0.37 $^{d***;c*}$	6.61 ± 1.03 ^{d**,c*}
Subtotal FA	14	2.30 ± 0.18 $^{d***;c*}$	13.2 ± 1.04 $^{d***;c*}$	4.66 ± 0.64 $^{d***;c*}$	152 ± 46 $^{b,e,f,g***;a**}$	119 ± 29 ^{a,b,e,f,g*}	2.88 ± 0.37 $^{d***;c*}$	6.61 ± 1.03 ^{d**,c*}
Glycerolipids								
DAG	20	14027.71 ± 858.67 ^{a***}	4910.17 ± 324.22 $^{a***;b*}$	3781.92 ± 422.55 $^{a***;b*}$	1456.87 ± 70.87 $^{a***;b**}$	2519.70 ± 325.54 $^{a***;b*}$	18415.56 ± 3 120.27 $^{a***;d**;c,e,f*}$	55008.16 ± 6999.58 $^{\tau***}$
TAG	44	4585.44 ± 240 $^{a,b,d,e,f***;c**}$	4910.17 ± 76.92 ^{a,b,g***}	1011.49 ± 124.02 ^{a,b,g***}	1391.58 ± 1456.87 ^{a,b,g***}	2435.74 ± 2 519.70 $^{a,b***;g**}$	15656.76 ± 466.5 $^{\tau***}$	38037.93 ± 519.71 $^{\tau***}$
TAG(O-)	3	2.42 ± 0.19 ^{a,b***}	1.48 ± 0.22 ^{a,b***}	3.08 ± 0.39 ^{a,b***}	1.19 ± 0.09 ^{a,b***}	2.65 ± 0.46 $^{a***;b**}$	46.83 ± 8.32 $^{a,d,e,f,g***;c**}$	133.93 ± 14.87 $^{\tau***}$
Subtotal GL	67	18616 ± 1038 $^{a***;b**;d,e*}$	5892 ± 358 ^{a,b***}	4796 ± 512 $^{a,b***;g*}$	2850 ± 241 $^{a,b***;g*}$	4958 ± 494 ^{a,b***}	34119 ± 3394 $^{a,c,d,e,f***;g**}$	93180 ± 6763 $^{\tau***}$
Sterol lipids								
COH	1	5912.37 ± 297.33 $^{a,b,c,d***;e**;f*}$	8819.47 ± 542.59 $^{a,b,c,d,e***;g*}$	3481.39 ± 349.42 $^{f***;g**;b*}$	1171.76 ± 69.38 ^{f,g***}	1818.28 ± 230.43 ^{f,g***}	808.01 ± 169.07 $^{f,g***;e*}$	2540.08 ± 325.85 ^{f,g***}
Desmosterol	6	18.84 ± 0.88 $^{a,b,c,d,e***;f**}$	13.45 ± 0.71 ^{g**}	12.01 ± 0.40 ^{g***}	9.36 ± 0.11 ^{g***}	9.21 ± 0.08 ^{g***}	12.35 ± 1.62 ^{g***}	11.27 ± 1.01 ^{g***}
OHC	10	15.95 ± 1.14 $^{\tau***}$	10.33 ± 0.38 $^{a,b,g***;c**}$	9.70 ± 0.42 $^{g***;a,b**}$	8.22 ± 0.78 $^{g***;a,b*}$	6.10 ± 0.33 $^{g***;f**}$	4.50 ± 0.72 $^{f,g***;e**;d*}$	4.17 ± 0.27 $^{f,g***;e**;d*}$
CE	27	3925.98 ± 236.69 $^{\tau***}$	818.25 ± 167.96 $^{g***;b,d*}$	498.76 ± 49.63 ^{g***}	123.59 ± 11.11 ^{g***}	125.52 ± 12.68 ^{g***}	69.39 ± 6.85 ^{g***}	117.9 ± 14.28 ^{g***}
oxCE	2	71.34 ± 4.97 $^{\tau***}$	33.52 ± 2.34 ^{g***}	24.13 ± 0.82 ^{g***}	31.09 ± 0.65 ^{g***}	29.40 ± 0.93 ^{g***}	42.15 ± 6.86 ^{g***}	39.62 ± 3.56 ^{g***}
Subtotal ST	46	317 ± 413 ^{a,b,c,d,e,***}	447 ± 620 ^{a,b,c,d,e,***}	178 ± 251 $^{b,f,g***;d**;c*}$	61.4 ± 82.1 $^{f,g***;e**;}$	93.5 ± 134 $^{f,g***;e*}$	42.4 ± 66.1 ^{e,f,g***}	130 ± 188 ^{f,g***}
Prenol Lipids								
Ubiquinone	1	238.41 ± 25.87 ^{e,f***}	621.84 ± 36.66 $^{\tau***}$	1165.46 ± 67.35 $^{\tau***}$	55.49 ± 5.78 ^{e,f***}	103.36 ± 15.10 ^{e,f***}	5.82 ± 0.37 ^{e,f***}	6.13 ± 0.40 ^{e,f***}
Subtotal Pr	1	238.41 ± 25.87 ^{e,f***}	621.84 ± 36.66 $^{\tau***}$	1165.46 ± 67.35 $^{\tau***}$	55.49 ± 5.78 ^{e,f***}	103.36 ± 15.10 ^{e,f***}	5.82 ± 0.37 ^{e,f***}	6.13 ± 0.40 ^{e,f***}

Glycerophospholipids								
LPC	61	469.32 ± 75.39 a,b,c,d***;e,f**	181.22 ± 17.31 g**;b,d*	248.78 ± 41.13 g**;b*	27.19 ± 1.50 g**;f*	62.66 ± 7.68 g***	15.83 ± 2.25 g***;e,f*	60.62 ± 6.15 g***
LPC(O-)	10	0.86 ± 0.11 f***;b**	2.25 ± 0.14 τ***	0.49 ± 0.07 f***	0.28 ± 0.03 f***	0.49 ± 0.05 f***	0.17 ± 0.02 f***	0.65 ± 0.08 f***
LPC(P-)	6	0.07 ± 0.007 c,d,e,f***	0.99 ± 0.06 a,b,d,g***;c*	0.83 ± 0.09 a,b,g***	0.60 ± 0.05 b,f,g***;a**	0.71 ± 0.09 a,b,f,g***	0.05 ± 0.01 c,d,e,f***	0.18 ± 0.03 c,e,f***d**
LPE	14	513.26 ± 46.99 τ***	140.99 ± 10.00 g***;b,d**;a*	142.41 ± 15.62 g***;b*	21.27 ± 1.28 g***;f**	46.98 ± 6.09 g***	12.13 ± 1.82 g***;f**;e*	25.37 ± 2.34 g***;f*
LPE(P-)	4	0.57 ± 0.07 e,f***;c**	11.99 ± 0.88 τ***	7.98 ± 0.88 a,b,d,f,g***;c*	1.94 ± 0.16 e,f,g***	4.05 ± 0.45 f***;b,g**;e*	0.46 ± 0.05 e,f***;c**	1.73 ± 0.25 e,f***
LPI	8	17.89 ± 1.46 τ***	3.74 ± 0.27 g***;b*	1.90 ± 0.16 g***	0.50 ± 0.03 g***	0.67 ± 0.05 g***	0.31 ± 0.04 g***;f*	0.58 ± 0.06 g***
LPS	4	0.37 ± 0.036 b,d***;c**	0.33 ± 0.03 b,d***;c*	0.30 ± 0.02 b**	0.17 ± 0.02 f,g***	0.21 ± 0.02 g**;f*	0.12 ± 0.02 f,g***;e**;a*	0.27 ± 0.02 b*
PC	68	9216.98 ± 587.49 a,b,c,d***; e,f**	5909.85 ± 260.94 a,b,d***; c,g**	7041.58 ± 663.25 a,b,d***; g**;c*	3033.14 ± 98.35 e,f,g***;b**	3910.61 ± 524.04 b,g***;f**;a,e*	297.12 ± 46.39 c,e,f,g***;d**	948.94 ± 106.52 e,f,g***;c*
PC(O-)	22	50.78 ± 3.98 a,b,f***	93.52 ± 5.32 τ***	36.10 ± 4.02 f***;b**	33.50 ± 0.97 f***;b**	34.98 ± 6.29 f***;b**	3.12 ± 0.42 f***;c,d**	15.37 ± 2.51 f***
PC(P-)	26	25.24 ± 1.59 d,e***;f**;c*	101.52 ± 7.28 b***;a,g**	230.80 ± 25.31 a,b,g***	159.85 ± 7.76 a,b,g***	139.06 ± 30.22 a,b**,g*	3.07 ± 0.46 d,e,f***;c**	12.10 ± 1.94 d,e***;c,f**
PE	37	8768.60 ± 578.37 τ***	5082.89 ± 235.50 a,b,c,d,g***	5383.97 ± 538.30 a,b,c,d,g***	726.62 ± 36.58 e,f,g***	1093.26 ± 186.78 e,f,g***	78.81 ± 11.04 e,f,g***	278.35 ± 31.27 e,f,g***
PE(O-)	14	14.20 ± 0.87 e,f***	72.24 ± 3.61 a,b,c,d,g***	72.79 ± 6.93 a,b,c,d,g***	17.00 ± 1.01 e,f,g***	32.84 ± 6.43 b,e,f,g***;a**	0.81 ± 0.10 c,e,f,g***	3.48 ± 0.53 e,f,g***;c**
PE(P-)	55	478.16 ± 29.06 e,f***	2292.72 ± 135.62 a,b,g***;d**;c*	4610.95 ± 452.93 a,b,c,d,g***	1087.56 ± 49.52 e***;f**	1383.14 ± 233.21 e***;f*	54.96 ± 7.64 e,f***	262.24 ± 49.14 e,f***
PG	4	94.59 ± 6.03 e***	80.71 ± 4.70 b,e**;a*	449.30 ± 43.05 a,b,c,d,g***;f**	52.52 ± 3.15 e***	66.37 ± 8.47 e***	1.37 ± 0.17 e***;f**	3.78 ± 0.31 e***;f*
PI	27	3151.23 ± 220.17 τ***	1467.80 ± 68.51 a,b,d,g***;c**	1072.04 ± 118.61 b,g***;a**	499.78 ± 23.44 f,g***	661.05 ± 102.45 g***;f**	36.13 ± 4.95 e,f,g***	111.45 ± 13.45 f,g***;e**
PS	7	537.89 ± 34.65 a,b,d,f***;c**	1147.16 ± 46.57 τ***	396.24 ± 36.33 f,g***;b**	138.72 ± 5.93 f,g***	207.00 ± 27.26 f***;g**	37.58 ± 5.48 f,g***;e**	134.36 ± 18.32 f,g***
Subtotal GP	367	23340 ± 1398 a,b,c,d***;f**	16590 ± 723 a,b,c,d***;g**	19696 ± 1903 a,b,c,d***	5787 ± 216 e,f,g***	7626 ± 1122 e,f,g***;b**	542 ± 79 e,f,g***;c**	1859 ± 224 e,f,g***

Sphingolipids								
Sph	3	75.88 ± 4.14 a,b,c,d***;e*	89.82 ± 4.50 a,b,c,d,e***	61.38 ± 4.12 b,c,d,f***;a**;g*	29.42 ± 0.51 e,f,g***	31.94 ± 1.49 e,f,g***	29.55 ± 0.93 e,f,g***	35.46 ± 2.42 f,g***;e**
Sph1P	5	2.34 ± 0.27	2.55 ± 0.21	2.54 ± 0.25	2.19 ± 0.13	2.26 ± 0.15	2.16 ± 0.23	2.72 ± 0.23
Cer	54	801.58 ± 40.03 τ***	498.95 ± 35.17 τ ***	139.45 ± 12.28 f,g***	66.66 ± 1.98 f,g***	85.42 ± 10.38 f,g***	83.02 ± 10.60 f,g***	176.34 ± 17.53 f,g***
Cer1P	1	0.05 ± 0.007	0.06 ± 0.005	0.05 ± 0.007	0.04 ± 0.003	0.04 ± 0.004	0.04 ± 0.005	0.05 ± 0.005
dhCer	6	12.37 ± 0.53 a,b,c,d,e,f***	6.55 ± 0.37 a,b,c,d,g***;e**	3.80 ± 0.21 g***;f**;b*	2.58 ± 0.13 f,g***	2.78 ± 0.14 f,g***	1.85 ± 0.20 f,g***;e*	2.83 ± 0.14 f,g***
SM	44	1067.38 ± 65.02 f***;b**;d*	3340.50 ± 186.96 a,b,c,d,e,g***	598.39 ± 60.38 f***	216.23 ± 6.77 f***;g*	301.59 ± 34.75 f***	88.56 ± 13.47 f***;g**	284.94 ± 36.42 f***
MHC	14	113.79 ± 9.33 b,d***;e**	89.00 ± 7.87 b,c*	16.30 ± 2.18 c***;g**	7.97 ± 0.68 c,g***	146.99 ± 29.12 b,d,e***;a**;f*	5.89 ± 0.52 c,g***;f*	45.63 ± 11.70 c**
DHC	10	17.43 ± 1.65 a,b,d***	12.64 ± 0.66 b***;a**;d*	20.21 ± 1.89 a,b,d***	6.87 ± 0.34 c,e,f,g***	20.79 ± 1.77 a,b,d***	1.69 ± 0.21 c,e,f,g***	4.80 ± 0.73 c,e,g***;f**
THC	6	1.07 ± 0.13	1.32 ± 0.12	1.17 ± 0.11	0.98 ± 0.13 a*	0.79 ± 0.08 a**	1.03 ± 0.06	1.59 ± 0.11 c**;d*
GM	8	17.45 ± 0.89 b***;d,e**;a*	17.01 ± 0.89 a,b,d***	31.53 ± 2.43 a,b,c,d***;g**	6.75 ± 0.55 e,f***;g**	13.91 ± 1.40 f***;b**	2.42 ± 0.28 e,f,g***;c**	7.44 ± 0.98 e,f***;g*
Sulfatides	6	0.33 ± 0.03 c***;f**	3.47 ± 0.68 b,d,e,g**	0.30 ± 0.05 c***;f**	0.27 ± 0.03 c***;f**	4.36 ± 0.96 a,b,d,e,g***	0.12 ± 0.02 c***;f**	0.72 ± 0.23 c***
Subtotal SP	157	2110 ± 102 τ***	4062 ± 216 τ***	875 ± 81.4 f,g***;b**;d*	340 ± 8.16 f,g***;e*	608 ± 68.9 f,g***	216 ± 24.4 f,g***;e**	563 ± 59.9 f,g***
Total lipids detected								
Total	652	54250 ± 2462 a,c,d,e***; b,f*	36874 ± 1833 a,d***; c,g*	30564 ± 2836 a,g***; d**	10528 ± 365 a,b,f,g***	15404 ± 1681 a,g***; b,d**	35823 ± 3658 a,d***; c,g*	98328 ± 7321 τ***

Values are expressed as mean ± SEM from 8-10 animals. Statistical analysis of each subclass concentrations across tissues analyzed by one-way ANOVA had a p value<0.001 in every subclass except for those species conjugated with phosphate. Sphingosine phosphate (Sph1P) p value was 0.7105 and for ceramide phosphate (Cer1P) p value was 0.2303. Post hoc Tukey multiple test was performed for each tissue and organ. Statistical significance is represented in the table by letters: a means is significantly different respect to subcutaneous adipose tissue (sat), b respect to visceral adipose tissue (vat), c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001.

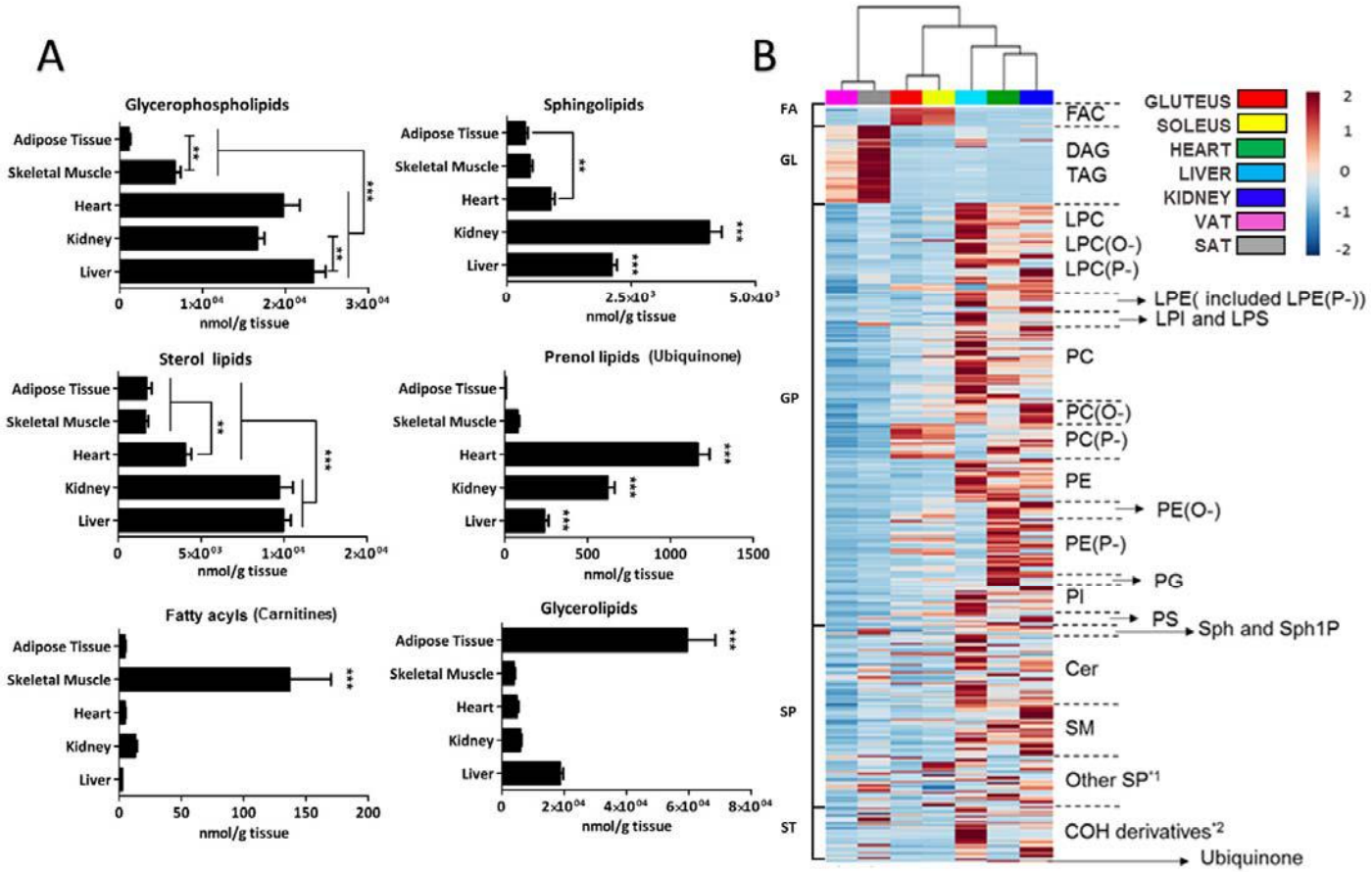

Figure 18. Lipid concentration and distribution across the different organs and tissues analyzed by a targeted lipidomic approach. A. Graph representation of average concentration in nmol/g of tissue of compounds detected by targeted lipidomics grouped by categories. Error bars denote SEM across 7-9 animals. Adipose tissue is comprised of VAT and SAT while gluteus and soleus comprised skeletal muscle. Statistical analysis performed was one-way ANOVA and post hoc Tukey multiple test. *p<0.05, **p<0.01 and ***p<0.001. B. Heat map of abundance of the detected lipid species across samples. Each line represents one compound colored by its normalized abundance to internal standard, baseline and mean across samples. The scale from 2 to -2 represents the normalized abundance of each lipid in arbitrary units[*1] gangliosides and sulfatides; [*2] hydroxycholesterol, desmosterol and cholesteryl esters.

The molar fractions of the number of carbon atoms and the degree of unsaturation of the FAC was similar between tissues (Figure 19B). Saturated FAC were more abundant, with the long chain species being more abundant, in particular acylcarnitine(16:0) and (18:0). Oppositely, acylcartinine(13:0) present lower concentrations in all the tissues (Table S6). FAC of 18 carbons with MUFA and PUFA chains were as well present in liver, heart, skeletal muscle and WAT.

Regarding GL category, a similar situation was observed, where WAT presented higher concentration of all of the subclasses (DAG, TAG and TAG(O-)) compared to the other tissues (Figure 19A). Further, it can be seen how GL abundance was higher in SAT rather than VAT for all of the subclasses. Apart from the differences with the WAT, total concentration of TAG in the liver was statistically higher compared to skeletal muscle, heart and kidney (Figure 19A). Concerning DAG species, none of them presented significant differences between both types of skeletal muscle and cardiac tissue. The most abundant DAG species in WAT were DAG(16:0/18:2), (18:1/18:2) and (18:1/18:1) (Table S8). DAG from 30 carbons to 38 were equally distributed in both types of WAT, while both DAG(38:6), DAG(18:2/20:4) and DAG(18:0/22:6), were particularly abundant in liver, DAG(16:0/16:0) in kidney as well as DAG(18:0/20:4), which also had high levels in cardiac and skeletal muscle (Table S8). Both types of skeletal muscle, gluteus and soleus, presented the same molar fraction pattern according the number of carbon atom and unsaturation degree (Figure 19B). For all the TAG species analyzed, SAT presented significantly a higher concentration except for TAG(18:0/18:0/18:0) equally concentrated in SAT and VAT. Regarding VAT, all the TAG species were more concentrated in this tissue compared to the other for 3 species, TAG(18:1/18:1/20:4), TAG(18:1/18:1/22:6) and TAG(18:2/18:2/20:4), higher in liver than in VAT. The most abundant TAG species in WAT were TAG(16:0/18:1/18:1), (16:0/18:1/18:2) and (18:1/18:2/18:2) (Table S8). TAG with 50 and 54 carbons and PUFA chains were abundant in all tissues. The configuration of number of carbon atoms and unsaturation degree was similar in every tissue, especially between both types of WAT (Figure 19B). Finally, all the three lipid species of TAG(O-) were more concentrated in WAT respect the other tissues, where no differences were found between VAT and SAT (Table S8 and S11).

4.1.3.2. Glycerophospholipids across mammalian tissues

GP category was the best-represented category in this targeted lipidomic analysis due to their importance role as structural and signaling lipids. The total concentration of the GP category is

represented in

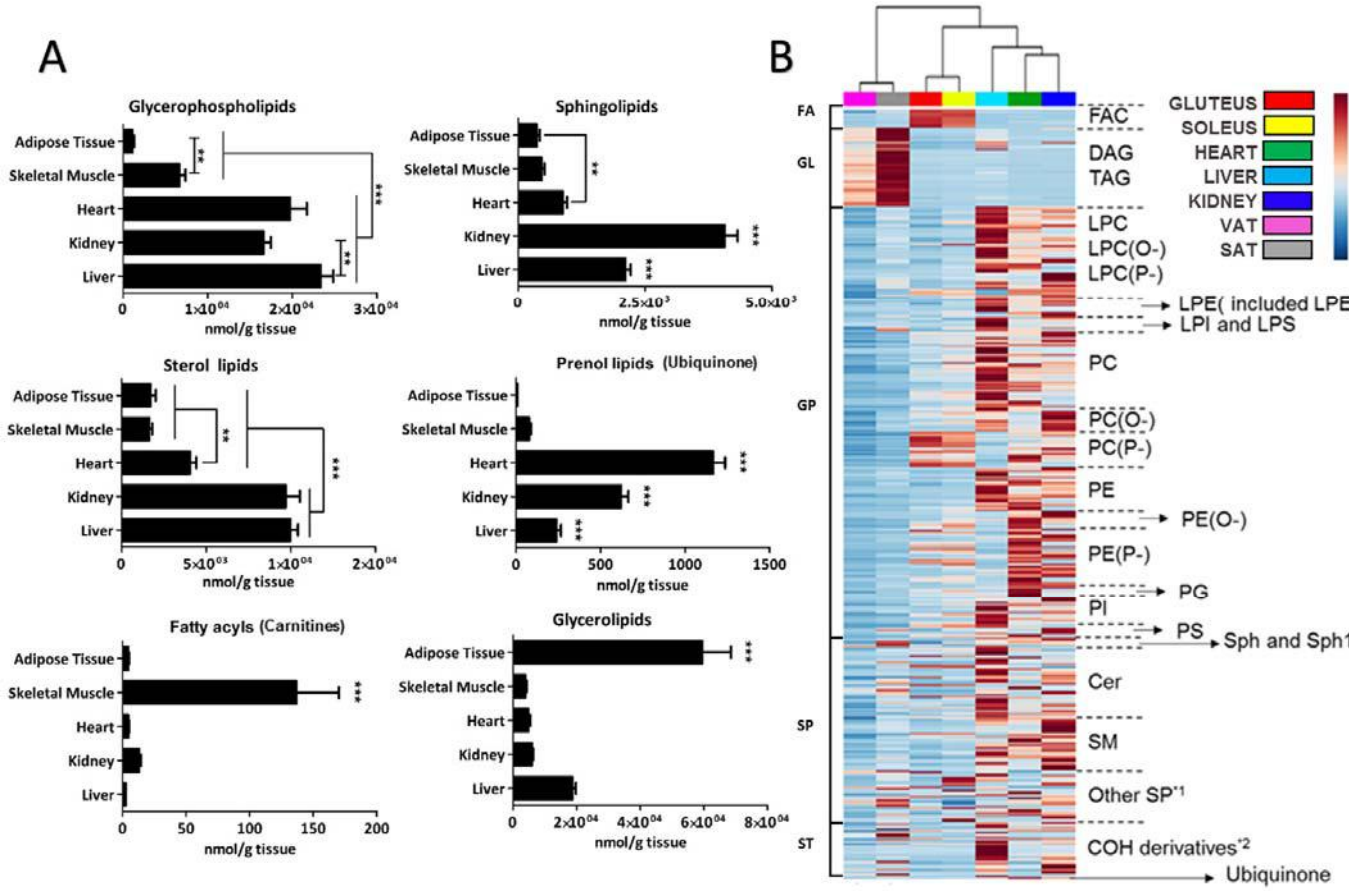

Figure 18, where can be appreciated a difference between on one hand heart, liver and kidney and on the other hand skeletal muscle and WAT.

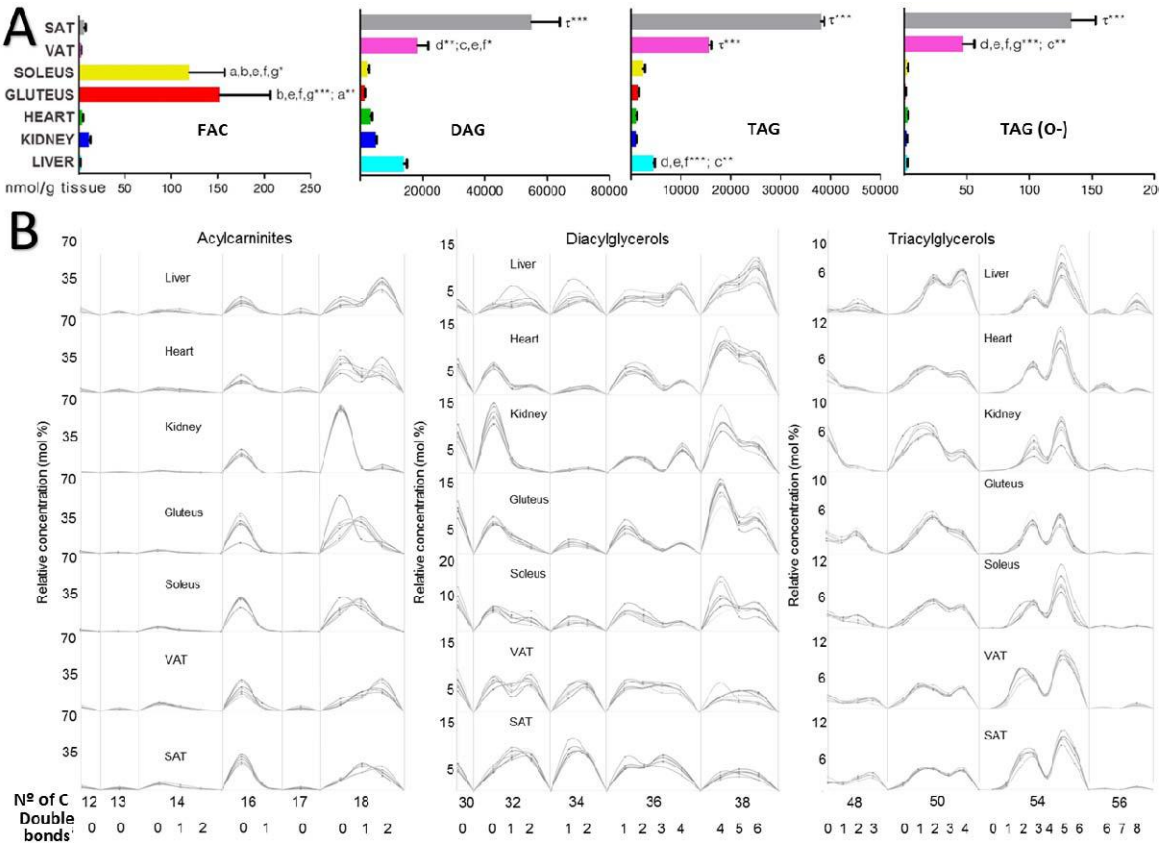

Figure 19. Fatty acylcarnitines and glycerolipids within mammalian tissues detected by targeted lipidomic analysis. A) FAC, DAG and TAG concentrations across tissues. Values are expressed as mean ± SEM from 8-10 animals. Statistical analysis was One-way anova and post hoc Tukey significance is represented in the bar chart. a significantly different respect to subcutaneous adipose tissue (SAT), b respect to visceral adipose tissue (VAT), c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001 D) FAC, DAG and TAG lipid composition within mammalian tissues. Relative concentration of lipids normalized per sample to the total abundance within this lipid class to obtain molar fractions. Each solid line indicated tissue from an individual rat. Gray vertical lines separate lipids by total number of acyl chain carbons. The number of double bonds is indicated below within each group.

Additionally, among heart, liver and kidney; the concentration of total GP detected only differed between liver and kidney. Respect skeletal muscle, it had a higher concentration of total GP than WAT

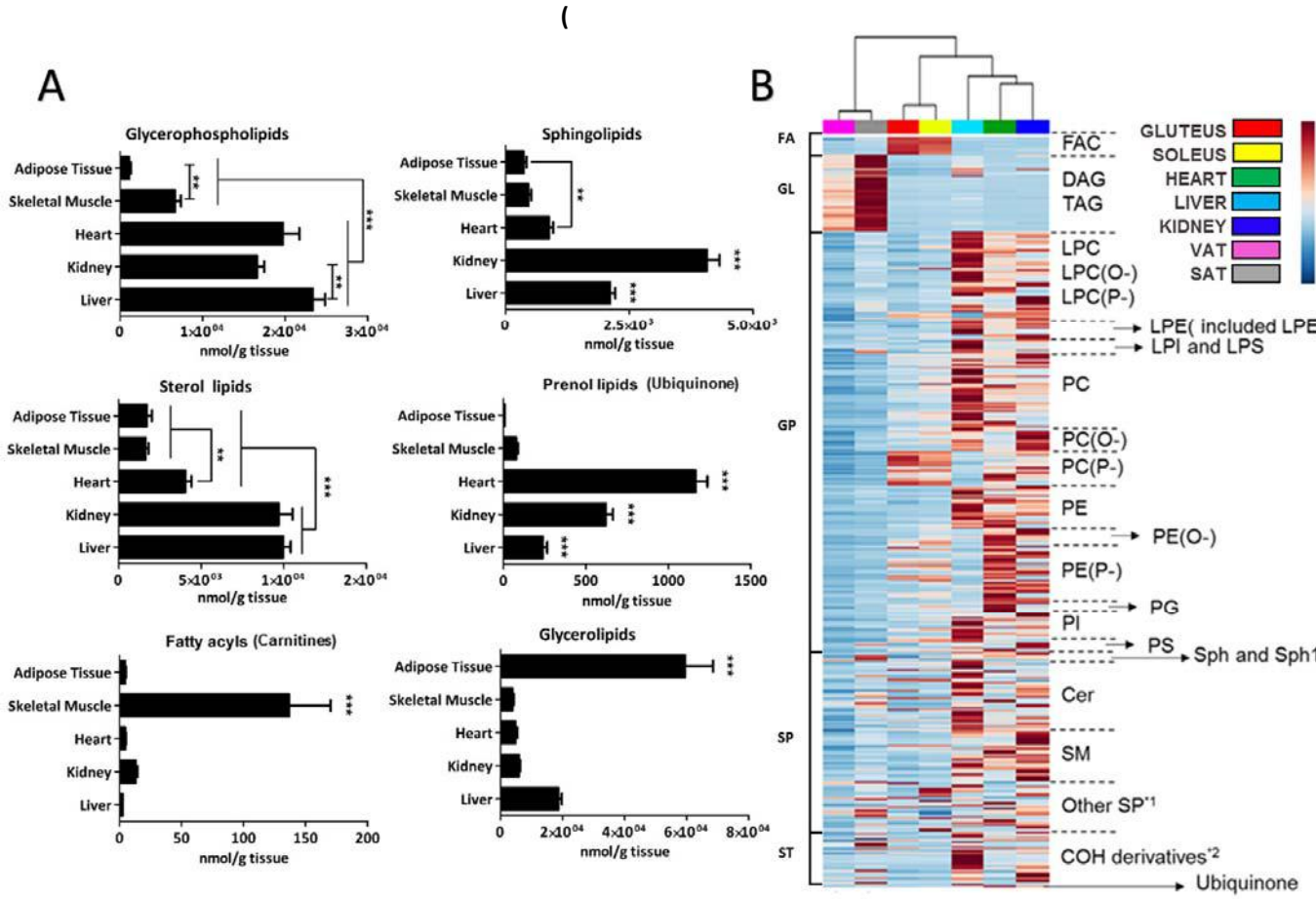

Figure 18). The concentration values shared by all tissues followed the next order: PC > PE > PI > PS. By tissues, the total concentration of GP was: liver > heart > kidney > soleus > gluteus > SAT > VAT (Table 14). These differences in the total GP concentrations are not maintained in every subclass analyzed. Glycerophosphocholines (PC) and ethanolamines (PE) abundance were higher in liver while the ether lipids –showed in the next section- of these species were mostly in heart and kidney. Heart was the tissue where glycerophosphoglycerol species (PG) were more concentrated followed by kidney; while glycerophosphoinositol (PI) species were more concentrated in liver and glycerophosphoserines (PS) in kidney (Figure 20A). Thus, the predominant PC molecular species among tissues were PC(16:0/18:2) and PC(16:0/18:1); for PE, PE(18:0/20:4) and PE(16:0/22:6); for PI, PI(18:0/20:4); and for PS, there were differences across tissues. PS(36:2) was for WAT, PS(38:4) for liver and kidney and PS(40:6) for muscle tissues (heart, gluteus and soleus) (Table S14). The number of carbon atoms and unsaturation degree patterns for PC were similar between hepatic, cardiac and renal tissues except for the PC(32:0), more abundant in kidney as well as in WAT. Both types, SAT and VAT have the same pattern and, likewise both skeletal muscle shared a different configuration (Figure 20B). For all the 68 PC species analyzed, none was significantly different between SAT and VAT and only 4 of them were

different between soleus and gluteus. Differences between cardiac and skeletal muscle were higher with a mean of 33.82% of significantly different PC species compared to total PCs. More than half of the PC lipid species were significantly different in hepatic tissue compared with the other tissues being PC(16:0/18:2), (16:0/20:4) and (18:0/20:4) the most concentrated PC species in liver (Table S15). The configuration of number of carbon atoms and unsaturation degree in liver for PE was similar to cardiac and skeletal muscle but liver had lower levels of PE(40:6). SAT and VAT had the same configuration while kidney presented the highest abundance of PE(38:4) (Figure 20B). In fact, PE(18:0/20:4) was one of the most concentrated PE species. No differences were found between SAT and VAT or between gluteus and soleus in any of the PE species (Table S15). The pattern of number of carbon atoms and unsaturation degree for PG was the same for all the tissues except for PG(36:2) lower in kidney and liver (Figure 20B). No differences were found between SAT and VAT or between gluteus and soleus. The most concentrated PG in all tissues was PG(34:1) followed PG(36:2) and PG(34:2) (Table S14). Regarding PI species, the number of carbon atoms and unsaturation degree pattern was similar between all the tissues analyzed except for PI(34:0) higher in kidney, PI(35:2) in VAT and PI(40:6) in both types of skeletal muscle (Figure 20B). In hepatic tissue, where almost 70% of the lipid species were significantly different from the other tissues, PI(18:0/20:4), the most concentrated specie was followed by PI(16:20:4) and PI(36:2) (Table S14). In the PS subclass, kidney and liver had the same number of carbon atoms and unsaturation degree pattern, while cardiac and skeletal muscle presented a different configuration as well as both types of WAT (Figure 20B). Nevertheless, concentration of three of the seven PS species analyzed was significantly different between VAT and SAT as well as between cardiac and skeletal muscle (Table S15). Inside the GP species of the targeted analysis several LGPs conjugated with choline (LPC), ethanolamine (LPE), inositol (LPI) and serine (LPS) were detected. The concentration values shared by all tissues followed the next order: LPC > LPE > LPI > LPS; while by tissues, the total concentration of LGP was: liver > heart > kidney > soleus > gluteus > SAT > VAT (Table 14).

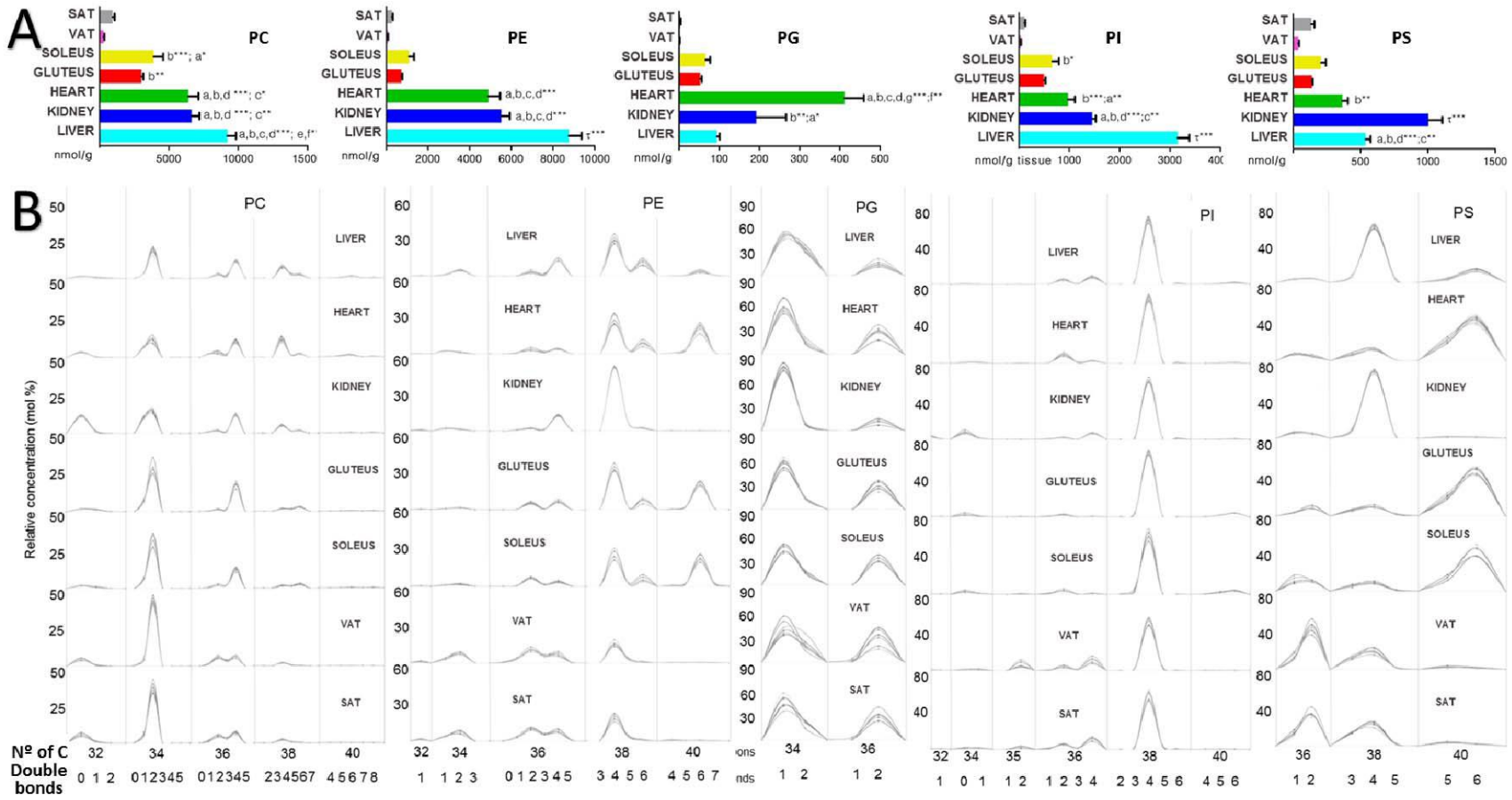

Figure 20. Glycerophospholipid within mammalian tissues detected by targeted lipidomic analysis. A) Total concentration of different GP subclasses (PC,PE,PG,PI and PS). Values are expressed as mean ± SEM from 8-10 animals. Statistical analysis was One-way anova and post hoc Tukey significance is represented in the bar chart. a significantly different respect to SAT, b respect to VAT, c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001. B) Relative concentration of lipids normalized per sample to the total abundance within this lipid class to obtain molar fractions. Each solid line indicated tissue from an individual rat. Gray vertical lines separate lipids by total number of acyl chain carbons. The number of double bonds is indicated below within each group**.**

Liver showed a statistically higher concentration compared to the other tissues for LPC, LPE and LPI species (Figure 21A). Following the hepatic tissue, heart and kidney total concentration of LPC and LPE were statistically different respect of VAT in the case of cardiac tissue and respect of both types of WAT and gluteus in the case of renal cortex (Figure 21A). The LPI total concentration was statistically higher in liver although comparing kidney and VAT, renal cortex presented as well a significantly higher concentration (Figure 21A). Concerning to LPS species, both types of WAT presented differences in the LPS total concentration being higher in SAT along with the other tissues compared to VAT and skeletal muscle (Figure 21A). The LGP pattern of number of carbon atoms and unsaturation degree for LPC and LPE species was similar between them (Figure 21B). Cardiac and hepatic tissue shared the same pattern being the predominant species those with (20:4) as PUFA chain. In hepatic tissue, fatty acid chains of (22:6), (20:4) and (18:0) were the constituents of the most concentrated LPC and LPE species.

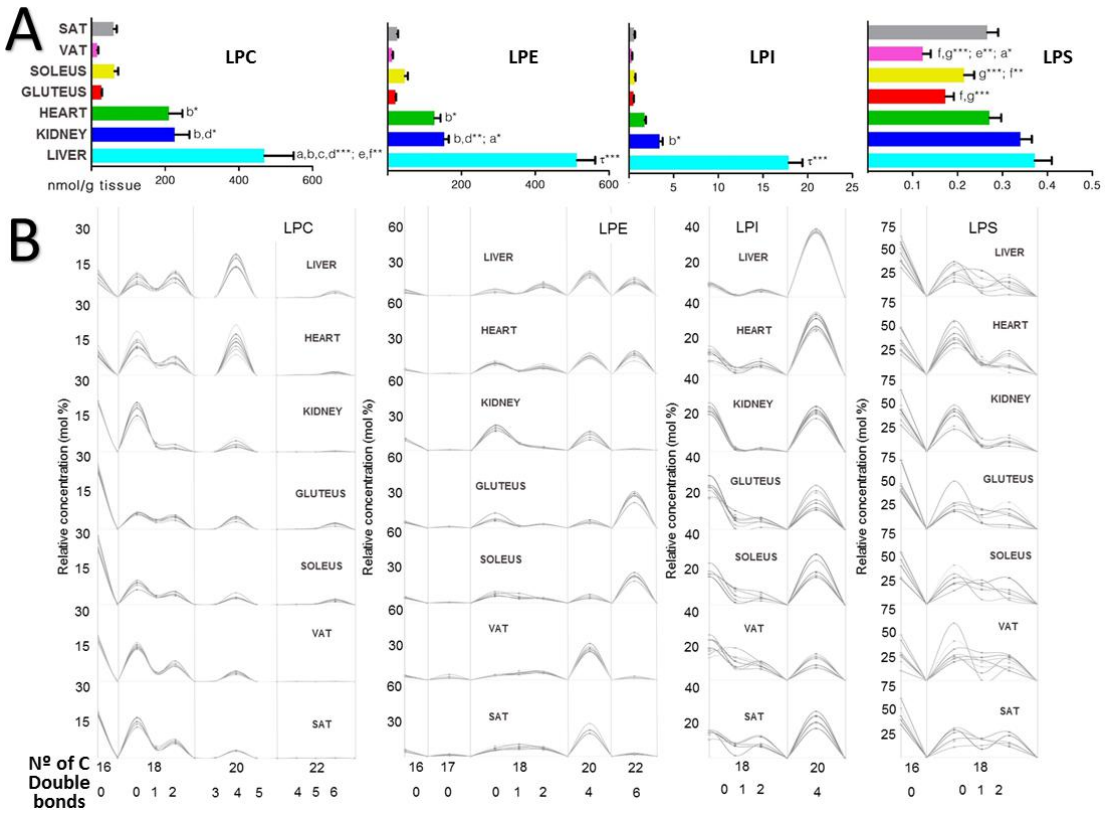

Figure 21. Lysoglycerophospholipid within mammalian tissues detected by targeted lipidomic analysis. A) Total concentration of different LGP subclasses (LPC,LPE, LPI and LPS). Values are expressed as mean ± SEM from 8-10 animals. Statistical analysis was One-way anova and post hoc Tukey significance is represented in the bar chart. a significantly different respect to subcutaneous adipose tissue (SAT), b respect to visceral adipose tissue (VAT), c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001. B) Relative concentration of lipids normalized per sample to the total abundance within this lipid class to obtain molar fractions. Each solid line indicated tissue from an individual rat. Gray vertical lines separate lipids by total number of acyl chain carbons. The number of double bonds is indicated below within each group.

Cardiac tissue presented differences compared to both types of skeletal muscle because soleus presented a more similar profile to cardiac tissue than gluteus. For LPE species, 57.14% of the detected species were significantly different between heart and gluteus while only the two isoforms of LPE(18:0) were different between soleus and cardiac tissue (Table S13). Despite those differences with cardiac tissue, both type of skeletal muscle shared the same pattern of number of carbon atoms and unsaturation degree with the LPC(16:0) and LPE(22:6) as the predominant species (Figure 21B). Renal cortex had a specific configuration with higher molar fractions of SFA of 18 carbons in both LPC and LPE (Figure 21B). The most concentrated LPC species for kidney were LPC(16:0) and LPC(18:0) while the highest concentrations of LPE species in kidney were for LPE(20:4) and LPE(18:0) Table S12. Finally, LPC and LPE configuration in both types of WAT showed SFA of 16 and 18 carbons were the most abundant species in the LPC subclass while for the LPE subclass, the fatty acid chain (20:4) presented the highest abundance in VAT and SAT (Figure 21B). LPC(22:0) was the only compound significantly different between VAT and SAT for LPC species and none of the LPE species were different between them Table S13. Amongst the LPI lipid species, those with (20:4) as fatty acid chain were more abundant than the 18 carbon atoms species in the hepatic and cardiac tissue while in renal cortex, skeletal muscle and WAT both, LPI(20:4) and (18:0), were the predominant species (Figure 21B). No significant differences were found between types of WAT or between muscular tissues Table S13. Finally, LPS pattern of number of carbon atoms and unsaturation degree seem to be specific for each individual rather than tissue-specific, even so saturated species of 16 carbon atoms presented the highest molar fractions for every tissue (Figure 21B).

4.1.3.2.1. Ether lipids across mammalian tissues

137 ether lipids of PE and PC were detected, more accurately, fourteen PE(O-), fifty-nine PE(P-); thirty two PC(O-) and thirty two PC(P-). The ether lipids detected were present in different concentration across tissues depending on their GP type (PE or PC) and ether bond (alkyl or alkenyl) (Figure 22A and C). Thus, the highest content was present in heart, where ether lipids represented 25.18% of the total GPs, followed by skeletal muscle (22.42% for gluteus and 20.86% for soleus), WAT (15.90% for SAT and 11.55% for VAT), kidney (15.48%), and finally with the lowest content in liver where ether lipid represented 2.5% of total GPs (Table 14). The main chemical form is represented by ether lipids of PE with a content ranging from 80% in liver to 94% in heart of total ether lipids. According to the GP type, ether lipids of PE percentage of total amount of PE, show a relevant presence for all tissue (60.3% gluteus, 56.4% soleus, 48.8% SAT, 46.5% heart, 41.4% VAT, and 31.7% kidney), with the exception of liver where ether lipids of PE

only represent about 5.4% of total PE in each tissue (Table 14). The most concentrated individual lipid species in all tissues were PE(P-16:0/20:4), PE(P-16:0/22:5n3), PE(P-16:0/22:6), PE(P-18:0/20:4), PE(P-18:0/22:6) and PE(P-18:1/20:4) (Table S16). Regarding ether lipids of PC, their concentration of the total amount of ether lipids in each tissue was 0.3% in liver, 1.17% kidney, 1.35% heart, 3.33% gluteus, 2.27% soleus, 1.14% VAT, and 1.47% SAT (Table 14). Both PC(P-16:0/20:4) and PC(P-16:0/22:6), followed by PC(P-16:0/16:0), PC(P-16:0/18:2) and PC(P-16:0/18:1) were the predominant molecular species (Table S16). According to the ether bond, alkyl species (O-) presented significantly higher levels in renal cortex compared to the other tissues for those species with choline (LPC(O-) and PC(O-)). In the case of PE(O-), heart and kidney levels were significantly higher compared to the other tissues (Figure 22A). The most concentrated LPC(O-) species in every tissue were LPC(O-16:0), (O-18:0) and (O-18:1) (Table S16). The PC(O-) number of carbon atoms and unsaturation degree pattern was different across tissues. PC(O-34:1), PC(O-36:4) and PC(O-38:5) were present in every tissue but the last two PC(O-) species were less abundant in skeletal muscle compared to the other tissues while PC(O-38:6) levels were higher in gluteus and soleus (Figure 22B). Between VAT and SAT there were no differences in any PC(O-) specie, while the differences between muscles were minimal. The highest concentration of PC(O-) species was found in the renal cortex tissue and almost every PC(O-) species were significantly different compared to the other tissues. PC(O-16:0/20:4) was the most concentrated in renal cortex as well as in hepatic and WATs (Table S16). Regarding the pattern of number of carbon atoms and unsaturation degree of the PE(O-) species, PE(O-38:4) was abundant in liver and kidney, PE(O-38:5) in both types of WAT, PE(O-38:6) in heart and skeletal muscle and lack of PE(O-) with 40 carbon atoms was characteristics of kidney (Figure 22B). None of the lipid species was statistically different between WAT or skeletal muscles types but half of the detected species were significantly different in cardiac and renal tissues compared to the other tissues (Table S17). Alkenyl species were more concentrated in skeletal muscle, especially those with choline (LPC(P-) and PC(P-)). PE(P-) species were more concentrated in heart and LPE(P-) levels were significantly higher in renal cortex compared to the other tissues (Figure 22C). PC(P-36:4) and PE(P-36:4) were present in every tissue but less abundant in skeletal muscle, where PE(P-38:5) and PE(P-40:6) were the most abundant species (Figure 22D). The forms alkyl- and alkenyl- LPC and LPE were minorities and all of them together represents the 0.006% in liver, 0.056% in kidney, 0.047% in heart, 0.048% in gluteus, 0.068% in soleus, 0.125% in VAT, and 0.137% in SAT respect the total amount of ether lipids in each tissue (Table 14). LPC(P-16:0) and LPE(P-16:0) were the most abundant species in every tissue except for liver, where LPE(P-18:0) was more concentrated (Figure 22D).

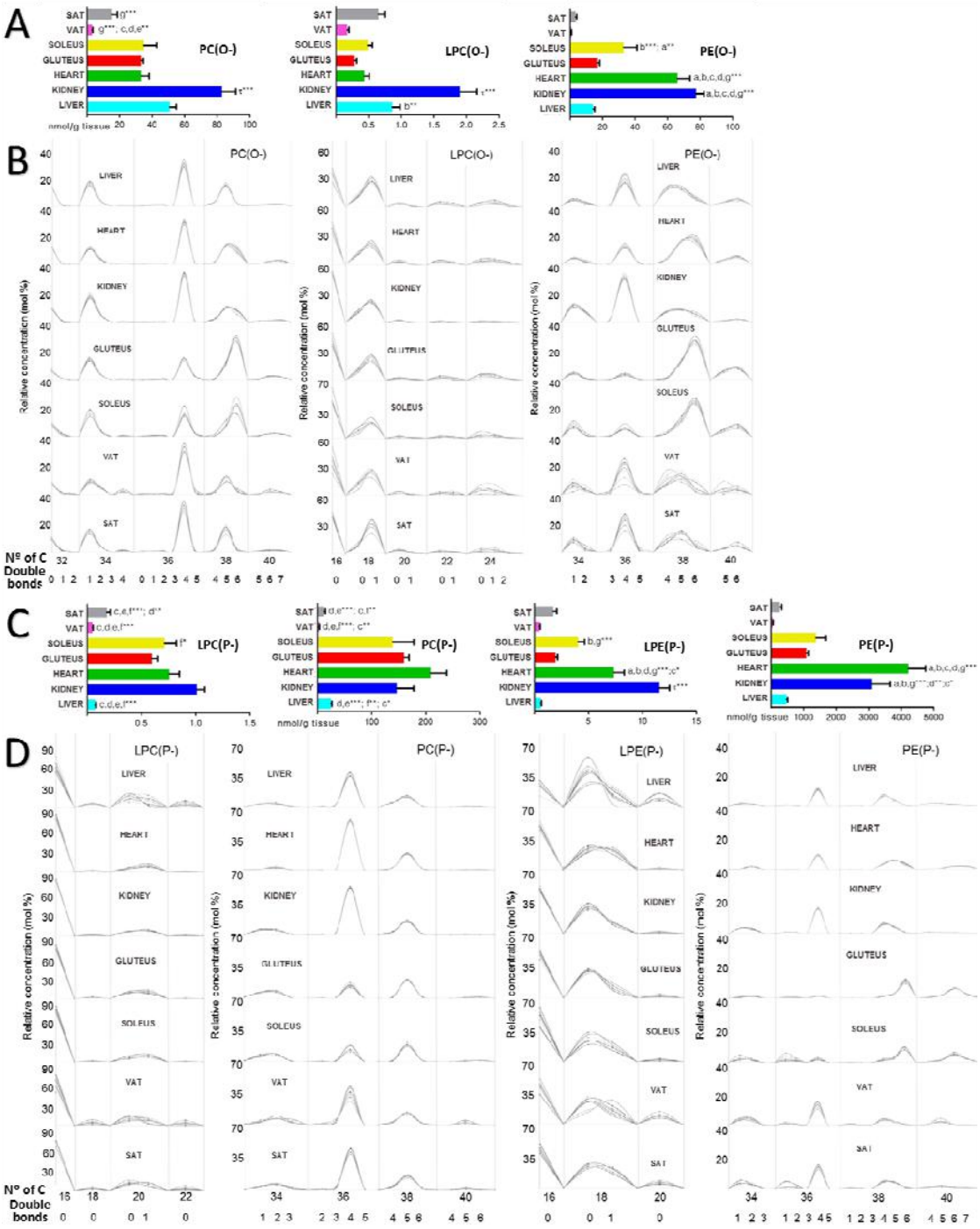

Figure 22. Ether lipids within mammalian tissues detected by targeted lipidomic analysis. A and C) Total concentration different subclasses of alkyl and alkenyl lipids, respectively. Values are expressed as mean ± SEM from 8-10 animals. Statistical analysis was one-way anova and post hoc Tukey significance is represented in the bar chart. a significantly different respect to SAT, b respect to VAT, c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001. B and D) Relative concentration of normalized alkyl and alkenyl, respectively, per sample to the total abundance within this lipid class to obtain molar fractions. Each solid line indicated tissue from an individual rat. Gray vertical lines separate lipids by total number of acyl chain carbons. The number of double bonds is indicated below within each group.

4.1.3.3. Sphingolipids across mammalian tissues

The lipid species from the SP category showed clear differences across tissues depending on the subclass as it can be seen in Figure 23A, C and E. The total concentration of SP followed the next order by tissues: kidney>liver>heart>soleus>SAT>gluteus>VAT; being ceramides (Cer) more concentrated in liver and SM in kidney. These results confirmed that the major SP in mammalian tissues was SM, with a range between 62 - 96% of total SP, followed by glycosphingolipids (monohexosylceramide, dihexosylceramide, and trihexosylceramide) (between 3-35%), gangliosides (GM) (0.5-5%), and finally sulfatides (0.03-0.9% of total SP). The highest concentration of SM was found in kidney followed by liver (Figure 23A), although the percentage of SM concentration respect of the total SP concentration was higher in gluteus (90.44% of total SP), heart (89.59%) and VAT (88.81%) than in liver where SM represented 87.67% of total SP (Table 14). The pattern of carbon atoms and unsaturation degree in kidney and liver was the same except for the 42 carbon atoms species, SM(42:1) was characteristic of liver while SM(42:2) was more concentrated in kidney. Both types of WAT shared the same pattern while muscular tissues showed similar patterns although SM(38:1) was higher in heart compared to skeletal muscle (Figure 23B). The most concentrated SM specie was SM(d18:1/16:0) in every tissue analyzed except for the skeletal muscle were the SM(d18:1/18:0) (Table S18). The species conjugated with phosphate (Sph1P and Cer1P) did not show differences across tissues while sphingosine (Sph) levels were significantly higher in heart, liver and kidney compared to VAT, SAT and both skeletal muscle types. Table S18 showed Sph and Sph1P species with (18:1) as fatty acid chain were the most concentrated, especially in renal cortex and the pattern composition of number of carbon atoms and unsaturation degree was similar in all the tissues (Figure 23B). Cer, including dihydroceramides (dhCer), were significantly higher in liver followed by kidney compared to the other tissues (Figure 23C and E). In Cer subclass, VAT and SAT had the same pattern of number of carbon atoms and unsaturation degree, skeletal muscle presented higher levels of Cer(36:1) and along with heart and both presented lower levels of Cer(38:1) (Figure 23D). Cer(d18:1/20:4) presented the highest concentration in every tissue specially in liver, heart and kidney while the most concentrated specie in VAT and SAT was Cer(d18:2/24:0) and in skeletal muscle Cer(d18:1/18:0) (Table S18). Inside the subclass of neutral glycosphingolipids, concentrations across tissues changed depending on how many conjugated hexoses molecules the lipid contains. Monohexosylceramide (MHC) were significantly higher in soleus compared to the other tissues except for the liver.

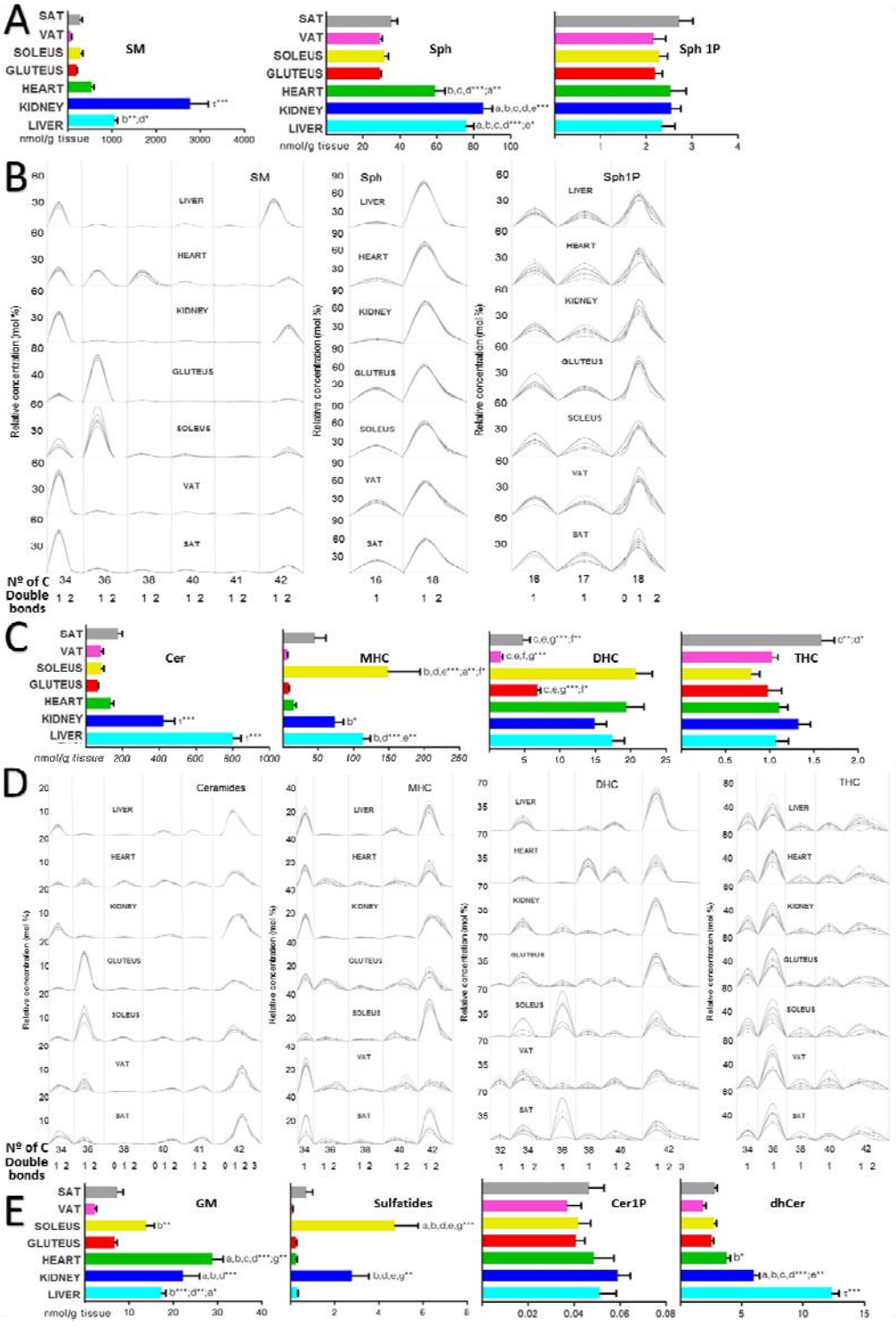

Figure 23. Sphingolipids within mammalian tissues detected by targeted lipidomic analysis. A, C and E) Concentration of sphingolipid subclasses. Values are expressed as mean ± SEM from 8-10 animals. Statistical analysis was One-way anova and post hoc Tukey significance is represented in the bar chart. a significantly different respect to subcutaneous adipose tissue (SAT), b respect to visceral adipose tissue (VAT), c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001. B and D) Relative concentration of lipids normalized per sample to the total abundance within this lipid class to obtain molar fractions. Each solid line indicated tissue from an individual rat. Gray vertical lines separate lipids by total number of acyl chain carbons. The number of double bonds is indicated below within each group.

Dihexosylceramide (DHC) concentrations were significantly lower in both types of WAT and gluteus while Trihexosylceramide (THC) were significantly more concentrated in SAT compared only to both types of skeletal muscle (Figure 23C). The MHC most concentrated species were Hex1Cer(d18:1/24:0) in liver, soleus and SAT; and Hex1Cer(d18:1/16:0) in heart, gluteus, kidney and VAT. Regarding the DHC subclass, Hex2Cer(d18:1/24:0) was the most concentrated specie in every tissue except for soleus, with Hex2Cer(d18:1/18:0) as the most concentrated DHC specie (Table S18). Finally, in the THC subclass the three most concentrated species in decreasing order for all tissues were Hex3Cer(d18:1/18:0), (d18:1/16:0) and (d18:1/24:0) (Table S18). Neutral glycosphingolipid composition seemed to be specific of each individual because of the heterogeneity on the abundance of the different lipid species across the animals. The patterns of number of carbon atoms and unsaturation degree for MHC and DHC species were different for each type of tissue while THC pattern was similar across tissues (Figure 23D). Regarding acidic glycosphingolipids, gangliosides (GM) were more abundant in heart followed by kidney and liver, while sulfatides were more concentrated in soleus and kidney compared to the other tissues (Figure 23E). However, the concentration of GM respect total SP was higher in all the muscle cells (heart, 4.72%; soleus, 2.84%; gluteus, 2.82%), followed by WAT (2.42% for VAT, and 2.15% for SAT) than in liver (1.43%) and kidney (0.49%). This pattern changed for sulfatides being the percentage of this subclass respect to total SP concentration higher in soleus followed by WAT (SAT>VAT) then gluteus, kidney, heart and finally liver (Table 14). Most of the GM detected were GM3 and the most concentrated GM specie in WAT, liver and kidney was GM3(d18:1/24:0). Though this specie was as well one of the three most concentrated in muscular tissues, GM3(d18:1/18:0) was the most concentrated in skeletal muscle and GM3(d18:1/20:0) in cardiac tissue. Finally, the sulfatides species presented differences between both types of skeletal muscles being more concentrated in soleus (Table S18). Sulfatide(d18:1:/24:0) was the most concentrated sulfatide in soleus while for the other tissues the hydroxyl form of this sulfatide presented higher concentrations (Table S18).

4.1.3.4. Sterol and prenol lipids across mammalian tissues

The lipid species of the ST category were more concentrated in kidney and liver compared to the other tissues. In turn, the concentration in heart was significantly higher compared to skeletal muscle and WAT

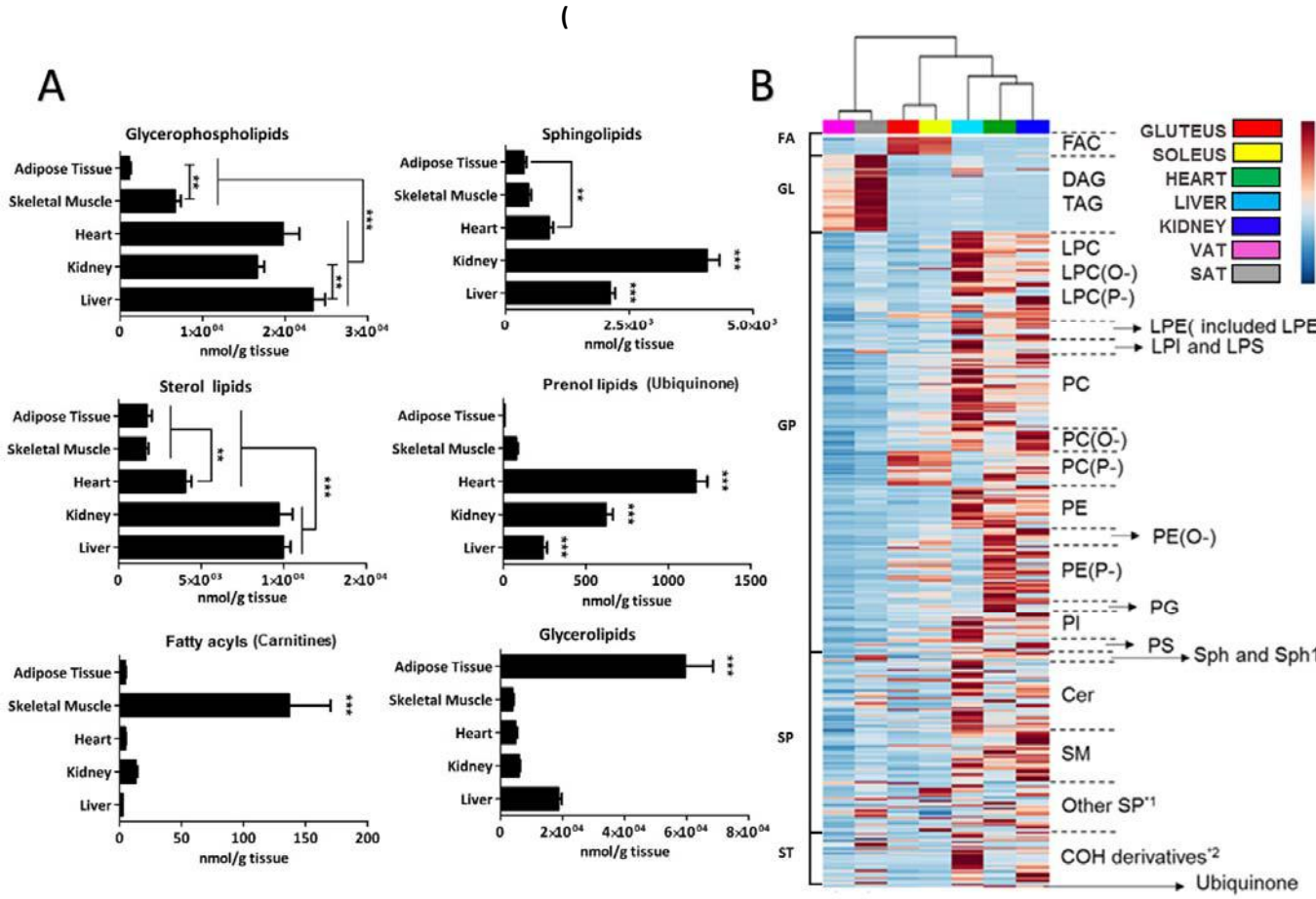

Figure 18). Cholesterol concentration was higher in kidney along with liver compared to the other tissues (from more to less, heart>SAT>soleus>gluteus>VAT). The cholesterol derivatives (CE, oxCE, desmosterol and hydroxycholesterol) were significantly higher in liver compared to the other tissues. The precursor in the cholesterol biosynthesis desmosterol showed the highest concentration in liver, being practically identical for the other tissues; and hydroxycholesterol, a cholesterol metabolite, shows a homogeneous distribution across tissues, although the highest concentration was again found at hepatic level, followed by kidney, heart and gluteus significantly different from WAT (Figure 24).

Regarding CE species, compared to the other tissues, liver and kidney of the CE individual species showed a significance difference of approximately 60% and 50%, respectively. CE(18:1) and (18:2) showed the highest concentration in liver. No differences were found between both types of WAT where the highest concentration was CE(18:1) and no differences were found in the skeletal muscle where the most abundant specie was CE(18:2). In the case of cardiac and renal tissue, CE(20:4) was the most concentrated CE specie (Table S20). Ubiquinone, the only lipid

detected in PR category, was more concentrated in heart, liver and kidney rather than skeletal muscle or WAT (Figure 24).

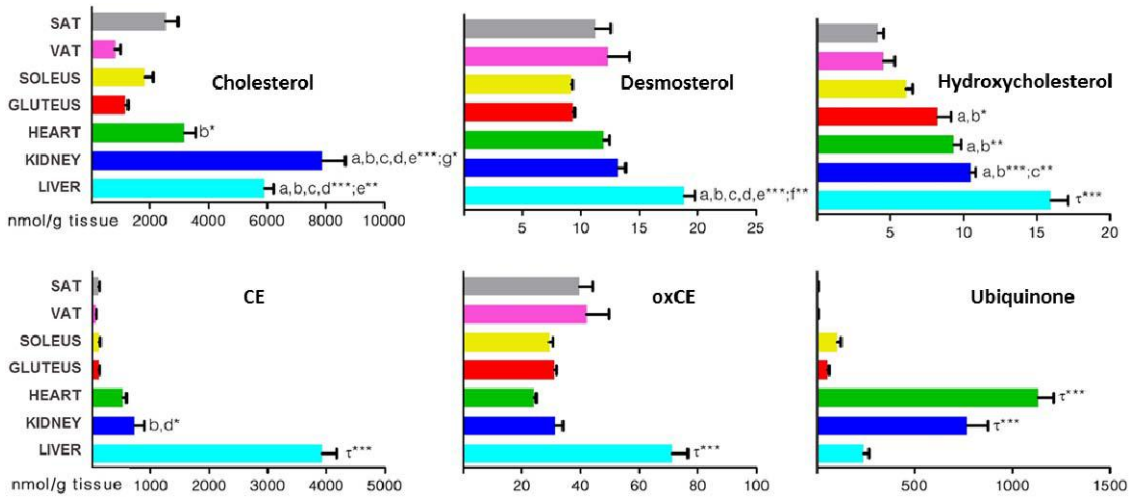

Figure 24. Sterol and prenol lipid concentrations across tissues and organs per targeted lipidomic analysis. Cholesterol (COH), derivatives of this molecule such as desmosterol, hydroxycholesterol, cholesteryl esters (CE) and oxidized CE, and ubiquinone values are expressed as mean ± SEM from 8-10 animals. Statistical analysis was one-way anova and post hoc Tukey significance is represented in the bars. a significantly different respect to subcutaneous adipose tissue (SAT), b respect to visceral adipose tissue (VAT), c respect to soleus, d respect to gluteus, e respect to heart and f respect to kidney, g respect to liver, τ respect to all. *p<0.05, **p<0.01 and ***p<0.001**.**

4.1.4. Distribution of targeted lipid species within tissues

Complementary to the information above, the lipid distribution within each tissue has been analyzed. All of the species detected in the targeted lipidomic analysis (652 species) were jointly analyzed by a Pearson correlation and the resulting matrix was organized by hierarchical clustering (Figure 25). This analysis revealed several clusters of lipids with similar abundance patterns in tissues and six clusters have been deeper studied and the lipid composition of each cluster is detailed in Table 15. First cluster, named (a) was consisted of GL, mostly TAG, and one oxidized cholesteryl ester (oxCE). This cluster was almost exclusively present in WAT, especially in SAT. Cluster (b) was formed by 27 species where the 66.66% of them were ether lipids, particularly PE(P-).These species were higher in cardiac muscle as well as skeletal muscle although not exclusively. The others analyzed clusters were mostly comprised by SP species. Cluster (c) and (d) had species with higher concentration in liver. SM was the most abundant lipid subclass in cluster (c) although PE, PI, Cer and CE were also found. On the other hand, Cer was the most abundant subclass in cluster (d) followed by LPE, LPI, PE, PI and SM. Both clusters seem to contain lipid species important for signaling, physiological functions and metabolism of

the liver. To end with, similarly to this previous cluster, (e) and (f) clusters could be combined as a renal cortex lipid species representation. In both of them, SM was the most abundant subclass followed by great amount of alkylGPs, mostly from choline but also with ethanolamine.

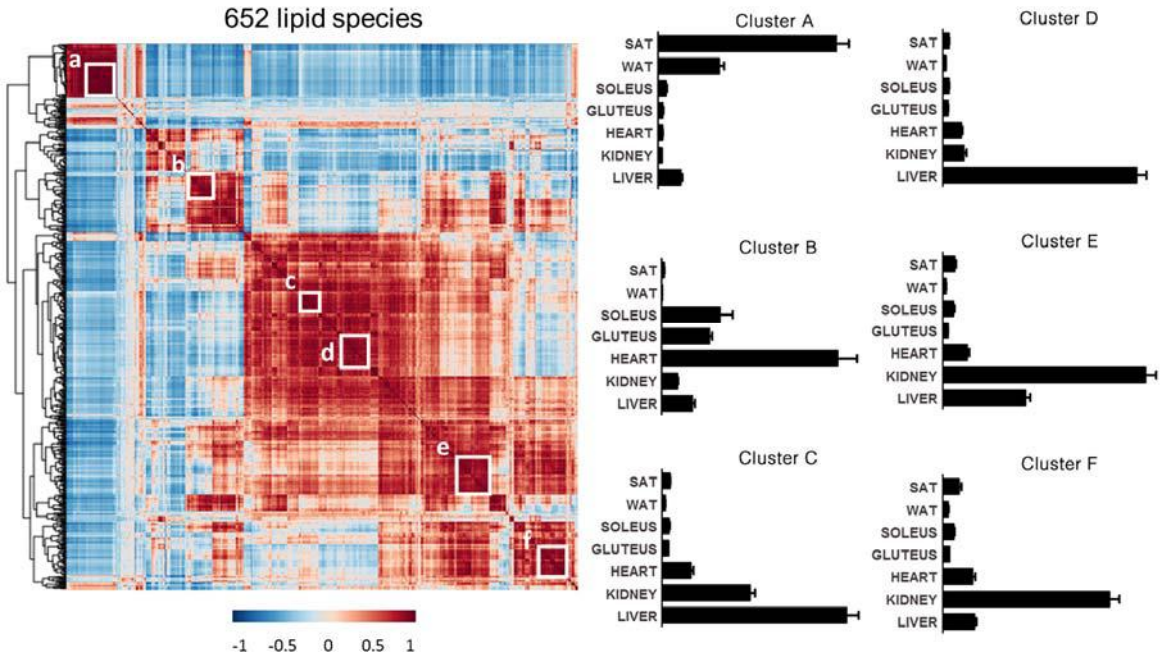

Figure 25. Cluster analysis of lipid profiles. *Left:* heat map of Pearson correlation matrix across the 652 targeted lipids with corresponding hierarchical tree. White boxes indicate lipid clusters chosen for further analysis. *Right:* Concentration of lipid clusters across the 7 rat tissues analyzed. For the information about the lipid species in each lipid cluster see **Table 15¡Error! No se encuentra el origen de la referencia.**.

Table 15. Clusters analysis of lipid profiles. Definition of the clusters chosen to be analyzed in the heat map of Pearson correlation matrix of Figure 25.

Cluster	Cluster a	Cluster b	Cluster c	Cluster d	Cluster e	Cluster f
Nº of lipid species	34	27	22	32	40	29
Nº of lipid classes	3	9	7	8	9	10
Most abundant lipid class	TAG	PE(P-)	SM	Cer	SM	SM
List of Lipids in each cluster	DG(16:0/16:1)	PC(P-38:5) (a)	LPC(20:2) [sn1]	LPE(18:2) [sn2]	LPC(18:0) [sn2]	LPC(24:0) [sn2]
	DG(16:1/18:1)	PC(P-38:5) (b)	PE(16:1/18:2)	LPE(18:2) [sn1]	LPC(19:0) [sn2] (a)	LPC(24:0) [sn1]
	DG(18:1/18:2)	PE(18:0/22:5) (n6)	PE(16:0/18:3) (a)	LPE(20:4) [sn2]	LPC(20:0) [sn2]	LPC(26:0) [sn2]
	TG(14:0/16:0/18:2)	PE(18:0/22:6)	PE(16:0/20:4)	LPE(20:4) [sn1]	LPC(20:0) [sn1]	LPC(26:0) [sn1]
	TG(14:0/16:1/18:1)	PE(O-16:0/22:6)	PE(16:0/20:5)	LPI(18:2) [sn2]	LPC(22:0) [sn2]	LPC(O-16:0)
	TG(14:0/16:1/18:2)	PE(O-18:0/22:5) (a)	PE(15-MHDA/20:4)	LPI(18:2) [sn1]	LPC(22:0) [sn1]	PC(31:0) (b)
	TG(14:0/18:0/18:1)	PE(O-18:0/22:6)	PI(16:0/20:3) (a)	LPI(20:4) [sn2]	LPC(22:1) [sn2]	PC(16:0/16:0)
	TG(14:0/18:2/18:2)	PE(O-18:1/22:6)	PI(16:0/20:4)	LPI(20:4) [sn1]	LPC(22:1) [sn1]	PE(16:0/16:0)
	TG(14:1/16:0/18:1)	PE(P-15:0/22:6) (b)	PI(20:0/20:4)	PC(16:1/18:2)	LPC(O-18:0)	PE(O-16:0/18:2)
	TG(14:1/16:1/18:0)	PE(P-16:0/22:5) (n3)	Cer(d17:1/16:0)	PC(16:0/18:3) (b)	LPC(O-18:1)	PE(O-18:1/18:2)
	TG(14:1/18:0/18:2)	PE(P-16:0/22:5) (n6)	Cer(d17:1/24:0)	PC(34:5)	LPC(O-20:0)	PE(O-16:0/20:4)
	TG(14:1/18:1/18:1)	PE(P-16:0/22:6)	Cer(d18:1/22:0) (a)	PC(35:5)	LPC(O-22:0)	PE(O-18:0/20:4)
	TG(15:0/16:0/18:1)	PE(P-17:0/22:6) (b)	Cer(d18:1/24:0) (a)	PE(16:0/18:2)	LPE(18:0) [sn1]	PE(P-15:0/20:4) (b)
	TG(15:0/18:1/18:1)	PE(P-18:0/22:5) (n6)	Cer(d18:1/24:1) (a)	PE(16:0/18:3) (b)	LPE(18:1) [sn1]	PE(P-16:0/18:3)
	TG(16:0/16:0/16:0)	PE(P-18:1/22:5) (a)	Cer(d19:1/24:0)	PE(15-MHDA/18:2)	PC(O-16:0/16:0)	PI(16:0/16:0)
	TG(16:0/16:0/18:1)	PE(P-18:1/22:5) (b)	Cer(d18:0/24:1)	PI(17:0/18:2) (a+b)	PC(O-35:4)	PI(34:0)
	TG(16:0/16:0/18:2)	PE(P-18:1/22:6) (a)	Cer(d18:0/16:0)	PI(16:0/20:3) (b)	PC(O-36:0)	PS(36:1)
	TG(16:0/16:1/18:1)	PE(P-18:1/22:6) (b)	Cer(d18:0/22:0)	PI(17:0/20:4) (a+b)	PC(O-18:0/18:2)	Sph(d18:2)
	TG(16:1/16:1/16:1)	PE(P-20:0/22:6)	Cer(d18:0/24:0)	Cer(d16:1/24:0)	PC(O-18:1/18:2)	SM(d18:1/16:0)
	TG(16:1/16:1/18:0)	PE(P-20:1/22:6) (a)	SM(41:0)	Cer(d16:1/24:1)	PC(O-16:0/20:3)	SM(d18:2/16:0)
	TG(16:1/16:1/18:1)	PG(34:1)	SM(43:1)	Cer(d17:1/22:0)	PC(O-16:0/20:4)	SM(34:3)

	TG(16:1/18:1/18:1)	PG(36:2)	CE(18:3)	Cer(d17:1/23:0)	PC(O-18:0/20:4)	SM(d18:1/17:0)/ SM(d17:1/18:0)
	Cluster a	**Cluster b**		**Cluster d**	**Cluster e**	**Cluster f**
List of Lipids in each cluster	TG(16:1/18:1/18:2)	PS(40:5)		Cer(d18:1/14:0)	PC(O-38:5)	SM(d18:2/17:0)
	TG(16:0/17:0/18:1)	PS(40:6)		Cer(d18:1/23:0)	PC(P-20:0/20:4)	SM(35:2) (b)
	TG(16:1/17:0/18:1)	SM(d18:2/20:0)		Cer(d19:1/22:0)	PI(16:0/16:1)	SM(d18:2/22:0)
	TG(17:0/18:1/18:1)	Hex2Cer(d18:1/20:0)		Cer(d19:1/23:0)	PS(38:3)	SM(d18:2/24:0)
	TG(16:0/17:0/18:2)	GM3(d18:1/20:0)		Desmosterol(18:2)	PS(38:4)	SM(43:2) (c)
	TG(18:0/18:2/18:2)			CE(16:1)	SM(d18:1/14:0)/ SM(d16:1/16:0)	SM(44:1)
	TG(14:0/16:0/18:1)			CE(17:0)	SM(d18:2/14:0)	SM(44:3)
	TG(18:1/18:1/18:1)			CE(17:1)	SM(d17:1/16:0)	
	TG(18:1/18:1/18:2)			CE(18:1)	SM(d18:0/16:0)	
	TG(18:1/18:2/18:2)			CE(18:2)	SM(d16:1/19:0)	
	TG(18:2/18:2/18:2)				SM(d18:2/18:1)	
	oxCE (18:2) [+2O]				SM(38:3) (b)	
					SM(d18:1/22:0)/ SM(d16:1/24:0)	
					SM(d18:1/24:0)	
					SM(d18:1/24:1)	
					SM(43:2) (b)	
					SM(44:2)	
					GM3(d18:1/16:0)	

4.2 Effects of aging in metabolism and the lipid profile of the different tissues in male rats

In order to evaluate the effects of aging in the metabolism a comparative analysis between the group of 8 months rats (adults) and the group of 26 months rats (old) was performed. Both groups have been fed with the same type and amount of diet, so differences found between both experimental groups can be attributed to the age difference. Untargeted metabolomics and lipidomics were the techniques used in this section and below have been represented the results obtained organized by sample type.

4.2.1. Skeletal muscle

Skeletal muscle untargeted results showed first that with the compounds detected the first differences between samples is the type of muscle. Metabolism in each muscle is more important than aging in order to separate samples with a hierarchical clustering algorithm (Figure 26). Gluteus and soleus samples are grouped separately and only inside each group, a difference between old and adult animals can be seen.

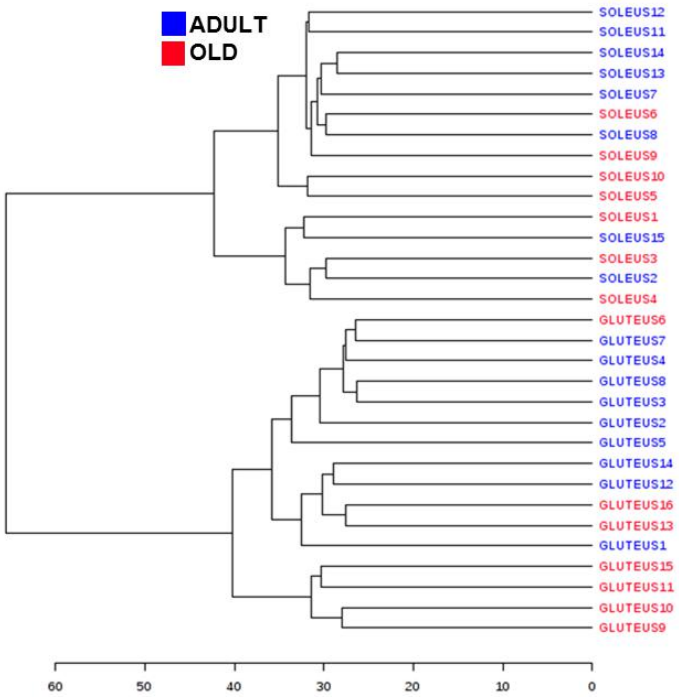

Figure 26. Skeletal muscle lipidomic profile distribution in adults and old animals. Hierarchical clustering algorithm showed two big groups, one with the gluteus samples and other with the soleus samples. Inside each group, there is a difference between old and adults animals.

However, when the most statistically different compound are used to analyze the groups, aging in rats showed a different lipid and metabolic profile as it is represented in Figure 27 by the heat map. In addition, same results were obtained with a supervised multivariate statistical analysis, specifically, a partial least squares discriminant analysis (PLS-DA). In the PLS-DA representation, both experimental groups are well separated and is inside each group where a division according to the type of skeletal muscle is visible.

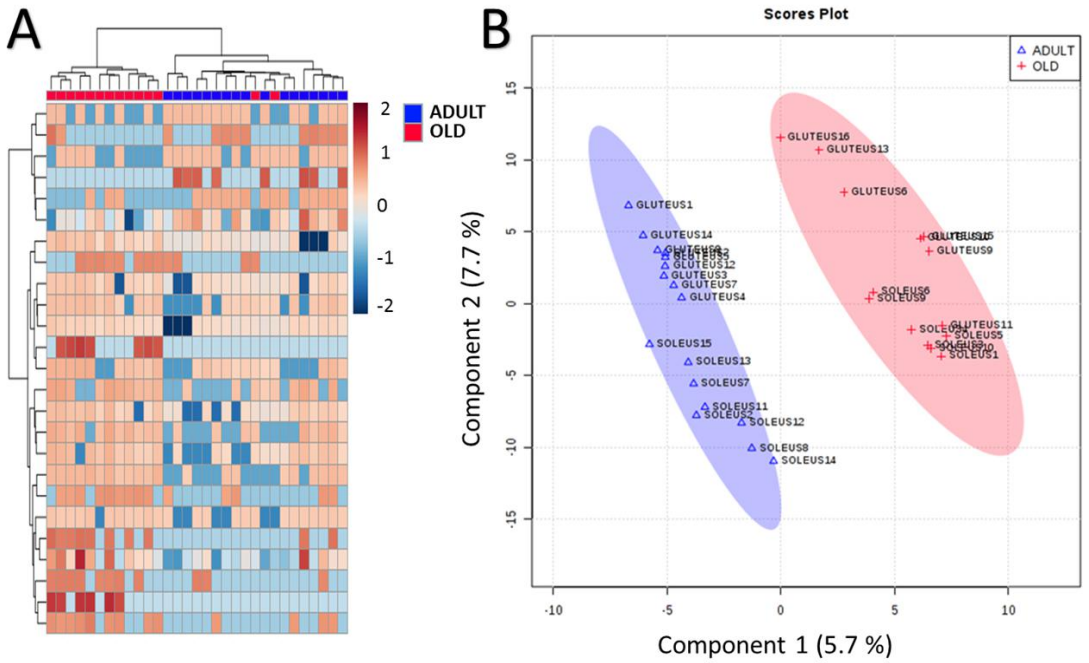

Figure 27. Multivariate statistics revealed different lipid profiles for skeletal muscle samples of adult and old animals. A) Heat map representation of hierarchical clustering analyses of the 25 most statistically different lipid species obtained non-parametric t-test in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units. B) Partial least squares discriminant analysis of gluteus and soleus samples from old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.7619, R^2 0.96124 and Q^2 0.23872.

A non-parametric t-test for equal variances was performed and from the 530 lipid species detected, forty lipid compounds were found to be statistically different of which twenty one were identified and from the 1319 metabolites detected, fifty one metabolites were found but unfortunately none of them were identified. The list of unidentified compounds can be found in Table S24 of annex. A list of these identified compounds is in Table 16. Between the lipid species are some SP increased by age and on the contrary some GPs decreased. However, most of the lipid species identified were TAGs, mainly increased in old animals. All of the non-identified compounds obtained by untargeted metabolomics and lipidomics are in Table S25 of annex.

Table 16. Skeletal muscle lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

CLASIFICATION	Compound	Product ion	m/z	RT	Log FC	p	Old vs Adult
Pr	all-trans-retinyl linoleate	M^+NH4^+	564,4935	6,51	-7,40	6,09E-03	down
FA	Linoleoyl-CoA	M^+H^+-2H2O	994,3246	9,39	-4,79	4,51E-02	down
	N-stearoyl glutamic acid	M^+H^+-H2O	396,3113	0,84	-6,05	3,21E-02	down
SP	Cer(d34:1)	M^+NH4^+	555,5453	9,17	0,20	1,91E-02	up
	N,N,N-trimethyl-Sph	M^+H^+-2H2O	306,318	2,85	7,13	1,97E-02	up
	SM(d31:0)	M^+NH4^+	680,5736	8,45	6,84	1,82E-02	up
GP	PE(P-36:4)	M^+NH4^+	741,5507	7,99	-5,12	4,83E-02	down
	PI(32:4)	M^+Na^+	825,4709	6,09	-4,81	4,37E-02	down
	LysoPI(20:4)	M^+H^+	621,3045	3,56	-6,03	6,31E-03	down
GL	DAG(34:2)	M^+NH4^+	610,5343	7,75	7,29	5,73E-03	up
	TAG(46:3)	M^+NH4^+	790,6862	9,28	6,04	3,63E-02	up
	TAG(55:4)	M^+H^+-H2O	851,7339	9,69	8,26	1,61E-03	up
	TAG(50:4)	M^+NH4^+	844,7347	9,54	4,96	1,86E-02	up
	TAG(51:2)	M^+NH4^+	862,7829	10,22	-4,00	3,94E-02	down
	TAG(52:4)	M^+H^+	855,7362	10,06	6,49	2,33E-02	up
	TAG(59:7)	M^+H^+-2H2O	911,7815	9,60	5,73	4,98E-02	up
	TAG(52:6)	M^+H^+	851,7251	9,72	-7,92	1,30E-02	down
	TAG(54:6)	M^+NH4^+	896,7647	9,62	6,45	3,45E-02	up
	TAG(62:4)	M^+NH4^+	1012,8995	9,93	5,41	4,18E-02	up
	TAG(56:6)	M^+NH4^+	924,8109	9,87	7,56	1,82E-02	up
	TAG(60:1)	M^+H^+-H2O	955,8963	10,22	0,19	3,36E-02	up

RT: retention time LogFC: Fold change logarithmic value

4.2.2. White Adipose Tissue

The comparative study between old and adult animals was also performed for both types of WAT. An untargeted lipidomic analysis was the technique employed and result obtained are shown below. As in skeletal muscle, metabolism in each type of WAT is more important than the age difference in order to separate samples with an unsupervised multivariate analysis. Figure 28 shows the PCA representation where the first component explaining for a 13.3% of the variability across the samples differentiates the set un two groups but not accordingly to the age of the animals. Each group represents a type of WAT, VAT and SAT, and therefore is the most important for clustering the samples the differences between both types of WAT rather than the age factor.

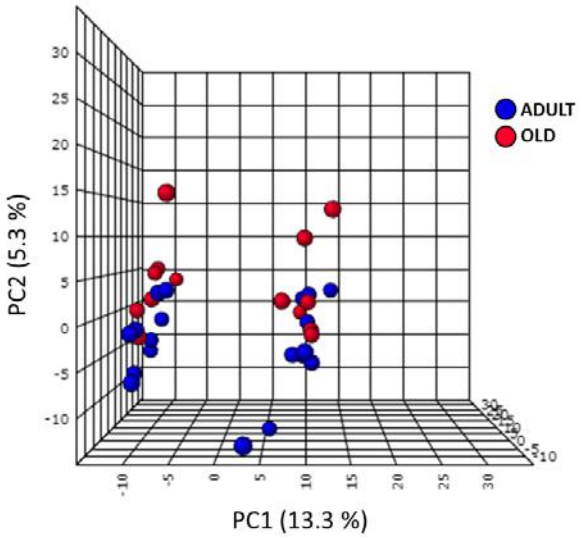

Figure 28. Multivariate statistics with an unsupervised PCA revealed that age difference is not the most important factor in the lipidomic profile for both types of adipose tissue. Each different group seen in the PCA correspond with a type of adipose tissue-visceral or subcutaneous. A division of the second component revealed little differences between old and adult animals. X: Principal component 1, Y: Principal component 2, Z: Principal component

Nevertheless, inside VAT and SAT groups of samples, the second component differentiates between old and adult animals. Thus, when the most statistically different compound are used to analyze the groups, aging in rats showed a different lipid profile as it is represented in Figure 29 by the heat map. In addition, same results were obtained with a supervised multivariate statistical analysis, specifically, a partial least squares discriminat analysis (PLS-DA). In the PLS-DA representation, both experimental groups are well separated. A non-parametric t-test for equal variances was performed and from the 702 lipid species detected, forty five lipid compounds were found to be statistically different of which twenty eight were identified. Non identified lipid species are in Table S26 of the annex and identified lipid species are listed in Table 17. Lipids from all the families can be found between the identified compounds. The fatty acyl CoA derivative found participates in α-Linolenic acid metabolism and it is upregulated in old animals. Most of the compound identified are GLs and some of them are upregulated in old animals while other are downregulated. TAG with higher number of carbons and unsaturations are the ones upregulated in old animals respect to the adult animals. All of the GPs identified are upregulated in old animals except for one plasmalogens that is downregulated compared to adult animals. In the Pr category a methyl ubiquinone was identified and it was downregulated in old animals. One compound of the cholesterol biosynthesis was also identified to be downregulated and finally, in the SP category, although the ones identified in skeletal muscle were upregulated, in WAT happened the contrary, except for the SM(d35:1).

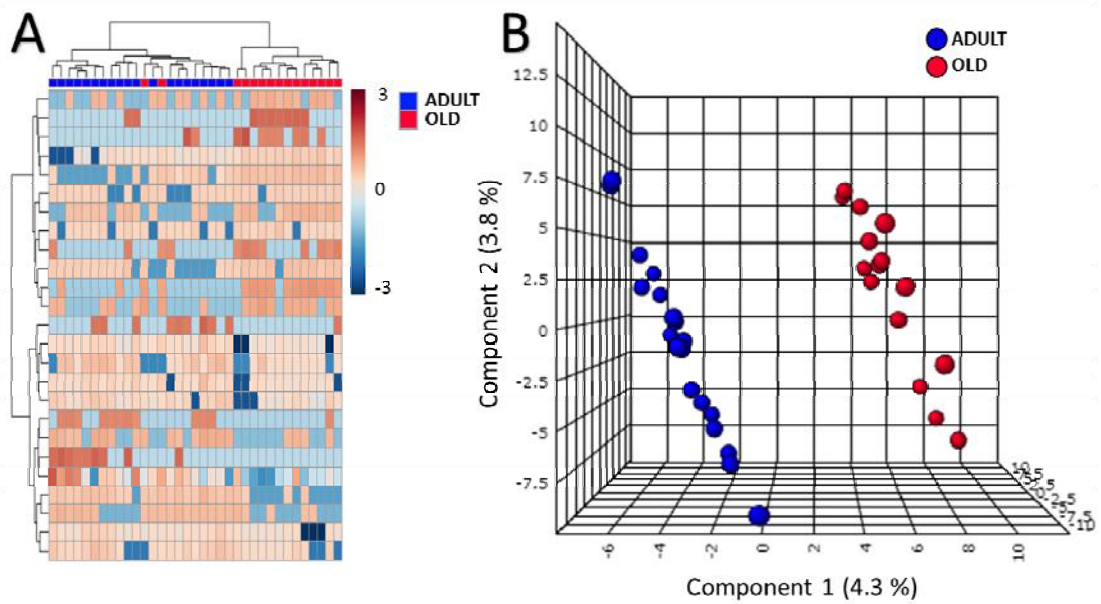

Figure 29. . Multivariate statistics revealed different lipid profiles for adipose tissue samples of adult and old animals. A) Heat map representation of hierarchical clustering analyses of the 25 most statistically different lipid species obtained non-parametric t-test in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units. B) Partial least squares discriminant analysis of visceral and subcutaneous adipose tissue samples from old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.75, R^2 0.99214 and Q^2 0.29382.

Table 17. Adipose tissue lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

CLASIFICATION	Compound	Product ion	m/z	RT	Log FC	p	Old vs Adult
FA	3-Hydroxy-OPC6-CoA	M^+Na^+	1054,2946	9,38	5,89	2,20E-02	up
GL	DAG(34:1)	M^+Na^+	617,5044	8,06	-6,10	4,04E-02	down
	DAG(36:4)	M^+NH4^+	634,5337	7,45	-4,02	2,95E-02	down
	TAG(42:0)	M^+NH4^+	740,6817	9,41	-5,47	3,81E-02	down
	TAG(42:3)	M^+Na^+	739,5977	8,75	-7,20	1,08E-02	down
	TAG(42:4)	M^+NH4^+	732,6052	8,52	-6,76	2,14E-02	down
	TAG(44:3)	M^+NH4^+	762,66	9,02	-4,42	1,48E-02	down
	TAG(44:4)	M^+NH4^+	760,6395	8,80	-9,66	1,18E-04	down
	TAG(46:5)	M^+H^+	786,6522	8,88	-6,67	1,13E-02	down
	TAG(49:0)	M^+NH4^+	838,7814	10,17	-8,50	1,92E-03	down
	TAG(53:5)	M^+H^+	884,7706	9,63	-6,94	1,64E-02	down
	TAG(54:6)	M^+H^+	879,7569	9,91	7,38	1,47E-02	up
	TAG(56:2)	M^+Na^+	937,8017	9,58	-8,31	4,57E-03	down
	TAG(56:6)	M^+NH4^+	924,8012	9,83	6,16	3,36E-02	up
	TAG(58:5)	M^+NH4^+	954,8432	10,19	6,87	2,32E-02	up

	TAG(62:4)	M^+NH4^+	1012,9221	10,55	8,04	4,45E-03	up
	TAG(66:4)	M^+NH4^+	1068,9869	10,79	5,17	3,52E-02	up
GP	LysoPA(17:1)	M^+Na^+	445,2321	1,29	6,22	4,21E-02	up
	LysoPE(20:5)	M^+Na^+	522,2526	0,85	4,04	1,28E-02	up
	PA(38:6)	M^+H^+-2H2O	685,4436	7,71	6,48	1,27E-02	up
	PE(20:2)	M^+H^+-H2O	642,4548	5,41	6,82	7,75E-03	up
	PE(O-16:0/O-16:0)	M^+H^+-H2O	646,5645	8,21	-5,97	3,07E-02	down
Pr	3-Demethyl ubiquinone-9	M^+H^+-2H2O	745,6011	8,18	-3,99	1,66E-02	down
SP	Cer(d38:1)	M^+K^+	632,5362	7,14	-3,89	3,87E-02	down
	GlcCer(d37:1)	M^+H^+-2H2O	706,5928	8,47	-0,76	9,82E-03	down
	N-Glycoloyl ganglioside GM2	M^+H^+-2H2O	708,6084	8,74	-0,75	3,50E-02	down
	SM(d35:1)	M^+NH4^+	734,6236	7,79	5,67	4,77E-02	up
ST	4α-Hydroxymethyl-4β-methyl-5α-cholesta-8,24-dien-3β-ol	M^+H^+	429,3638	7,55	-7,63	1,88E-03	down

4.2.3. Kidney

Comparative study between old and adult animals in renal cortex samples was also performed and results are below. Untargeted lipidomic and metabolomic analyses were employed and unsupervised multivariate statistical analysis did not show clear difference between the experimental groups. The first component of the PCA showed a little differences between age and adults explaining both principal components (PC1 and PC2) an 18.7% of the variability across the samples for the lipidomic analysis. Thus, lipidomic profiles of the renal cortex do not seem to be highly altered by the aging process (Figure 30). However, when the most statistically different compound between old and adult animals are used to analyze the experimental groups, aging in rats showed a different lipid profile as it is represented in Figure 31, by the hierarchical algorithm represented as a heat map. In addition, same results were obtained with a supervised multivariate statistical analysis, specifically, a partial least squares discriminant analysis (PLS-DA). In the PLS-DA representation, both experimental groups are well separated, although the values obtained by 10-fold cross validation indicates that PLS-DA model is not very accurate. In order to identify those metabolites responsible for the differences between old and adult animals a non-parametric t-test for equal variances was performed.

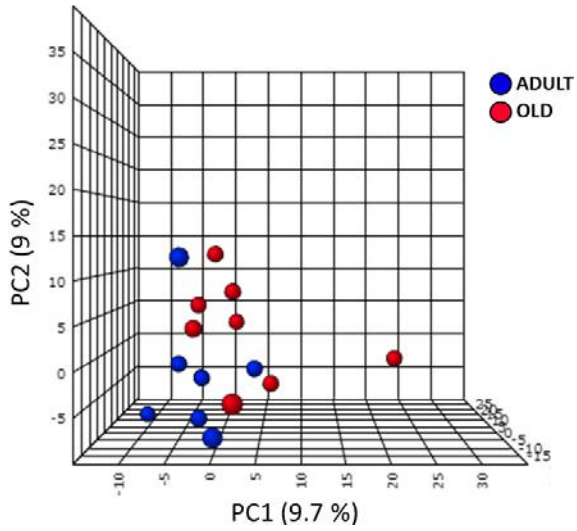

Figure 30. Multivariate statistics with an unsupervised PCA did not reveal differences between lipidomic profile renal cortex samples of old and adult animals. Division between experimental groups is not clear in those two components.

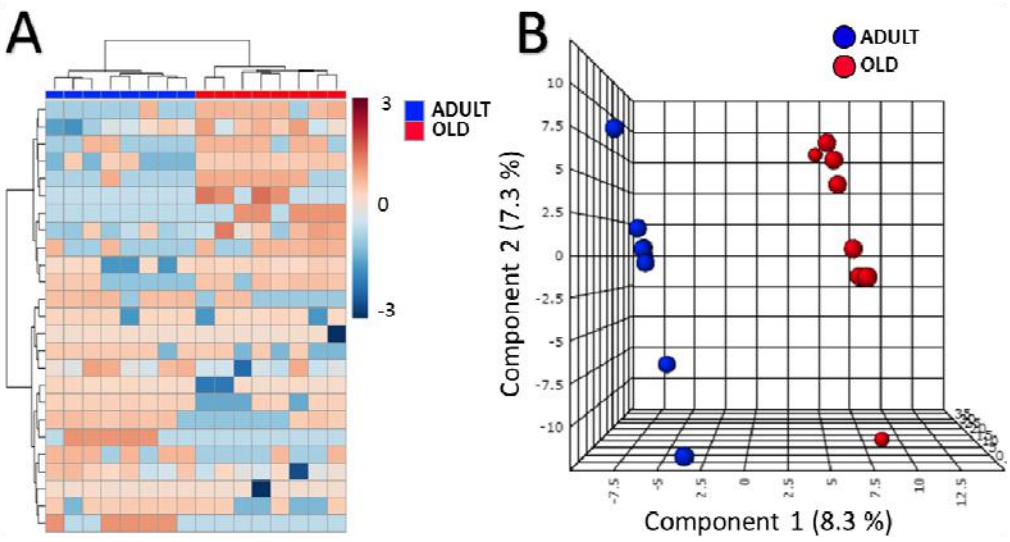

Figure 31. Multivariate statistics revealed different lipid profiles for renal cortex samples of adult and old animals. A) Heat map representation of hierarchical clustering analyses of the 25 most statistically different lipid species obtained non-parametric t-test in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units. B) Partial least squares discriminant analysis of renal cortex samples from old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.625, R^2 0.9593 and Q^2 0.010293.

In the lipidomic analysis, from the 528 lipid species detected, twenty-eight lipid compounds were found to be statistically different of which six were identified. In the metabolomic analysis, from the 839 metabolites detected, thirty-one metabolites were found of which six of them

were identified. All of the non-identified compounds obtained by untargeted lipidomics and metabolomics are in Table S27 and S28 respectively and identified compounds from both methods are listed in Table 18. In the untargeted lipidomic analysis, five of the six lipids identified are upregulated being almost all of them GL species except for one ether lipid of PC. On the other hand, the identified compounds of the metabolomic analysis were downregulated with advancing age, except for the palmitaldehyde. Between them, compounds like ADP-ribose and NADH were significantly decreased in aged animals and interestingly, several oxylipins some of them derived from AA were identified.

Table 18. Renal cortex lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic and metabolomic analysis with positive ESI polarity.

Method	Compound	ion	m/z	RT	Log FC	p	Old vs Adult
Lipidomic analysis	PC(O-34:3)/PC(P-34:2)	M^+H^+	742.5863	7.64	7.83	2.53E-02	up
	MAG(18:0)	M^+Na^+	381.2909	4.47	13.00	1.59E-03	up
	DAG(32:2)	M^+H^+-H2O	529.4520	8.41	7.02	3.89E-02	up
	TAG(50:2)	M^+NH4^+	848.7654	9.55	9.02	1.34E-02	up
	TAG(56:8)	M^+H^+	903.7554	9.78	-8.74	3.72E-02	down
	TAG(56:5)	M^+NH4^+	926.8102	10.01	9.15	2.42E-02	up
Metabolomic analysis	Palmitaldehyde	M^+NH4^+	258.2738	9.11	7.20	9.55E-03	up
	EET methyl ester	M^+H^+-H2O	317.2477	11.83	-6.73	4.73E-02	down
	AA methyl ester	M^+NH4^+	336.2908	11.80	-6.85	2.75E-02	down
	Dihomo-PGI2	M^+H^+-H2O	363.2525	11,47	-9,34	4,01E-03	down
	ADP-ribose	M^+H^+-H2O	542.0597	0.58	-9.47	4.23E-02	down
	NADH	M^+Na^+	688.1027	5.90	-8.42	4.18E-02	down

4.2.4. Heart

Comparative study between lipidomic and metabolomic profiles of old and adult animals in heart samples was also performed. As in the rest of the tissues, lipidomic and metabolomic profiles underwent similar changes, these profiles in heart samples exhibited differences in how the process of aging influence them. Unsupervised multivariate statistical analysis showed clear difference between techniques, experimental groups are clearly separated in the metabolomic PCA while samples are mix in the lipidomic PCA. So, metabolomic profile of the heart samples seem to be more altered by the aging process than the lipidomic profile (Figure 32). In addition, when a hierarchical clustering algorithm is used to study how the compounds found in the samples are distributed, different results from both techniques were obtained.

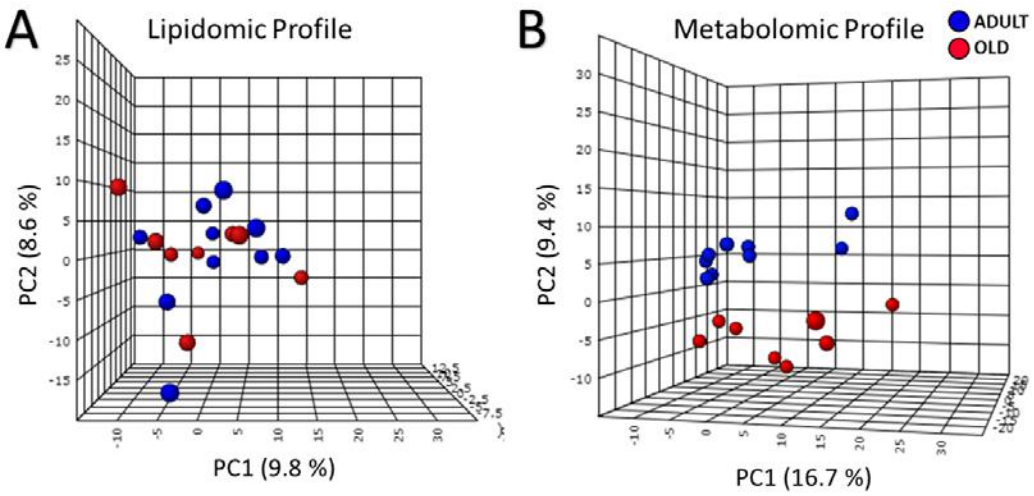

Figure 32. Multivariate statistics with an unsupervised PCA revealed difference between lipidomic and metabolomic profiles in heart samples of old and adult animals. A) Representation of the lipidomic profile where division between experimental groups is not clear. B) Representation of the metabolomic profile where division between experimental groups is perfectly clear in those two components.

In lipidomic analysis, only with the most statistically different compound, aging in heart samples showed a different lipid profile between the experimental groups while this fact happened with the whole set of metabolites found. The results of hierarchical clustering algorithm performed can be seen in Figure 33 represented as heat maps. In both of them, experimental groups showed clearly different profiles influenced by age but in the lipidomic profile this fact only occurs with the 25 most statistically different lipid species obtained by t-test. A non-parametric t-test for equal variances was performed and from the 513 lipid species detected, nineteen were found to be statistically different of which ten were identified and from 534 metabolites detected, forty five metabolites were found of which fourteen of them were identified. All of the non-identified compounds obtained by untargeted lipidomics and metabolomics are in Table S29 and S30 of annex. Table 19 showed the identified compounds from the untargeted lipidomic analysis and Table 20 the ones identified in the metabolomic analysis. The untargeted lipidomic analysis detected 513 lipid species in at least the 50% of all the samples of one condition, therefore there just a few lipids in heart samples affected by the process of aging. Between them, three lipids from the fatty acyl category were identified, including thromboxane B2. In the GLs category two TAGs were identified; one of them saturated and the other unsaturated. Regulation is different for each other being upregulated the TAG(50:0). All of the lipid species identified from the GP and SP category were upregulated. In the GP category, there was a PC and in the SP category one hexosylceramide (HexCer) and one sphingosine 1-phosphate (Sph-1P). Finally, similarly to the GL category, two sterol lipid with opposite regulation were

identified. 4,4-Dimethyl-5a-cholesta-8,24-dien-3b-ol is an intermediate in the sterol biosynthesis and 3α,7α,12α,25-Tetrahydroxy-5β-cholestan-26-oic acid is a twenty seven carbon bile acid.

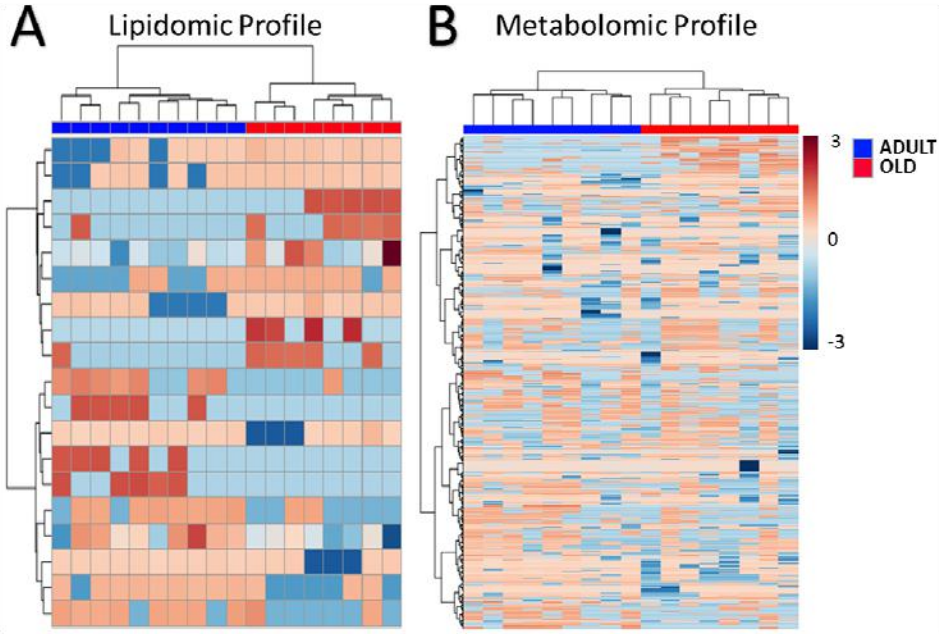

Figure 33. Heat map of lipids and metabolites distribution in heart samples of old and adult animals A) Heat map representation of hierarchical clustering analyses of the 19 most statistically different lipid species obtained non-parametric t-test in positive ESI polarity. B) Heat map representation of 534 metabolites found in heart samples in positive ESI ionization. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units.

Table 19. Heart lipid species statistically different between adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

CLASIFICATION	Compound	Product ion	m/z	RT	Log FC	p	Old vs Adult
FA	DiHOME	M^+K^+	353,219	0,81	7,71	8,37E-03	up
	3-oxo-tridecanoic acid	M^+Na^+	251,1668	0,79	-6,04	4,28E-02	down
	TXB2	M^+Na^+	393,2337	0,82	-7,86	1,72E-02	down
GL	TAG(50:0)	M^+NH4^+	852,7911	10,22	8,06	2,04E-02	up
	TAG(56:4)	M^+H^+	928,8271	10,09	-9,27	1,09E-02	down
GP	PC(38:6)	M^+NH4^+	823,5951	5,59	7,92	4,17E-02	up
SP	LacCer(d18:0/26:1)	M^+H^+	1002,7732	7,07	6,25	4,14E-02	up
	C16 Sphingosine-1P	M^+NH4^+	369,2413	3,57	9,79	1,24E-03	up
ST	3α,7α,12α,25-Tetrahydroxy-5β-cholestan-26-oic acid	M^+H^+-H2O	449,3305	4,76	7,97	4,14E-02	up
	4,4-Dimethyl-5a-cholesta-8,24-dien-3b-ol	M^+NH4^+	432,4262	7,25	-7,41	1,73E-02	down

In Table 20 are listed the metabolites identified of the forty five differential obtained by t-test. All of the metabolites are upregulated in old animals respect to adult ones except for one nucleotide, UDP-N-acetyl-D-galactosamine 4-sulfate. Between nucleotides, ADP-ribose can be found again (it was downregulated in renal cortex of old animals) but the regulation in heart is the opposite. Although a specific lipidomic method was performed, some lipids also appear in the metabolomic method. With lower values of retention time, only hydrophilic metabolites will appear but then with higher values of retention time hydrophobic metabolites also appear. Hence, some lipids can be detected with the metabolomic method.

Table 20. Heart metabolites statistically different between adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

CLASIFICATION	Compound	Product ion	m/z	RT	Log FC	p	Old vs Adult
Nucleotides	ADP-ribose	M+H+-H2O	542,0633	0,79	14,07	1,57E-03	up
	UDP-N-acetyl-D-galactosamine 4-sulfate	M+K+	725,9959	0,85	-6,88	1,79E-02	down
Dicarboxylic acid	Succinic acid	M+H+	119,0307	0,67	12,18	4,94E-03	up
Sterol lipid	26-hydroxycholesterol 3-sulfate	M+H+	483,3112	11,05	11,26	1,79E-02	up
Eicosanoids	10-F2-dihomo-IsoP	M+H+	397,2862	10,50	14,54	1,76E-03	up
	Leukotriene B4	M+Na+	359,227	9,05	8,62	2,92E-02	up
GP	LysoPE(22:4)	M+H+	530,3162	10,79	7,15	4,42E-02	up
Fatty ester	2-Methyl butyroyl carnitine	M+H+	246,1633	1,82	10,07	2,81E-02	up
	Elaidic carnitine	M+H+	426,3561	10,12	9,82	3,76E-02	up
	Hexanoyl carnitine	M+H+	260,1788	2,88	12,72	1,37E-02	up
	Isobutyryl carnitine	M+H+	232,1485	1,17	11,27	8,49E-03	up
	Linoleyl carnitine	M+H+	424,3466	9,72	11,34	9,64E-03	up
	Myristoyl carnitine	M+H+	372,3075	9,15	13,76	2,68E-02	up
	trans-Hexadec-2-enoyl carnitine	M+H+	398,3229	9,44	11,03	2,09E-02	up

Most of the lipids identified with this method were from the fatty acyls category, eicosanoids and fatty esters. One sterol lipid derivative from the cholesterol and important in lipid metabolism regulation was identified. Also, two types of eicosanoids, a leukotriene and isoprostane, both related to inflammation, were upregulation besides the only GP identified, LysoPE(22:4). Finally, the most part of the identified metabolites were fatty acyl carnitines of short and long chain fatty acids, all of them, upregulated in old animals respect to the adult ones.

4.2.5. Liver

Comparative study between lipidomic and metabolomic profiles of old and adult animals in liver samples was also performed. At liver samples, lipidomic and metabolomic profiles underwent similar changes how the process of aging influence them. After data filtering, in the metabolomic analysis 1060 entities were detected and in the lipidomic analysis 610 entities. Analyzing there was not clear differences in the distribution of these entities between old and adult animals. Unsupervised multivariate statistical analysis showed, on one hand the lipidome explains approximately 20% of the variability between the samples and the principal component 1 showed a separation due to the age factor. On the other hand, the metabolome explains better the variability across samples than the lipidome but this variability was not due to the age differences between the experimental groups (Figure 34).

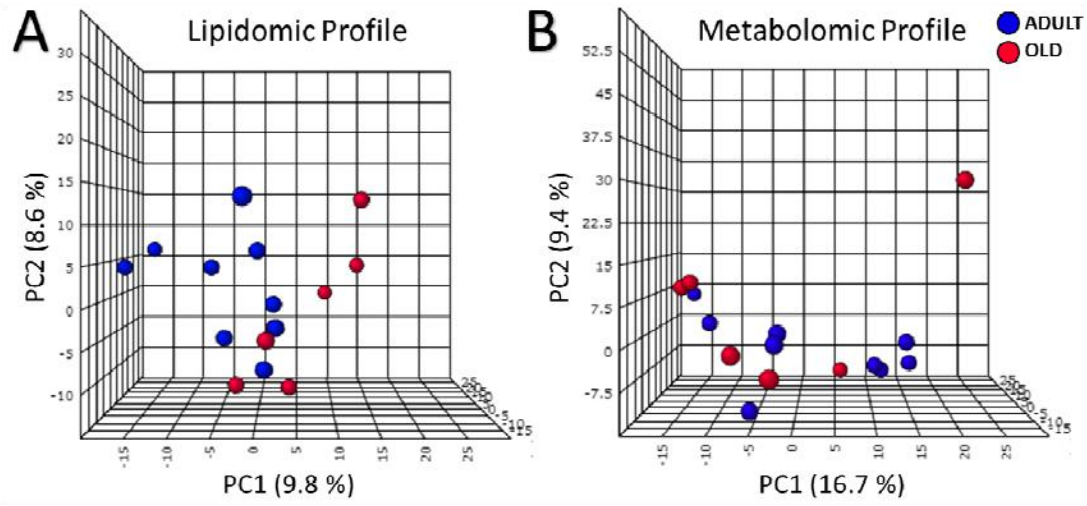

Figure 34. Multivariate statistics with an unsupervised PCA revealed no difference between lipidomic and metabolomic profiles in liver samples of old and adult animals. A) Representation of the lipidomic profile where division between experimental groups is not clear in those two components. B) Representation of the metabolomic profile where division between experimental groups is not clear in those two components.

Notwithstanding, when the twenty-five most statistically different compounds are used to analyze the experimental groups with the multivariate statistics, aging in liver samples of rats showed differences in both lipidomic and metabolomic profiles as it can be appreciated in the results of hierarchical clustering algorithm performed are represented in Figure 35, as a heat map. In both of them, experimental groups showed clearly different profiles influenced by age in the regulation of this twenty-five top compounds obtained by t-test, whose regulation depend on the specific metabolite and being the aging process able to increase or decrease their hepatic levels. In agreement with the unsupervised multivariate analysis, the results obtained with the supervised multivariate statistical method, PLS-DA, are represented in Figure 36. Hepatic tissue showed clear differences caused by the physiological process of aging and its effects are well reflected in the lipidome, and metabolome of this tissue. The PLS-DA representation of the lipidomic and metabolomic analysis, both experimental groups are well separated. In order to identify those metabolites responsible for the differences between old and adult animals a non-parametric t-test for equal variances was performed. In the metabolomic analysis, from the 610 metabolites detected, twenty-five metabolites were found of which only three of them were identified.

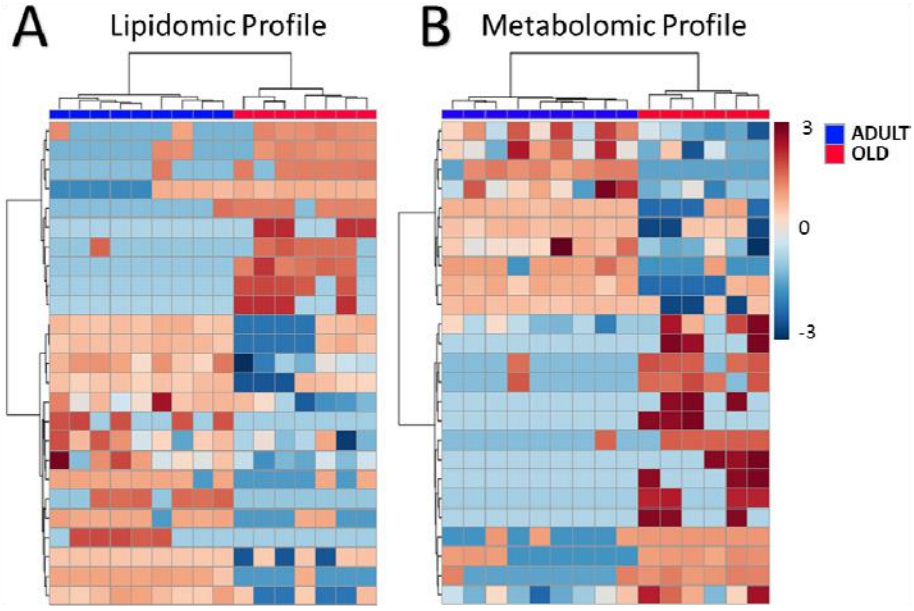

Figure 35. Heat map of lipids and metabolites distribution in liver samples of old and adult animals. A) Heat map representation of hierarchical clustering analyses of the 25 most statistically different lipid species obtained non-parametric t-test in positive ESI polarity. B) Heat map representation of the 25 most statistically different metabolites obtained non-parametric t-test in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units.

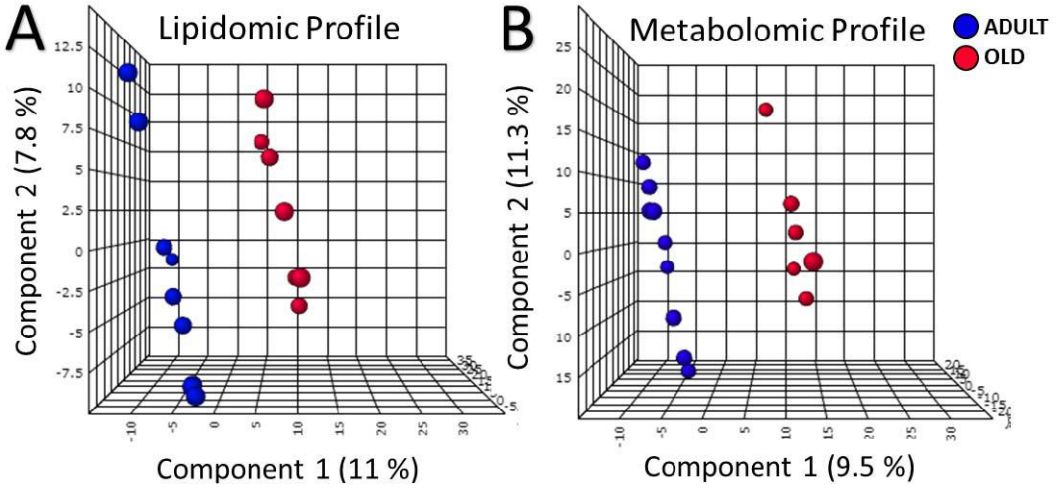

Figure 36. Multivariate statistics revealed different lipid profiles for liver samples of adult and old animals. A) Partial least squares discriminant analysis of the lipid profile of liver samples from old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.6875, R2 0.99949 and Q2 0.26789. B) Partial least squares discriminant analysis of the metabolic profile of liver samples from old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.66667, R2 0.99998 and Q2 0.24989.

In the lipidomic analysis, from the 1060 lipid species detected, forty species were found to be statistically different of which eighteen were identified. All of the non-identified compounds obtained by untargeted metabolomics and lipidomics are in Table S31 and S32 of the annex. Table 21 showed the identified compounds from the untargeted metabolomic analysis and Table 22 the ones identified in the lipidomic analysis. Amongst the identified metabolites, some fatty acyls such as AA can be found. Although a specific method for lipidomics was performed, as it has been seen some lipid species appear as well in the metabolomic method where the more hydrophilic compounds are eluted first and the more hydrophobic, appear at higher retention times. Of the free fatty acids identified, AA was upregulated with advancing age as well as N-ribosylhistidine, a derivative of the histidine synthesized by the action of $NAD(P)^+$ nucleosidase, nucleotide pyrophosphatase and 5'-nucleotidase.

Table 21. Liver metabolites statistically different between adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

CLASIFICATION	Compound	ion	m/z	RT	Log FC	p	Old vs Adult
Fatty acyls	Arachidonic Acid	M^+H^+-2H2O	269,2201	10,96	9,35	1,96E-02	up
	Nonadecenoic acid	M^+Na^+	319,2562	11,72	-6,09	3,44E-02	down
Amino acids	n-Ribosylhistidine	M^+K^+	326,0694	2,45	7,93	2,66E-02	up

On the other hand, the list of the lipid species identified is in Table 22. The untargeted lipidomic analysis detected 610 lipid species where forty of them were found significantly affected by the process of aging and seventeen identified. Most of them were from the GLs category, DAG and TAG, both SFA and UFA. In addition, the regulation in this category does not seem to follow any pattern with advancing age. Among the SP species, one HexCer was identified to be downregulated. Finally, five lipid species from the GP category were identified. Two species of PI, one with and ether bond and the other phosphorylated, both upregulated. The other GP species were PEs, all of them unsaturated. The lipid specie of PE with a MUFA chain was up regulated while the others, both PUFA, were downregulated in old animals respect to the adult ones.

Table 22. Liver lipid species statistically different between adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

CLASIFICATION	Compound	Product ion	m/z	RT	Log FC	p	Old vs Adult
SP	LactosylCer(d43:1)	M^+Na^+	1010,7737	8,51	-8,25	1,57E-02	down
GP	PE(34:1)	M^+Na^+	740,5159	6,81	13,19	1,18E-03	up
	PE(34:2)	M^+H^+	716,5163	6,88	-0,73	6,07E-04	down
	PE(36:5)	M^+H^+	738,5068	6,83	-15,12	6,29E-06	down
	PI(O-31:1)	M^+K^+	819,4716	3,24	7,76	3,80E-02	up
	PIP2(36:2)	M^+NH4^+	1040,5126	0,86	6,95	4,89E-02	up
GL	DAG(34:1)	M^+NH4^+	612,5458	8,05	8,28	2,75E-02	up
	DAG(38:4)	M^+H^+-H2O	627,525	6,01	-9,76	1,03E-02	down
	DAG(42:0)	M^+H^+	708,6871	8,8	-0,39	1,06E-02	down
	TAG(42:1)	M^+NH4^+	738,6608	9,22	11,49	5,02E-04	up
	TAG(48:4)	M^+NH4^+	816,6996	9,35	-9,03	4,27E-02	down
	TAG(55:5)	M^+H^+-H2O	877,761	9,74	-12,55	1,04E-02	down
	TAG(57:2)	M^+NH4^+	946,8548	9,9	-8,4	2,80E-02	down
	TAG(56:3)	M^+H^+	913,795	9,76	-8,25	2,74E-02	down
	TAG(63:8)	M^+NH4^+	1018,8479	9,57	6,97	2,84E-02	up
	TAG(66:6)	M^+NH4^+	1064,9331	10,83	13,24	8,96E-06	up
	TAG(66:5)	M^+Na^+	1071,9034	10,91	8,04	4,66E-02	up

4.3 Effects of the methionine restriction diet on aging in an animal model

In order to achieve the objectives proposed in this work it has been rated the effect of a methionine restriction diet in aging at metabolomic and lipidomic level of an experimental model.

4.3.1. Skeletal muscle

Following the same pattern of the other sections in this work, metabolomic and lipidomic profile of each type of sample have been analyzed. Below result from both types of skeletal muscle are represented although this time each type was analyzed independently.

4.3.1.1. Gluteus

Multivariate statistics of the untargeted lipidomic analysis showed little differences between the experimental groups (Figure 37). The PCA showed a clear difference between the controls (old and adult animals) and most of the samples corresponding to the restricted animals are in the middle of the control groups. While the multivariate analysis was done with the 50 most statistical significant lipid species, differences between the experimental groups growth. The first division separate almost all the old control animals from the rest. Hence, the differences in the lipidomic profile of the animals bring closer the adult control and the RMet old animals. Despite this fact, looking at the intensity of the different lipid entities, characteristics areas for each experimental group can be seen suggesting different characteristic lipid profiles for each experimental group. In order to identify those lipid species responsible for a specific lipid profile for the RMet old animals a one-way analysis of variance test was performed with a post hoc Tukey to compare all of the groups between them. From the 610 lipid species detected and filtered in the untargeted lipidomic analysis, sixty six were significantly different between groups and twenty one of them were identified. Table 23 contains all of the identified lipid species and the regulation of these compounds in the RMet animals respect to both control groups. All of the non-identified compounds obtained by untargeted lipidomics are in Table S33 of annex. In the table appear one derivative from the adenosine which levels are increased in RMet old animals. It also appear a few GPs of ethanolamine, choline or inositol. Cer and SMs are the representation of the SPs altered in the RMet old animals.

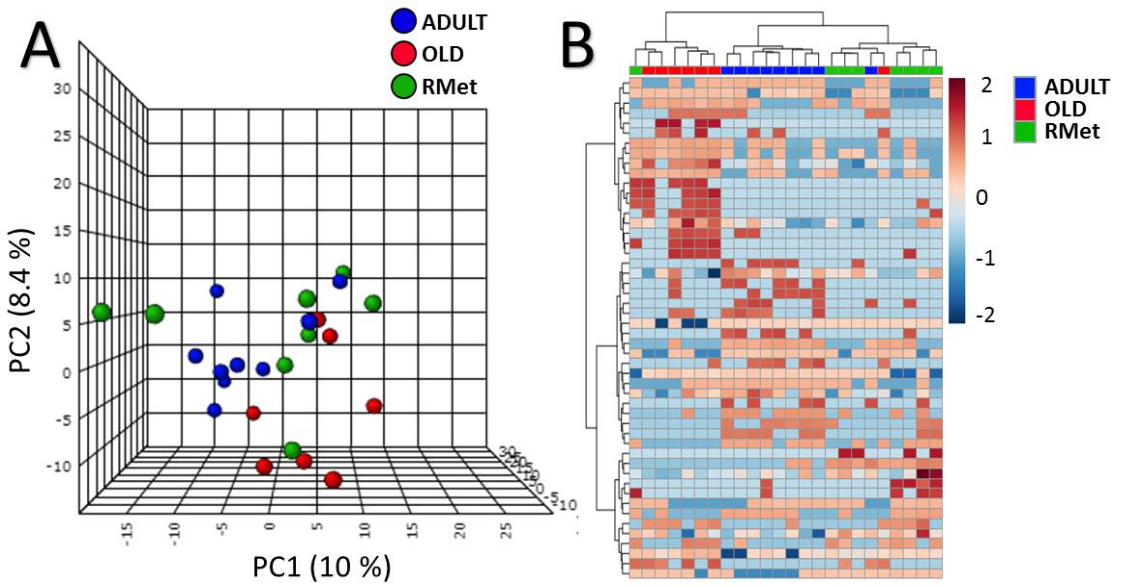

Figure 37. Lipidomic differences between control and restricted animals in gluteus samples. A) Multivariate statistics with an unsupervised PCA revealed differences between adult control, old and methionine restricted old animals. Data was obtained by untargeted lipidomic analysis with ESI(+). B) Heat map representations of hierarchical clustering analyses using 50 most statistical significant lipids species (one-way anova) between experimental groups. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units.

Finally, most of the lipid species identified were TAGs, both with SFA and UFA chains. Some of this lipid species were identified in section 4.2.1 when the effect of aging was analyzed in old and adults animals. More concretely, LysoPI(20:4), PI(32:4), Cer(d34:1), SM(d31:0), TAG(52:4), TAG(54:6) were regulated differently between old and adult animals. Both of PI species were downregulated in old control animals compared to adults ones while in the RMet old animals levels of PI and LPI are significantly upregulated or the trend is to present more similar levels compared to the adult control animals. Intensity values of this lipid species obtained in the mass spectrometry analysis are represented in Figure 38. PI(32:4) is significantly different in both control groups but it is not in the RMet old group where levels are higher than in the old control animals but lower than samples from the adult group. In both LPI species identified there is a significant difference between the RMet old animals and the old control group. Certain TAG species found altered by the effect of the RMet showed age-related changes in their levels that has been presented in the section 4.2.1. that corresponds with the aged skeletal muscle. In this sense, TAG(52:4) and TAG(54:6) were altered in old control animals showing higher levels compared to the adult animals.

Table 23. Gluteus lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of ESI(+) untargeted lipidomics.

Compound	m/z	RT	p	Log FC RMet vs OLD	RMet vs OLD	Log FC RMet vs ADULT	RMet vs ADULT
2-Phenylamino adenosine	359,1352	0,78	5,55E-03	14,55	up	10,84	up
LysoPE (18:4)	474,239	0,76	8,30E-03	-8,30	down	5,34	up
LysoPI(19:0)	632,3778	0,84	9,15E-03	11,98	up	5,77	up
LysoPI(20:4)	621,3053	3,57	1,31E-02	7,33	up	0,22	up
PC(42:2)	870,6925	7,40	2,01E-02	1,96	up	-6,63	down
PC(P-40:1) PC(O-40:2)	828,684	7,85	4,99E-02	-0,09	down	0,22	up
PI(32:4)	825,4673	6,09	4,13E-02	5,13	up	-3,93	down
Cer(d34:1)	555,5453	9,17	2,44E-04	-0,16	down	0,23	up
CerP(d42:1)	768,5493	7,34	2,05E-02	2,08	up	-6,96	down
GlcCer(d40:2)	764,6372	8,43	3,18E-02	7,66	up	-2,22	down
SM(d42:1)	816,7008	9,32	8,84E-03	-8,03	down	2,35	up
SM(d31:0)	680,5761	8,44	8,13E-03	-7,46	down	2,13	up
TAG(46:1)	794,7168	9,69	2,43E-03	-1,92	down	-0,48	down
TAG(51:0)	849,7666	9,55	3,18E-02	-10,15	down	-3,61	down
TAG(52:1)	861,758	9,73	2,18E-02	2,18	up	-7,09	down
TAG(52:4)	855,7385	10,06	3,28E-02	-9,14	down	1,56	up
TAG(54:6)	896,7639	9,62	1,78E-02	-1,31	down	6,83	up
TAG(56:3)	930,8445	10,23	2,64E-02	8,16	up	6,67	up
TAG(56:7)	922,7938	9,70	2,04E-02	-6,41	down	4,65	up
TAG(57:3)	891,8052	10,07	6,58E-03	-13,44	down	-4,78	down
TAG(60:1)	955,8986	10,22	5,01E-03	-0,11	down	0,25	up

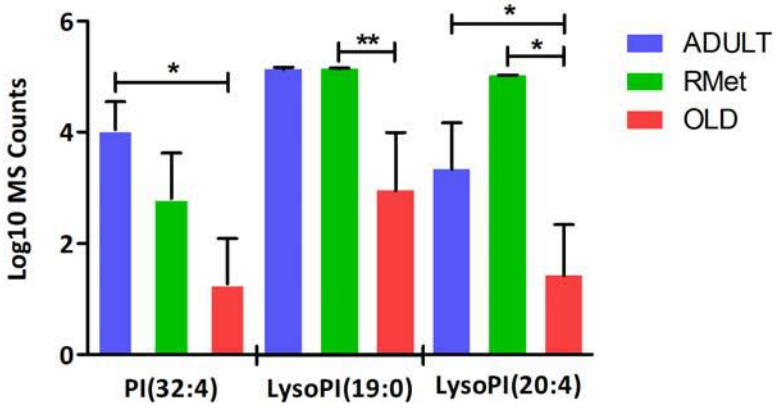

Figure 38. Intensities of three phosphatidylinositol species from gluteus samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05,**p<0.01 and ***p<0.001**.**

The 80% RMet has changed the levels of the TAG levels showing lower levels of this lipid species and therefore similar intensities between adult control animals and restricted animals can be seen. Figure 39 illustrates the intensities of both of these TAG species and also the TAG(57:3) where there is a significant change in the restricted animals compared to the old control group. In all of the TAG species represented the trend in the restricted animals is lower levels of this lipid species if they are compared to the same age control animals.

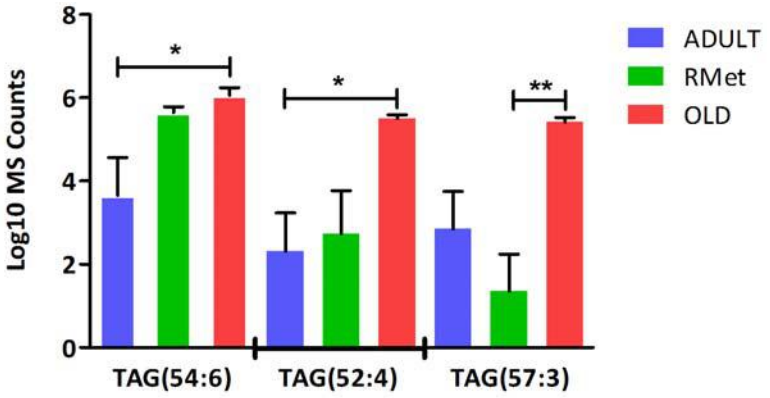

Figure 39. Intensities of three triacylglycerol species from gluteus samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05,**p<0.01 and ***p<0.001**.**

On the other hand, results obtained with the untargeted metabolomic analysis of gluteus are presented below. Multivariate statistics showed differences between the analysis of the whole metabolome detected or just the most statistically different compounds (Figure 40). If the whole set of metabolites is analyzed no difference between the experimental groups is observed. Few restricted samples of old animals are clustered with adult control animals but most of the samples, no matter which group they belong, are mixed. On the contrary, if the top 25 most statistically significant metabolites are analyzed the experimental groups are perfectly separated. Although, RMet animals have more similarities in their metabolome compared with old control than with adult control animals, there are several compounds increased just in the RMet group compared to both control animals, meaning that the restricted diet is able to change part of the metabolome in a characteristic manner. The statistical analysis one-way ANOVA with Tukey post hoc was performed and the list of identified metabolites is in Table 24 while all of the non-identified compounds are in Table S34 of annex. Of the 1219 metabolites detected, two hundred and fifty were found statistically different between the experimental

groups and twenty-one of them with the Benjamini Hochberg correction but only twenty-two were identified.

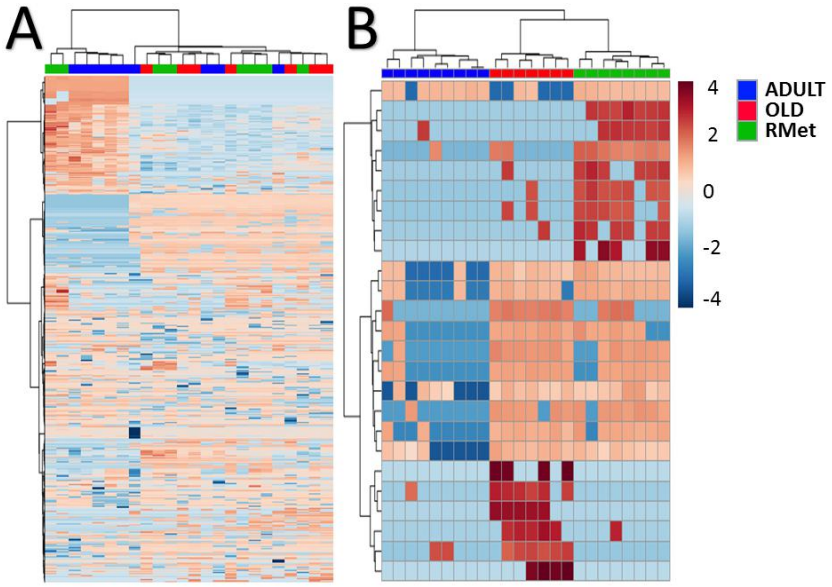

Figure 40. Metabolites distribution in gluteus samples of restricted animals, old control and adult animals. A) Heat map representation of 1219 metabolites found in gluteus samples in positive ESI polarity. B) Heat map representation of the 25 most statistically different metabolites obtained one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -4 (blue) to 4 (red) represents this normalized abundance in arbitrary units**.**

Most of the metabolites identified belong to the fatty acyl category such as carnitines, coenzyme A derivatives and docosanoids. Bile acids like cholic and deoxycholic acid were found to be increased by the RMet. Several oxylipins were downregulated by the diet compared to the age matched control. LGPs found were mostly increased by the effect of the diet respect both control groups. Finally, compounds of the purine metabolism were upregulated by the RMet in old animals.

Table 24. Gluteus metabolites statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity**.**

Compound	m/z	RT	p value	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
N-Glycosyl-L-asparagine	295,1121	8,31	4,85E-02	-0,18	down	0,23	up
Deoxycholic Acid	393,3036	8,66	2,69E-02	-0,14	down	1,78	up
Cholic Acid	426,3221	9,50	1,01E-02	1,40	up	2,99	up
2E-octenoyl-CoA	909,2513	13,64	4,12E-02	-1,40	down	1,63	up
Docosahexaenoyl -CoA	1100,3195	13,81	9,61E-04	-1,35	down	2,52	up

Hexanoyl-CoA	866,187	11,45	9,31E-03	0,43	up	-2,56	down
10,11-DiHDPE	363,2474	11,39	4,06E-02	-2,43	down	-2,23	down
20-carboxy-LTB4	367,2171	7,31	3,63E-02	-0,78	down	1,79	up
PGJ2	373,1868	6,83	2,51E-02	-2,04	down	0,16	up
FAHFA(18:0/9-O-18:0)	549,5206	13,14	4,47E-03	-0,16	down	-3,14	down
3-hexenedioic acid	167,0278	11,84	3,37E-02	-1,72	down	2,04	up
Heptadecanoyl carnitine	436,3369	11,84	3,28E-02	-1,58	down	1,92	up
Propionyl carnitine	235,1679	9,11	3,97E-02	0,43	up	-1,84	down
LysoPE(20:1)	546,3037	8,31	4,89E-02	-2,33	down	0,39	up
LysoPC(13:0)	471,3276	10,19	7,59E-03	2,17	up	-1,09	down
LysoPC(22:4)	554,373	11,08	4,88E-02	0,60	up	2,65	up
LysoPE(12:0)	415,2478	4,49	4,19E-04	2,43	up	3,33	up
C25:3 Highly branched isoprenoid A	369,3451	12,79	5,79E-03	0,02	up	2,93	up
Guanosine 3’DP 5’TP	700,9639	11,25	3,01E-03	2,95	up	0,59	up
Adenosine tetraphosphate	625,9242	12,13	2,92E-02	0,17	up	2,45	up
ADP-ribose	560,0719	0,77	5,37E-08	3,72	up	4,01	up
Thyroxine	794,7161	14,22	4,05E-02	-2,25	down	1,09	up

Figure 41 showed the intensities of three of these compounds. The metabolic pathways where they are involved are fatty acid elongation in the mitochondria and in the reticulum or inflammation through the AA metabolism in the case of 20-carboxy-LTB4 and PGJ2. Both docosonaids were upregulated in old control animals but the restricted diet decreased the levels of these compounds. This regulation pattern is the most found between the fatty acyls metabolites. Levels in the restricted animals are downregulated when compared to the old control animals but up regulated respect to adult control animals. This same regulation pattern was found in compounds of the alanine, aspartate and glutamate metabolism and tyrosine metabolism. On the other hand, another group of metabolites increased in the restricted animals compared to both control groups was identified. Most of these compounds participate in the purine metabolism, such as adenosine diphosphate ribose, adenosine 5’ tetraphosphate and guanosine 3’ diphosphate 5’ triphosphate (Guanosine 3’DT 5’TP). The intensities of this last metabolite involved in purine metabolism are represented in Figure 42 along with the thyroxine. Furthermore, LPCs or LPEs, cholic acid and a highly branched isoprenoid were increased in the restricted animals compared to both control groups.

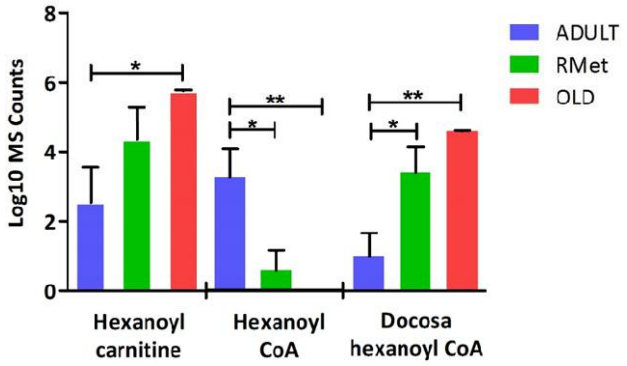

Figure 41. Intensities fatty acyl species from gluteus samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

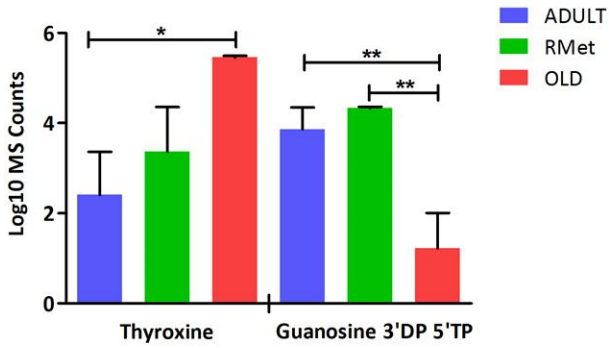

Figure 42. Intensities of different metabolites identified from gluteus samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

4.3.1.2. Soleus

Results from soleus analysis are described below. Multivariate statistics of the untargeted lipidomic analysis showed little differences between the experimental groups (Figure 43). The PCA showed a clear difference between both old experimental groups (control and RMet) while the adult control group is in the middle of the old experimental groups. The multivariate analysis performed using only the top 25 statistical significant lipid species increased the observed differences between the experimental groups. The first division separate almost all the old control animals from the rest. Hence, the differences in the lipidomic profile of the animals bring closer the adult control and the RMet old animals. Looking at the intensity of the different lipid entities, common areas for both controls as well as areas in common with the RMet animals can be seen.

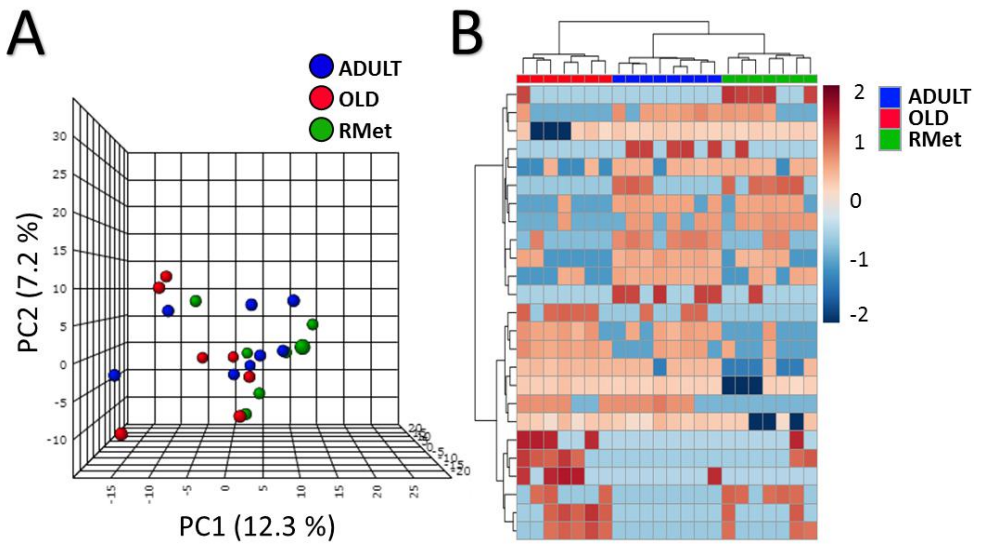

Figure 43. Lipidomic differences between control and restricted animals of soleus samples. A) Multivariate statistics with an unsupervised PCA revealed differences between adult control, old and methionine restricted old animals. Data was obtained by untargeted lipidomic analysis with ESI(+). B) Heat map representations of hierarchical clustering analyses using 25 most statistical significant lipids species (one-way anova) between experimental groups. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units**.**

In order to identify those lipid species responsible for a specific lipid profile for each experimental group, a one-way ANOVA test was performed with a post hoc Tukey to compare all of the groups between them. From the 613 lipid species detected and filtered in the untargeted lipidomic analysis, forty nine were significantly different between groups and eighteen of them were identified. All of the non-identified compounds obtained by untargeted lipidomics are in Table S35 of annex. Table 25 contains all of the identified lipid species and the regulation of these compounds in the RMet animals respect to both control groups. Between the compounds identified, there are AA conjugates and product of its metabolism downregulated in the restricted animals. Two of the lipid species identified, PI(32:4) and SM(d31:0), were also statistically different in gluteus samples. PI(32:4) regulation in the RMet animals respect to the adult control group is the same for gluteus and soleus samples, is decreased in the restricted animals. However, the intensity in the old control animals is decreased in soleus samples, unlike what happened in gluteus where the old control group had the higher levels of this lipid. The rest of the identified species can be classified in GPs and TAGs. The 80% RMet causes a decrease in the lipid species from these big families except for the PCs identified where the effect is the opposite. TAGs are downregulated in the restricted animals respect to the old control group except for one saturated lipid where the regulation is upregulated, TAG(45:0).

Table 25. Soleus lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
N-arachidonoyl L-serine	430,2439	0,83	2,00E-02	-7,54	down	-7,73	down
Arachidonyl carnitine	526,3792	0,87	2,87E-02	-4,91	down	-10,88	down
dhk-PGA2	691,4076	0,85	3,52E-02	-6,21	down	-9,18	down
LysoPC(22:2)	593,4187	0,84	4,99E-02	6,68	up	9	up
PC(P-38:2) PC(O-38:3)	820,6149	8,69	4,93E-02	2,37	up	-6,91	down
PE(49:0)	968,7302	8,06	2,37E-02	-6	down	2,01	up
PI(32:4)	825,469	6,09	2,94E-03	-10,51	down	-8,77	down
PI(O-42:4)	951,6304	4,64	3,64E-02	-5,95	down	-8,89	down
SM(d31:0)	680,5733	8,45	1,66E-02	-11,53	down	-6	down
TAG(42:0)	740,6724	9,45	2,56E-02	-9,11	down	-1,97	down
TAG(45:0)	782,7037	9,76	1,08E-02	4,29	up	10,62	up
TAG(46:3)	790,6826	9,29	1,30E-02	-12,28	down	-3,81	down
TAG(48:2)	820,735	9,7	4,74E-02	-1,22	down	-0,83	down
TAG(50:4)	844,7383	9,53	4,46E-02	-1,71	down	6,42	up
TAG(54:2)	904,8247	10,23	2,92E-02	-3,59	down	8,6	up
TAG(60:4)	984,8839	9,75	9,60E-03	-11,95	down	-9,93	down
TAG(62:4)	1012,916	9,92	3,28E-02	-4,68	down	-10,3	down
TAG(64:3)	989,9148	10,07	7,41E-03	-6,84	down	4,22	up

Figure 44 represent the intensities of some of the identified TAGs and in most of them, the RMet causes a decrease in their levels.

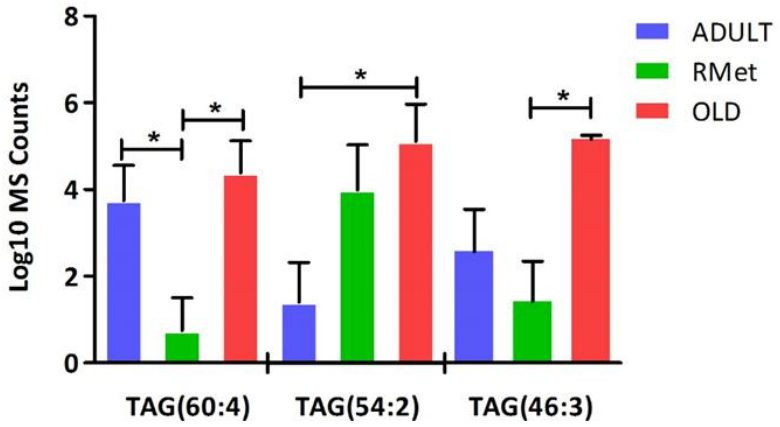

Figure 44. Intensities of triacylglycerol species from soleus samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001.

On the other hand, results obtained with the untargeted metabolomic analysis of soleus samples are presented below. In this case, soleus and gluteus results shared some similarities. As what happened in gluteus the multivariate statistics showed differences between analyzing the whole metabolome set detected and just the most statistically different compounds (Figure 45). If the whole set of metabolites is analyzed no difference between the experimental groups is observed. Few restricted samples of old animals are clustered with adult control animals but most of the samples, no matter which group they belong, are mixed. On the contrary, if the 25 most statistically significant metabolites are analyzed with the hierarchical clustering algorithm the experimental groups are perfectly separated between each other. As what happen in the lipidomic analysis, the first division separate almost all the old control animals from the rest. Hence, the differences in the metabolomic profile of the animals bring closer the adult control and the RMet old animals. Looking at the intensity of the different lipid entities, common areas for RMet animals and adult control group can be seen, while the old control group presents a characteristic metabolome profile.

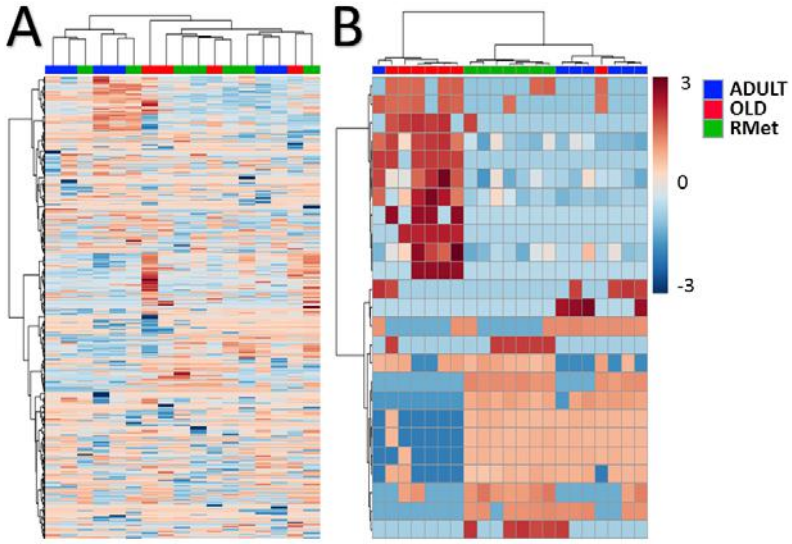

Figure 45. Metabolites distribution in soleus samples of restricted animals, control old and adult animals. A) Heat map representation of 1199 metabolites found in gluteus samples in positive ESI polarity. B) Heat map representation of the 25 most statistically different metabolites obtained one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units**.**

In order to identify those entities responsible for a specific metabolic profile for each experimental group, a one-way ANOVA test was performed with a post hoc Tukey to compare all of the groups between them. From the 1199 metabolites detected and filtered in the untargeted

metabolomic analysis, ninety seven were significantly different between groups and eighteen of them were identified. All of the non-identified compounds obtained by untargeted metabolomic analysis are in Table S36 of annex. Table 26 contains all of the identified metabolites and the regulation of these compounds in the RMet animals respect to both control groups.

Table 26. Soleus metabolites statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity**.**

Compound	m/z	RT	p	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
5-Methylcytidine	258,0927	0,42	4,21E-02	-1,70	down	1,98	up
Dihomomethionine	195,1187	1,56	4,12E-02	3,17	up	1,46	up
3-Oxotetradecanoyl-CoA	1030,25	12,88	4,04E-02	1,58	up	1,41	up
Propionyl-CoA	841,1956	11,44	3,98E-02	0,38	up	0,12	up
Arachidonyl carnitine	526,3878	10,54	3,13E-02	-3,10	down	-1,74	down
Heptadecanoyl carnitine	436,3485	11,84	5,60E-03	-3,82	down	-0,53	down
Stearoylcarnitine	450,3553	10,05	2,81E-02	-1,91	down	2,87	up
Deoxycholic Acid	410,3197	12,08	4,39E-02	-2,00	down	3,02	up
5α-dihydrotestosterone	291,2394	9,85	8,01E-03	3,73	up	2,05	up
LysoPA(20:0)	467,3178	4,91	4,56E-02	-1,43	down	1,71	up
LysoPC(9:0)	380,2213	7,32	7,82E-04	-2,30	down	3,90	up
LysoPC(15:0)	520,2701	8,31	7,76E-03	0,30	up	-2,95	down
LysoPC(16:1)	476,3016	4,89	4,99E-02	0,32	up	0,02	up
LysoPG(14:1)	455,2331	7,15	1,97E-04	4,38	up	3,43	up
LysoPG(20:0)	505,3219	11,04	4,68E-02	0,39	up	0,12	up
PI-3P	975,5211	13,25	8,39E-04	3,93	up	2,55	up
Sphinganine (Spa)	284,299	11,62	3,21E-02	0,24	up	3,41	up
13(S)-HODE methyl ester	293,2402	10,76	3,28E-02	-1,15	down	-3,33	down

Between the identified species a modified nucleoside derived from 5'-methylcytosine is found to be downregulated in restricted animals respect to old control group. The metabolite dihomomethionine showed higher levels in RMet animals respect both controls. As what happened in gluteus samples, same fatty acyls conjugate with coenzyme A or carnitine can be found between the differential compounds. In soleus samples, the fatty acyls conjugated with coenzyme A are upregulated in restricted animals respect to both control groups while the compounds conjugated with carnitine presented the opposite regulation. Some LPC, LPA and LPG species are also modified by the RMet intervention. Most of them upregulated in the RMet

animals respect to both control groups as is the case of the PI-3P illustrated in Figure 46 along with 5α-dihydrotestosterone and 13(S)-HODE methyl ester. The steroid hormone is upregulated in the restricted animals compared to both controls and statistically different from the old control group. On the other hand, the 13(S)-HODE methyl ester is downregulated in the RMet animals respect both control groups. In fact, this metabolite showed higher levels in the adult animals and it is statistically different from the restricted animals.

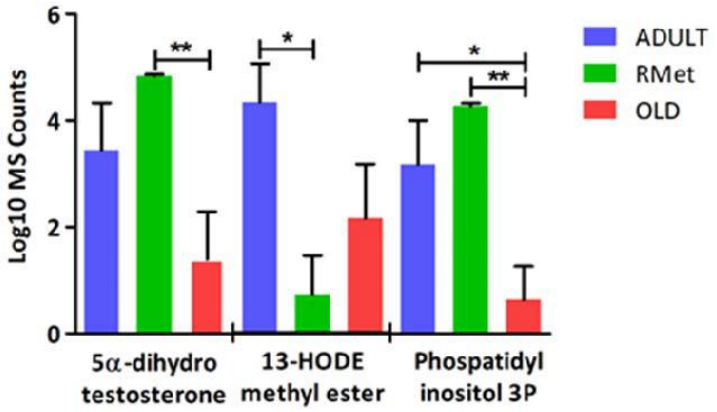

Figure 46. Intensities of different metabolites from soleus samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

4.3.2. White Adipose Tissue

The effect of the restriction of methionine in male Wistar rats was also studied in the lipidome of both types of WAT, VAT and SAT. First of all, both type of WAT were analyzed together in order to evaluate if the effect of diet was more important than the nature of the WAT. In section 4.2.2. when aging effect was evaluate in adipose tissue, age difference was not the most important factor to discriminate sample. In that case, the type of WAT, VAT or SAT, was the most important factor. Now, the global analysis of diet in both types of WAT with a multivariate statistical analysis revealed a difference between the adult control group and restricted old animals while the old control animals were not clearly separated from any of the other groups. Results from this analysis are shown in Figure 47 where in both types of test, principal component analysis and the hierarchical clustering analysis, a first division can be seen between the adult control animals and restricted old animals. Samples of WAT from old control experimental group were spread between both groups (adult control and restricted old animals). However, this fact could be as a result of analyzing different types of WAT. Hence, from now on each type of WAT will be analyzed independently.

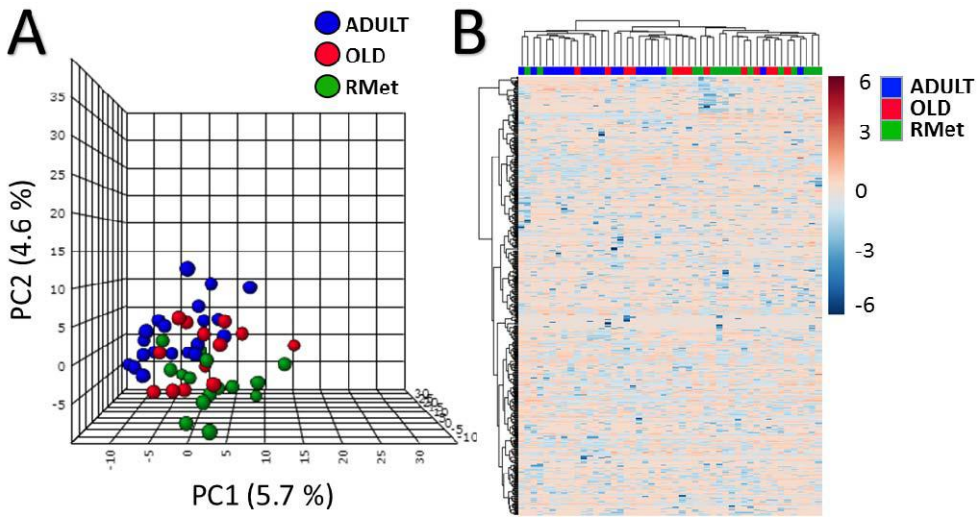

Figure 47. Lipidomic differences between experimental groups in two types of adipose tissue samples of rats. A) Multivariate statistics with an unsupervised PCA revealed differences mainly between adult control group and the groups of old animals. Data was obtained by untargeted lipidomic analysis with positive polarity of electrospray ionization. B) Heat map representation of 513 lipid species found in adipose tissue in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -6 (blue) to 6 (red) represents this normalized abundance in arbitrary units**.**

4.3.2.1. Visceral adipose tissue

Result from the untargeted lipidomic analysis of the VAT are described below. An unsupervised multivariate analysis of the sample did not show clear differences between the experimental groups. Neither the hierarchical clustering algorithm represented in Figure 48 by a heat map. Nevertheless, when a supervised multivariate analysis was performed, such as the partial least square discriminant analysis, the experimental groups were perfectly clustered together (Figure 49). This fact is also supported when the hierarchical clustering algorithm is performed only with the 25 most statistically significant lipid species. In this heat map, represented in Figure 49, the first division separates the adult control group from both of the old groups (RMet and control animals). In order to identify those lipid species responsible for a specific lipid profile for each experimental group, a one-way analysis of variance test was performed with a post hoc Tukey to compare all of the groups between them. From the 621 metabolites detected and filtered in the untargeted lipidomic analysis, fifty-three were significantly different between groups and twenty-six of them were identified. All of the non-identified compounds obtained by untargeted metabolomic analysis are in Table S37 of annex. Table 27 contains all of the identified metabolites and the regulation of these compounds in the RMet animals respect to both control groups.

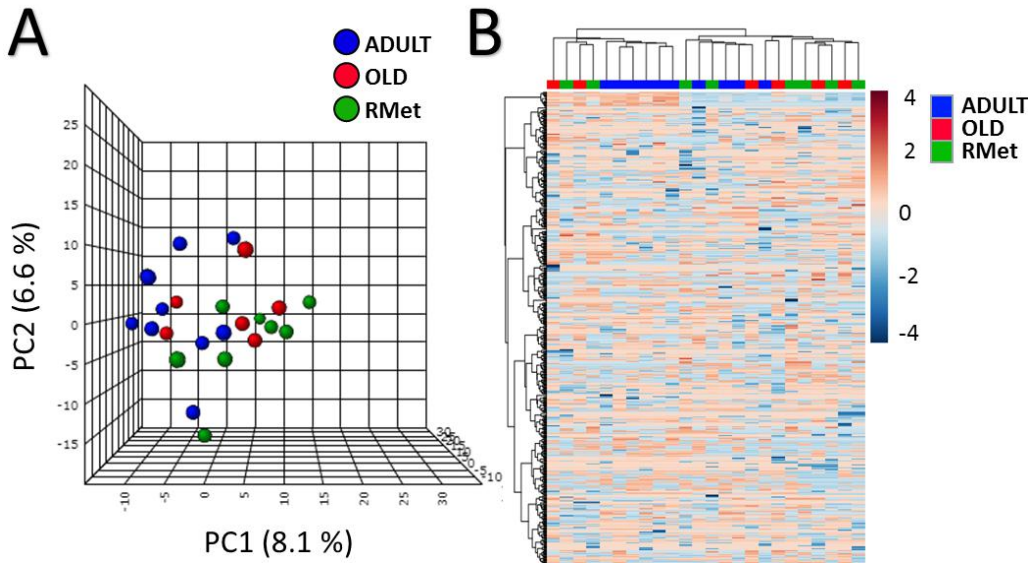

Figure 48. Lipidomic profiles of visceral adipose tissue samples from rats of the different experimental groups. A) Multivariate statistics with an unsupervised PCA did not reveal clear differences between the experimental groups. Data was obtained by untargeted lipidomic analysis with positive polarity of electrospray ionization. B) Heat map representation of 621 lipid species found in visceral adipose tissue in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -4 (blue) to 4 (red) represents this normalized abundance in arbitrary units**.**

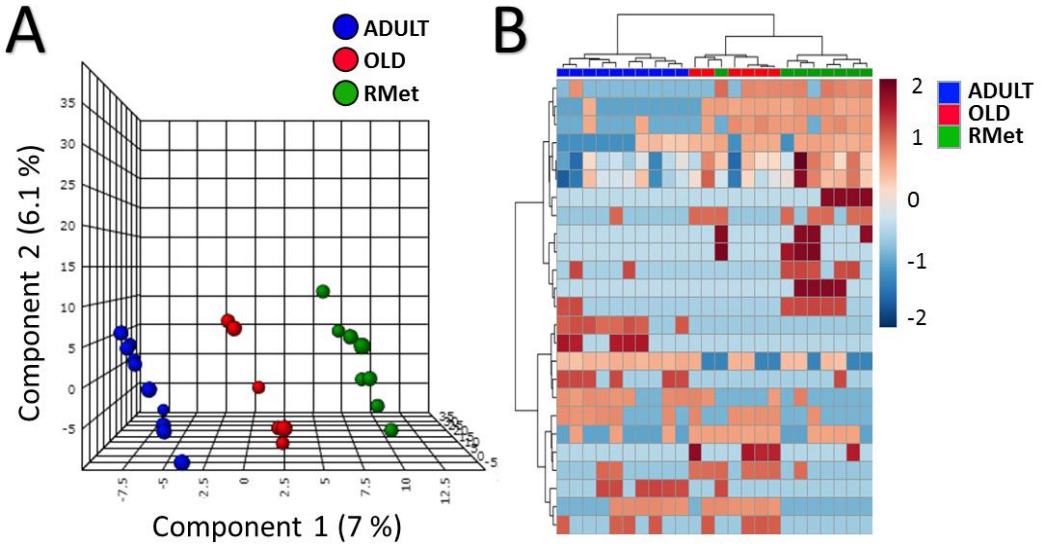

Figure 49. Multivariate statistics revealed different lipid profiles for visceral adipose tissue samples restricted animals and adult and old control animals. A) Partial least squares discriminant analysis of the lipid profile of visceral adipose tissue samples. 10-fold cross validation details of the PLS-DA model were accuracy 0.75, R^2 0.99998 and Q^2 0.45914. B) Heat map representation of the 25 most statistically different metabolites obtained one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units**.**

Between the identified compounds a metabolite of the arginine degradation pathway, 4-Guanidinobutanamide, was found to be upregulated in RMet old animals respect to the old animals with control diet but no respect to the adult control group. Two members of the fatty acyl category were found to be downregulated in the RMet animals respect to the old controls but upregulated when compared to the adult control experimental group. One of them was a metabolite of the AA and a precursor in the synthesis of 5-HETE, 5(S)HpEPE. The other, was a fatty acyl conjugated with coenzyme A, butyryl CoA. The rest of the identified compounds were GPs, SPs, GLs and one ST lipid derivative from cholesterol. This lipid was downregulated in the RMet animals compared to both experimental control groups.

Table 27. Visceral adipose tissue lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity**.**

Compound	m/z	RT	p	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
4-Guanidino butanamide	109,0886	0,83	3,92E-02	5,23	up	-0,10	down
5(S)-HpEPE	357,2031	0,83	4,38E-02	-1,95	down	6,00	up
Butyryl-CoA	855,2073	6,29	4,40E-02	-1,89	down	5,33	up
LysoPC(O-18:0)	548,333	0,83	2,77E-02	-7,26	down	-1,45	down
PE(30:2)	642,456	5,41	4,54E-02	-4,93	down	4,67	up
PE(33:4)	680,4792	7,71	2,93E-02	-0,01	down	7,58	up
PE(40:9)	803,5359	4,76	4,93E-02	11,04	up	4,39	up
Cer(d38:1)	632,5362	7,14	7,67E-03	-0,04	down	-7,78	down
Lactosylceramide (d44:1)	1002,7797	7,07	4,47E-02	9,83	up	5,16	up
SM(d33:1)	721,6027	8,43	4,07E-02	8,65	up	1,01	up
SM(d35:0)	736,632	8,11	4,89E-03	8,31	up	8,33	up
SM(d38:2)	671,5376	8,52	2,54E-02	10,74	up	7,27	up
DAG(34:3)	638,5655	8,10	1,28E-02	0,28	up	0,53	up
DAG(36:2)	634,5331	7,45	2,78E-02	6,53	up	-0,07	down
DAG(36:4)	613,4643	8,54	4,43E-03	8,37	up	8,40	up
DAG(41:5)	685,5765	8,71	3,89E-02	-2,61	down	-7,89	down
DAG(43:5)	695,5941	8,37	2,04E-02	-11,87	down	-8,16	down
TAG(42:1)	738,6624	9,20	2,74E-02	-10,61	down	-7,49	down
TAG(38:1)	703,5272	8,71	4,01E-02	-2,73	down	-8,08	down
TAG(42:4)	732,6059	8,52	3,67E-02	-3,66	down	-10,12	down
TAG(44:4)	760,6387	8,81	1,85E-02	-0,50	down	-9,13	down
TAG(53:5)	884,7731	9,63	4,80E-02	1,95	up	-6,87	down
TAG(52:7)	866,7393	9,21	1,83E-02	-13,00	down	-8,73	down
TAG(58:6)	952,834	10,09	4,68E-02	2,21	up	-6,48	down
TAG(62:5)	1010,9259	10,44	4,91E-02	0,71	up	5,98	up
4α-methyl-24-methylene cholestan-3β,8β,11β-triol	429,3648	7,55	3,09E-06	-0,04	down	-13,59	down

The identified compounds from the SP category were Cer, HexCer and SM species. Except for the Cer(d38:1), all of the SP species identified were upregulated in the RMet animals respect to both control groups as in the case of the lactosylceramide(d44:1). In the case of Cer(d38:1), RMet in old animals decreases the levels of this lipid specie compared to both control animals. Between the GP species identified, PEs were the most abundant. A plasmalogen of LPC and alkyl ether bond was also identified. Most of the GPs were downregulated respect to old control and upregulated respect to adult control in the RMet animals. PE(30:2) intensity values are represented in Figure 50. and this patter in the regulation can be seen. Along with this PE are represented two DAGs. In this group, the regulation was heterogeneous between the lipid species. Some of them were upregulated respect to the control groups, such as DAG(34:6), and others downregulated, as in the case of DAG(43:5). Thus, the remodeling of the DAG composition in VAT by the RMet in old animals is specific of each lipid species inside the DAG subclass.

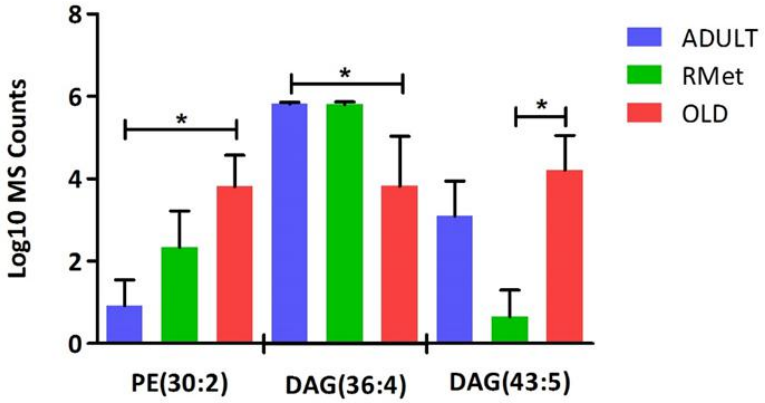

Figure 50. Intensities of different lipid species from visceral adipose tissue samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

Finally, between the identified statistically different lipid species there were several TAG species. In this subclass, the effect of the RMet produces a decrease in these lipid species in VAT. Almost all of this lipid species are downregulated in the RMet animals compared to both control groups, adults and old animals. In fact, the intensity values of three different MUFA and PUFA TAG species are illustrated in Figure 51. Thus, the most common regulation pattern in the TAGs was a downregulation in animals with the RMet diet respect to both groups with a control diet.

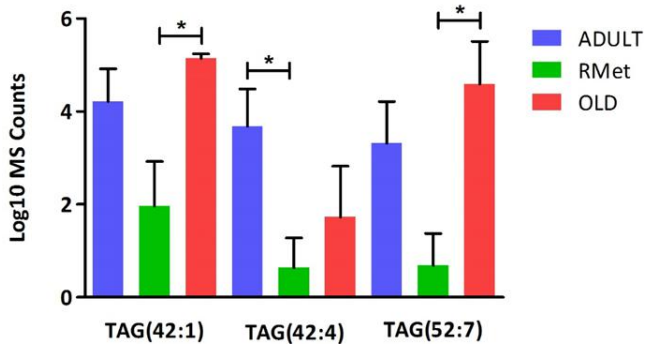

Figure 51. Intensities of triacylglycerol species from visceral adipose tissue samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

4.3.2.2. Subcutaneous adipose tissue

Result from the untargeted lipidomic analysis of the SAT are described below. This time the PCA showed clear differences between the adult control group and the RMet group. The old control group of animals were mixed between the other two experimental groups as what happen when both types of WAT were analyzed altogether. This result is illustrated in Figure 52 along with a hierarchical clustering algorithm performed only with 25 most statistically significant lipid species and represented as a heat map.

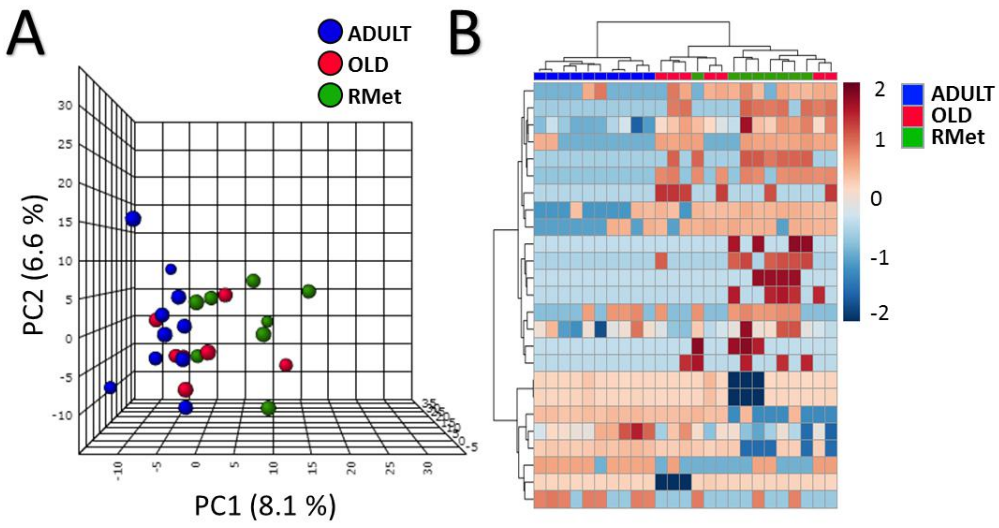

Figure 52. Multivariate statistics revealed different lipid profiles for subcutaneous adipose tissue samples restricted animals and adult and old control animals. A) The unsupervised PCA revealed differences mainly between control adult and methionine restricted old animals. Data was obtained by untargeted lipidomic analysis with ESI(+). B) Heat map representation of the top 25 most statistically metabolites obtained one-way anova. Each line of this graphic represents an accurate mass ordered by RT, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units**.**

First division of the heat map separates the adult control group from both of the old groups (RMet and control animals) as what happened in the VAT. In order to identify and verify if similar lipid species between both types of WAT were responsible for a specific lipid profile for each experimental group, a one-way ANOVA test was performed with a post hoc Tukey to compare all of the groups between them in subcutaneous samples. Table 28 contains all of the identified metabolites and the regulation of these compounds in the RMet animals respect to both control groups. All of the non-identified compounds obtained by untargeted metabolomic analysis are in Table S38 annex.

Table 28. Subcutaneous adipose tissue lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
2E-hexadecenoyl-CoA	968,2893	6,76	1,63E-02	-6,09	down	-5,93	down
3Z-dodecenoyl-CoA	965,2881	6,76	1,84E-02	-6,67	down	-6,56	down
PA(42:0)	806,684	8,73	3,10E-02	-0,68	down	-9,83	down
PC(37:0)	804,6657	8,48	1,44E-02	-0,19	down	-0,88	down
PC(42:1)	872,7202	7,71	1,31E-02	-3,28	down	-10,85	down
PE-Cer(d36:2)	704,5757	8,18	5,44E-03	-0,41	down	-1,29	down
Cer(d38:1)	632,5899	8,00	4,59E-02	-8,21	down	-9,69	down
SM(d35:1)	734,6244	7,79	7,69E-04	2,92	up	12,16	up
DAG(34:1)	595,5225	8,04	3,84E-02	6,16	up	10,70	up
DAG(34:3)	613,4669	8,54	1,03E-02	6,26	up	-5,51	down
DAG(36:4)	617,5054	8,06	1,17E-02	-6,01	down	-11,23	down
DAG(36:5)	615,4896	7,72	4,68E-02	5,90	up	0,13	up
DAG(42:1)	745,5998	8,18	1,57E-02	-6,12	down	-9,09	down
TAG(40:1)	715,5829	8,94	3,14E-02	1,60	up	-7,37	down
TAG(42:1)	738,6628	9,20	4,41E-02	-5,85	down	-9,56	down
TAG(47:4)	749,6343	8,72	4,08E-02	-1,78	down	7,46	up
TAG(48:2)	820,7418	9,30	2,43E-02	7,88	up	11,04	up
TAG(49:1)	836,7657	9,98	4,60E-02	-0,38	down	-8,46	down
TAG(51:3)	825,7369	9,65	3,86E-02	1,84	up	-7,55	down
TAG(52:7)	849,7089	9,03	1,18E-02	0,47	up	11,00	up
TAG(54:1)	911,7847	9,53	3,20E-02	-9,10	down	1,78	up
TAG(56:6)	924,8045	9,39	3,73E-03	9,37	up	9,42	up
TAG(58:1)	962,8995	10,62	2,99E-04	-10,52	down	1,98	up
TAG(58:6)	935,7995	9,44	4,08E-02	3,72	up	8,64	up
TAG(62:4)	1012,9223	10,54	2,58E-04	0,59	up	13,41	up
TAG(62:5)	1010,8358	8,84	3,34E-02	-2,46	down	-8,34	down
TAG(66:5)	1031,9362	10,36	3,71E-02	7,81	up	9,21	up

From the 585 lipid species detected and filtered in the untargeted lipidomic analysis, fifty-eight were significantly different between groups and twenty-seven of them were identified. Of the fifty-eight significantly different compounds, ten of them were commons between both types of WAT although only six common compounds between both types of WAT have and identity. Amongst them are one Cer, two DAG and three TAG species. Between the identified lipid species altered by RMet in SAT of old animals there are two fatty acyls conjugated with coenzyme A both of them down regulated in RMet animals respect to experimental groups with the control diet, as it can be seen in Figure 53. With the same regulation pattern, there was a few GPs, one phosphatidic acid and two PC species. Between the SP species identified, one Cer was also significantly different in the VAT and the regulation in both type of WAT was the same. Hence, both types of WAT (SAT and VAT) presented the same regulation for SP species. For the Cer subclass, species were downregulated in RMet animals while for the species of the SM subclass RMet increases their levels respect to both control groups being a regulation diet specific. Finally, most of the lipid species identify were GLs as much as DAG and TAG species. Regulation was heterogeneous in the compounds of this category and a pattern was not recognized for the GLs of the SAT.

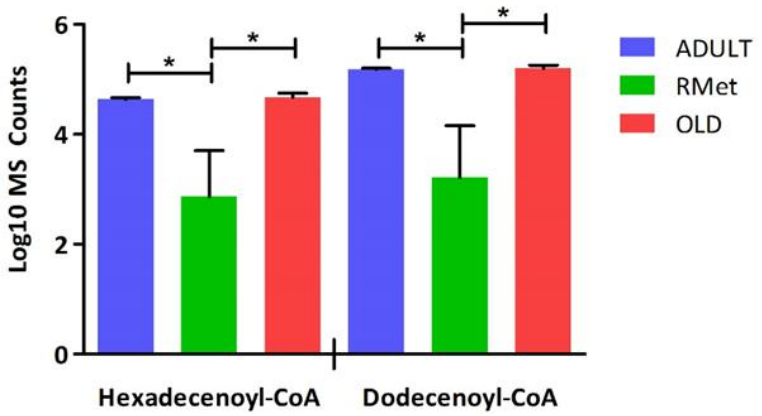

Figure 53. Intensities of fatty acyls species conjugated with coenzyme A from subcutaneous adipose tissue samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

For example, in Figure 54 are represented the intensities of several GLs with MUFA chains. In the case of the DAG species, RMet diet altered the concentration in both cases but in opposite sense. The DAG with less number of carbons was upregulated in the RMet animals while the one with more number of carbon atoms was downregulated. However, TAG species despite

heterogeneous regulations between the experimental groups a trend can be appreciated. TAG levels in RMet animals were among both of experimental control groups. The TAG of forty carbon atoms showed higher levels in adult control group, less in RMet animals and even less in old control group. The opposite situation can be seen for the TAG(54:1), where the experimental group with higher levels was the old control group of animals and the adult control group the one with less amount of this lipid, being among them the animals with the RMet diet.

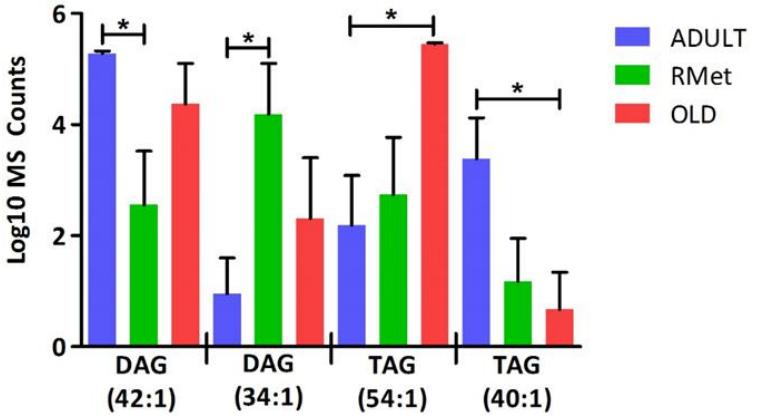

Figure 54. Intensities of glycerolipids species from subcutaneous adipose tissue samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

4.3.3. Kidney

In order to evaluate the effect of the RMet diet in the renal cortex samples of the rats, untargeted metabolomic and lipidomic analyses were performed and results are described below. Results from both of the analysis, lipidomic and metabolomic, were very similar. The unsupervised approach in the multivariate statistical analysis did not show clear differences between the experimental groups. PCA and hierarchical clustering analyses were performed for each type of untargeted experiment and in Figure 55 are illustrated the PCA from the untargeted lipidomic analysis and the hierarchical clustering analysis represented by a heat map from the compounds detected and filtered from the untargeted metabolomic analysis. However, when the most statistically different compound are used to analyze the experimental groups, as what happened studying the effect of aging, RMet diet in renal cortex samples of rats showed a different lipid and metabolic profile. In addition, same results were obtained with a supervised multivariate statistical analysis, specifically, a partial least squares discriminant analysis (PLS-DA)

for both profiles, lipidomic and metabolomic. The results for the untargeted lipidomic analysis are represented in Figure 56.

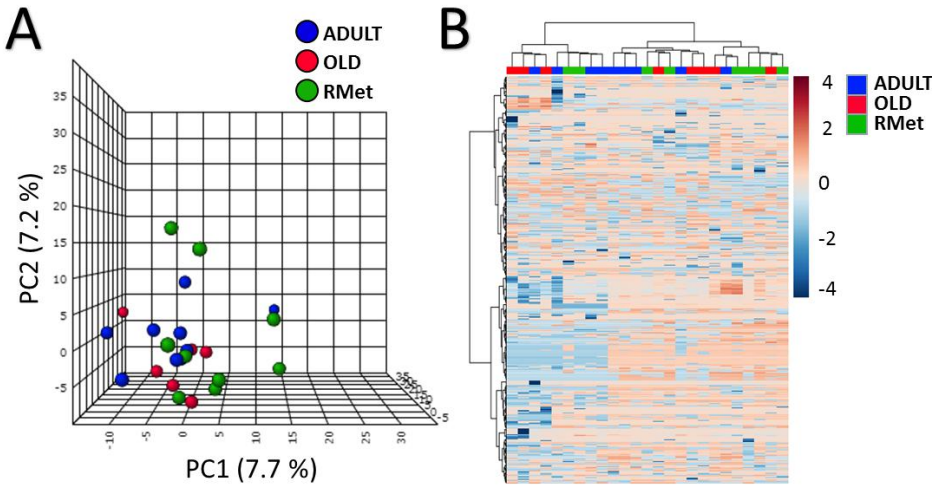

Figure 55. Lipidomic and metabolomic profiles of renal cortex samples from rats of the different experimental groups. A) Multivariate statistics with an unsupervised PCA did not reveal clear differences between the experimental groups. Data was obtained by untargeted lipidomic analysis with ESI(+). B) Heat map representation of 925 metabolites found in renal cortex samples by untargeted metabolomic analysis with positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -4 (blue) to 4 (red) represents this normalized abundance in arbitrary units.

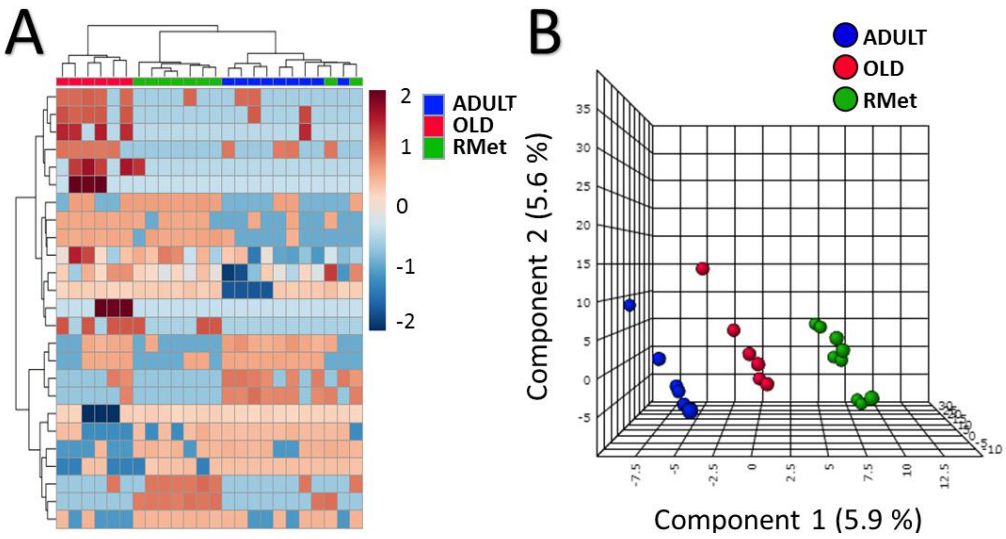

Figure 56. Multivariate statistics revealed different lipid profiles for renal cortex samples of RMet animals and adult and old control animals. A) Heat map representation of hierarchical clustering analyses of the 25 most statistically different lipid species obtained by one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units. B) Partial least squares discriminant analysis of renal cortex samples from RMet old animals and control old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.75, R^2 0.99976 and Q^2 0.15442.

Hierarchical clustering algorithm illustrated as a heat map show a clear separation between the experimental groups with a first division that put off the old control group from the rest. However, this fact only occurs with the 25 most statistically different lipid species obtained by one-way anova. In Figure 56, the PLS-DA representation of the untargeted lipidomic analysis also showed a perfectly clear separation between the experimental groups with a model accuracy of 0.75 obtain by the 10-fold cross validation test. In order to identify those entities responsible for a specific lipid profile for each experimental group, a one-way analysis of variance test was performed with a post hoc Tukey to compare all of the groups between them. From the 583 lipid species detected and filtered in the untargeted lipidomic analysis, forty six were significantly different between groups and fifteen of them were identified. All of the non-identified compounds obtained by untargeted lipidomic analysis are in Table S39 annex. Table 29. contains all of the identified lipids and the regulation of these compounds in the RMet animals respect to both control groups. Between the identified compounds there are mostly GPs although some SPs and GLs too. Regarding SP compounds, only two species were identified, a SM and a derivative of a HexCer. As in previous results, the regulation in RMet animals respect to control groups in these compounds was opposite. In the case of the SM, levels of this lipid were upregulated in RMet animals while Cer levels were downregulated in RMet animals respect to both control groups.

Table 29. Renal cortex lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity**.**

Compound	m/z	RT	p value	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
LysoPE(18:3)	493,303	0,83	1,97E-02	10,67	up	5,68	up
LysoPI(15:0)	559,2942	2,97	2,34E-02	-9,06	down	-0,03	down
PA(P-30:1)	585,4237	6,41	6,62E-06	14,26	up	12,35	up
PC(20:0)	604,3236	2,13	1,28E-02	10,73	up	7,02	up
PC(38:6)	823,5946	5,58	2,46E-03	8,39	up	0,07	up
PC(42:2)	870,688	7,40	4,78E-02	-7,80	down	-7,05	down
PC(P-38:2) PC(O-38:3)	820,6198	8,70	2,48E-03	-7,57	down	-0,07	down
PG(32:1)	721,5002	7,72	3,97E-02	0,05	up	-0,12	down
PS(P-29:0)	642,453	5,67	3,00E-02	-5,80	down	1,62	up
GlcAβ-Cer(d36:1)	742,5863	7,64	2,00E-03	-10,15	down	-1,76	down
SM(d30:0)	666,5661	8,41	2,00E-02	9,08	up	7,20	up
MAG(20:3)	381,2906	4,48	4,82E-03	-6,16	down	8,82	up
DAG(32:2)	529,4533	8,41	1,73E-02	0,61	up	7,37	up
TAG(40:2)	848,7654	9,56	1,88E-03	-10,11	down	1,85	up
TAG(61:6)	941,8264	9,94	2,35E-02	11,11	up	1,74	up

In addition, different types of GLs were identified both MAG, DAG and TAG species. All of them presented PUFA chains and upregulated in RMet animals respect to adult control groups. However, regulation in RMet animals respect to old control group was different for each lipid and no pattern was detected. Finally, the effect of RMet in the regulation of llipid species inside the GP category in kidney is heterogeneous and no pattern was detected. Among the PC species identified, half of them are upregulated in RMet animals respect to both controls and the other half is downregulated. Same happened with the LGPs identified and in other like PG(32:1) or PS(P-29:0) regulation in the RMet is different respect to each control group. In Figure 57 are illustrated some of the lipids species belonging to the GP category.

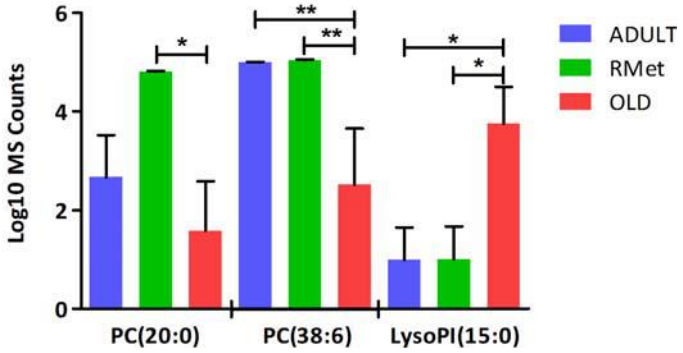

Figure 57. Intensities of glycerophospholipids species from renal cortex tissue samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

As for the results of the untargeted metabolomic analysis, the situation was very similar to the one with the lipid profiles. When the most statistically different compound are used to analyze the experimental groups, RMet diet in renal cortex samples of rats showed a different metabolic profile, as what happened with the lipid profile and also studying the effect of aging in renal cortex samples. In addition, same results were obtained with a supervised multivariate statistical analysis, specifically, a partial least squares discriminant analysis (PLS-DA). Results from both types of analysis, heat map and the PLS-DA, are represented in Figure 58. Hierarchical clustering algorithm illustrated as a heat map show a clear separation between the experimental groups with a first division that put off the adult control group from both of the old groups. In order to identify those entities responsible for a specific metabolic profile for each experimental group, a one-way ANOVA test was performed with a post hoc Tukey to compare all of the groups between them.

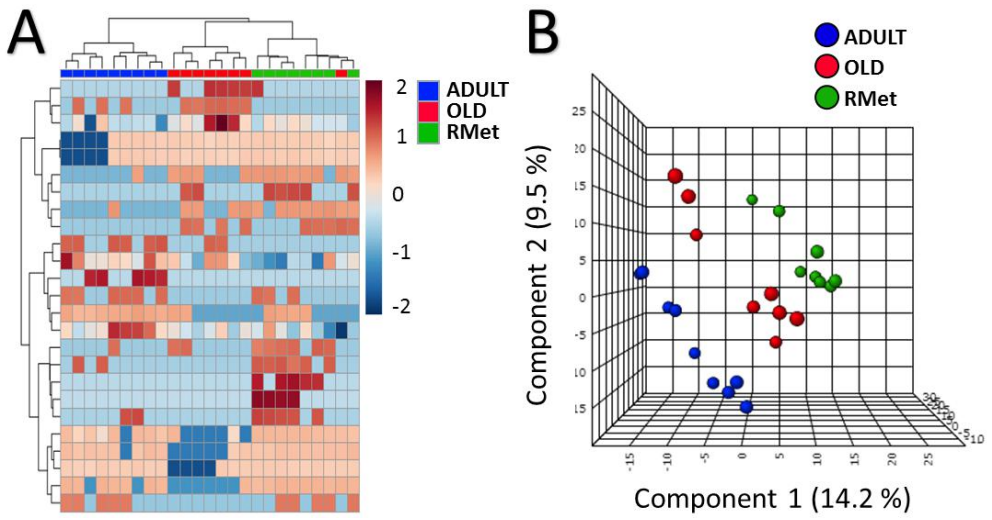

Figure 58. Multivariate statistics revealed different metabolomic profiles for renal cortex samples of RMet animals and adult and old control animals. A) Heat map representation of hierarchical clustering analyses of the 25 most statistically different metabolites obtained by one-way anova in ESI(+). Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -2 (blue) to 2 (red) represents this normalized abundance in arbitrary units. B) Partial least squares discriminant analysis of renal cortex samples from RMet old animals and control old and adult animals. 10-fold cross validation details of the PLS-DA model were accuracy 0.76, R^2 0.99533 and Q^2 0.28966**.**

From the 925 metabolites detected and filtered in the untargeted metabolomic analysis, seventy-one were significantly different between groups and fifteen of them were identified. All of the non-identified compounds obtained by untargeted metabolomic analysis are in Table S40 of annex, while Table 30. contains all of the identified metabolites and the regulation of these compounds in the RMet animals respect to both control groups. Between the identified species, there are a few metabolites that were also altered in other tissues. For example, 10,11-DiHDPE and 20-carboxy-LTB4 that were affected by the RMet in gluteus; 5-methylcytidine in soleus or ADP-ribose in SAT. From purine metabolism, inosine was also altered in RMet animals being upregulated respect to the old control experimental group. Intensities of the docosanoid species identified, 10,11-DiHDPE and 4,5-epoxy-HDHA along with angiotensin (1-7) are represented in Figure 59. As in other tissues, renal cortex fatty acyls conjugated with coenzyme A or acylcarnitine species were altered in RMet animals, mostly upregulated respect to both control groups. A bile alcohol and a bile acid were also identified, this last compound upregulated in RMet animals respect to both controls. Finally, glutathione disulfide (GSSG) and a prostaglandin were found to be downregulated in RMet animals respect to both experimental control groups.

Table 30. Renal cortex metabolites statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
5-Methylcytidine	258,0986	0,48	2,24E-02	-2,27	down	0,69	up
ADP-ribose	542,0597	0,58	3,60E-03	-0,02	down	-2,36	down
Inosine	269,0814	0,67	2,91E-02	0,01	up	-0,12	down
Glutathione disulfide	613,1499	0,46	1,69E-02	-2,46	down	-0,51	down
Angiotensin (1-7)	937,4213	11,50	3,75E-02	2,29	up	2,58	up
4,5-epoxy-17R-HDHA	399,2466	10,04	1,83E-02	2,62	up	0,48	up
10,11-DiHDPE	363,2511	11,47	2,36E-02	2,35	up	0,05	up
20-carboxy-LTB4	367,2129	7,33	1,43E-02	-0,11	down	0,00	down
6-keto PGE1	369,2334	6,89	1,92E-02	-2,37	down	-0,51	down
5β-Cholestane-3α,7α-diol	427,3541	13,89	2,42E-02	-0,07	down	1,98	up
Glycocholic Acid	466,3105	8,93	1,76E-04	2,89	up	2,85	up
3Z-dodecenoyl-CoA	912,2679	13,69	4,35E-02	-1,18	down	1,03	up
Formyl-CoA	778,0916	10,56	2,15E-02	0,55	up	-1,75	down
Palmitaldehyde	258,2745	9,11	4,61E-03	0,01	up	2,69	up
Propionyl-L-carnitine	235,1639	9,19	2,78E-02	0,00	up	2,36	up

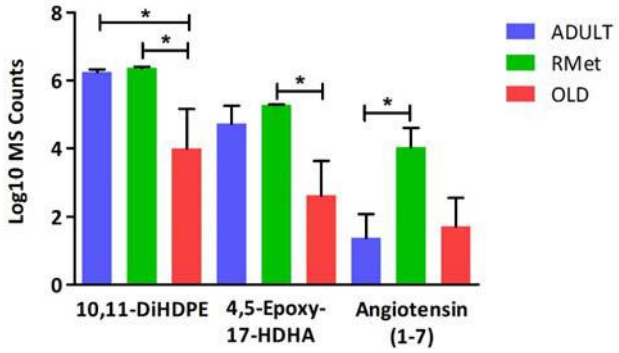

Figure 59. Intensities of different metabolites from renal cortex tissue samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001.

4.3.4. Heart

In order to evaluate the effect of the RMet diet in the heart samples of the rats, untargeted metabolomic and lipidomic analyses were performed and results are described below. First, it have been described the results obtain with the untargeted lipidomic analysis. The unsupervised approach in the multivariate statistical analysis did not show clear differences between the experimental groups. This fact can be appreciated in the principal component analysis illustrated in Figure 60 A. However, when the most statistically different compound are used to analyze the experimental groups, as what happened studying the effect of aging, RMet diet in heart samples of rats showed a different lipid profile for each type of experimental group of samples. Hierarchical clustering algorithm illustrated as a heat map with the 19 most statistically different compounds showed a clear separation between the experimental groups with a first division that put off the old control group from the rest (Figure 60 B). In order to identify those entities responsible for a specific lipid profile for each experimental group, a one-way analysis of variance test was performed with a post hoc Tukey to compare all of the groups between them. From the 532 lipid species detected and filtered in the untargeted lipidomic analysis, only nineteen were significantly different between groups and seven of them were identified.

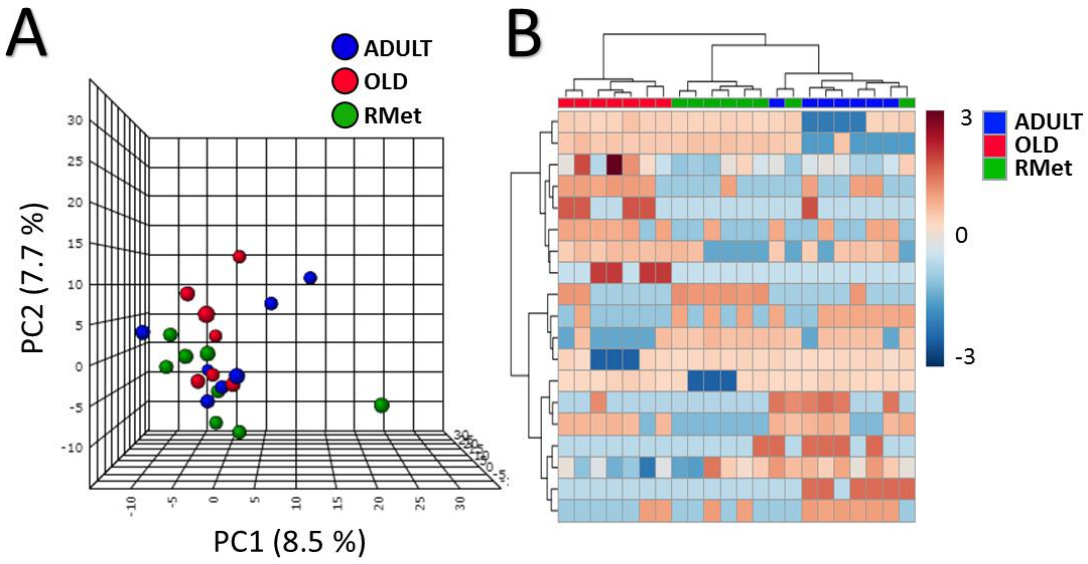

Figure 60. Multivariate statistics lipid profiles for heart samples in restricted animals and adult and old control animals. A) The unsupervised PCA did not reveal differences between control groups and methionine restricted animals. Data was obtained by untargeted lipidomic analysis with positive polarity of electrospray ionization. B) Heat map representation of the 19 most statistically different metabolites obtained one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units.

All of the non-identified compounds obtained by untargeted lipidomic analysis are in Table S41 of annex. Table 31 contains all of the identified lipids and the regulation of these compounds in the RMet animals respect to both control groups.

Table 31. Heart lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	Log FC RMet vs OLD	RMet vs OLD	Log FC RMet vs ADULT	RMet vs ADULT
9K,12,13-diHODE	309,2097	0,80	1,21E-02	-12,16	down	-4,94	down
GA2(d30:1)	1008,6528	4,99	3,49E-02	-0,49	down	-8,34	down
PA(27:1)	599,3815	1,24	4,90E-02	7,86	up	-1,54	down
MAG(16:0)	369,2413	3,57	1,89E-03	-8,88	down	0,09	up
TAG(52:2)	881,7527	10,06	4,43E-02	-10,22	down	-7,92	down
TAG(53:7)	885,6846	9,55	1,90E-03	-11,89	down	-9,28	down
TAG(56:4)	928,8271	10,09	1,35E-02	-0,29	down	-9,70	down

The number of compounds statistically different between the experimental groups was only a 3,6% of the total, which correlates with the results observed with the multivariate analysis where the whole lipidomic profile detected in heart samples did not separate the experimental groups but analyzing the most statistically significant compounds experimental groups were clustered separately (Figure 60). Hence, modifications in the lipidomic profile of heart samples of rats by RMet diet were limited to a few lipid species. Between the identified compounds an octadecanoid, 9K,12,13-diHODE, was downregulated in RMet respect to both control as well as one SP, ganglioside GA2 (d30:1). One phosphatidic acid was identified to be altered in RMet animals being upregulated respect to old control group and downregulated compared to adults. Finally, a few GLs were identified, a MAG with an SFA chain and three TAGs with PUFA chains, all of them downregulated in RMet animals respect to both control groups. In Figure 61 are represented the intensity values of the hydroxy-octadecanoid and two of the TAG identified. The regulation pattern in all of them is the same, being the levels of this compounds downregulated by the effect of the RMet in the diet. Unlike what happened with the results from the lipidomic profiles, data analyzed from the untargeted metabolomic analysis showed differences between the experimental control groups with the whole set of metabolites detected and filtered. Analyzing the effect of aging in section 4.2.4 same situation happened with these heart samples.

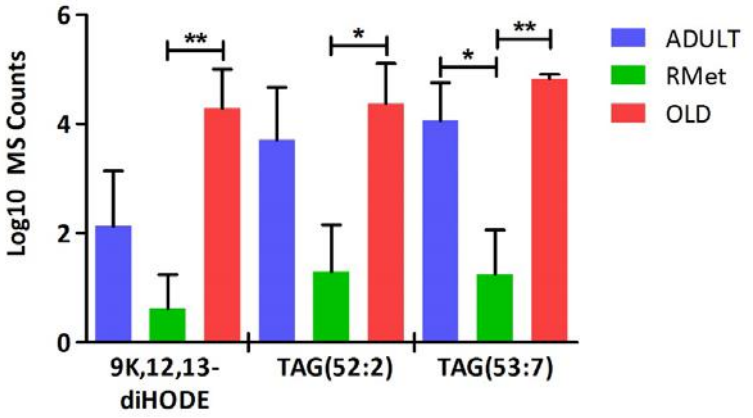

Figure 61. Intensities of different lipid species from heart samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

Results from the unsupervised approach in the multivariate statistical analysis are represented in Figure 62. Both, PCA and heat map from the hierarchical clustering analysis showed clear differences between the experimental control groups being the RMet samples mixed in between them.

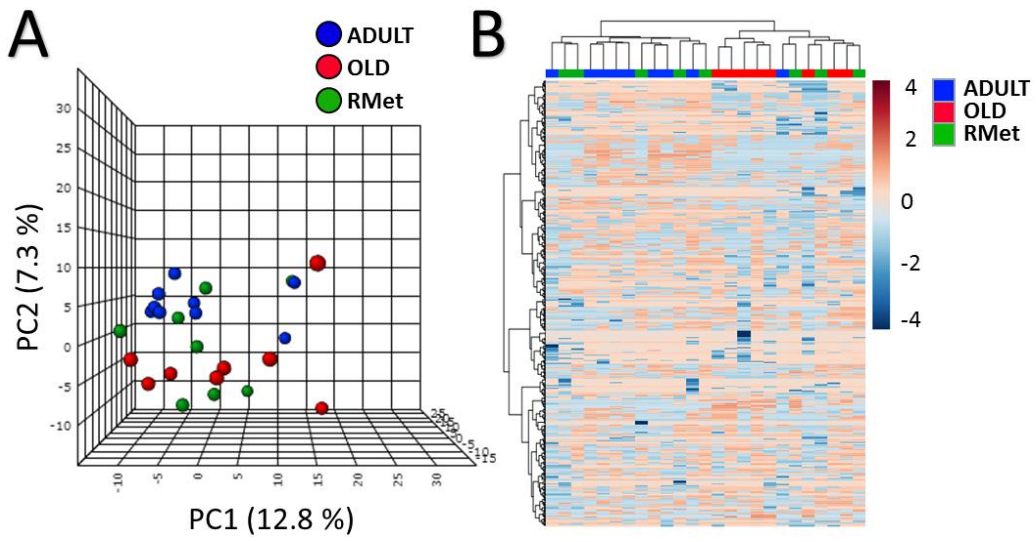

Figure 62. Multivariate statistics revealed different lipid profiles for heart samples of restricted animals and adult and old control animals. A) The unsupervised PCA revealed differences mainly between both control groups, adult and old animals being the methionine restricted old animals in between. Data was obtained by untargeted lipidomic analysis with positive polarity of electrospray ionization. B) Heat map representation of 569 metabolites found in heart samples by untargeted metabolomic analysis with positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to median/mean across the samples. The scale from -4 (blue) to 4 (red) represents this normalized abundance in arbitrary units**.**

From the 569 metabolites detected and filtered in the untargeted metabolomic analysis, sixty-one were significantly different between groups and twenty-five of them were identified. All of the non-identified compounds obtained by untargeted metabolomic analysis are in Table S42 of annex. Table 32. contains all of the identified metabolites and the regulation of these compounds in the RMet animals respect to both control groups. First metabolite in this table is succinic acid, involved in several metabolic pathways such as citrate cycle, oxidative phosphorylation in the electron transport chain, cAMP signaling and some amino acid metabolism.

Table 32. Cardiac metabolites statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
Succinic acid	119,0306	0,68	2,24E-02	-2,18	down	0,55	up
ADP-ribose	542,0604	0,74	7,28E-05	-1,72	down	2,14	up
Phosphoribosyl-AMP	560,0784	0,71	1,53E-02	1,68	up	-0,12	down
Guanosine 3'P	364,0558	0,50	6,76E-03	2,84	up	1,67	up
Hypoxanthine	137,0374	0,87	1,49E-02	3,38	up	4,05	up
Ouabain	567,2782	5,89	2,92E-02	1,74	up	-0,61	down
Anandamide	354,2806	9,05	1,78E-02	-0,50	down	2,54	up
FAHFA(18:0/9-O-18:0)	549,5199	13,18	2,11E-02	-1,59	down	1,04	up
2-docosanamido ethanosulfonic acid	448,345	9,73	4,91E-04	-1,91	down	2,30	up
10-F2-dihomo-IsoP	397,2882	10,50	2,78E-02	-1,94	down	1,50	up
Leukotriene C4	626,2913	5,89	4,21E-02	1,63	up	-0,15	down
2-Methylbutyroylcarnitine	246,1638	1,81	4,72E-02	0,06	up	2,16	up
Elaidic carnitine	426,3561	10,12	4,98E-02	-2,98	down	-0,96	down
Hexanoylcarnitine	260,1788	2,88	6,82E-03	-2,38	down	0,51	up
Isobutiryl carnitine	232,1485	1,17	3,80E-02	-2,72	down	-0,25	down
Linoleyl Carnitine	424,3466	9,72	9,13E-03	-3,49	down	-1,01	down
Myristoylcarnitine	372,3075	9,15	5,26E-03	-3,19	down	0,02	up
trans-Hexadec-2-enoyl carnitine	398,3308	9,44	5,00E-02	-1,80	down	0,59	up
26-hydroxycholesterol 3-sulfate	483,3112	11,05	2,01E-02	0,87	up	3,33	up
Taurocholic acid	533,3309	7,70	3,31E-02	2,28	up	-0,25	down
LysoPA(20:4)	497,1975	10,26	3,50E-02	-2,05	down	-2,53	down
LysoPG(13:0)	443,2286	8,63	2,96E-03	1,21	up	-2,45	down
LysoPG(19:0)	527,3369	11,11	3,38E-02	-0,53	down	-2,43	down
LysoPG(20:5)	569,2287	10,26	4,38E-02	0,16	up	-2,03	down
LysoPG(O-18:0)	516,3656	7,94	9,95E-04	1,29	up	-2,57	down

Succinic acid was found to be downregulated in RMet animals respect to old control animals and levels of this metabolite in the RMet old animals were more similar to the adult control group.Intensity values of succinic acid are illustrated in Figure 63. Along with the succinic acid, intensities of two other metabolites involved in the purine metabolism, ADP-ribose and hypoxanthine, are represented in Figure 63. In section 4.2.4, when the effect of aging in cardiac metabolism was study, ADP-ribose was one of the metabolites identified to be upregulated in old animals respect to the adult group. Now, with the RMet diet levels of this compound are downregulated respect to the old control experimental. Thus, RMet returns levels of ADP-ribose closer to a younger phenotype in cardiac tissue. On the other hand, hypoxanthine levels in RMet animals was upregulated respect to both control groups as well as the metabolite guanosine 3' phosphate (Guanosine 3'P). This last metabolite, 8-oxo-dGMP or Guanosine 3'P, has two possible identities because with this method it cannot be discriminated between the position of the oxygen double bond and the hydroxyl group that differentiates both molecules. Therefore, RMet affects purine metabolism in two different manners, returning the levels of the compounds towards a younger phenotype or readjusting the concentration of a few compounds in a specific way. Indirectly related with the purine metabolism through the histidine metabolism, phosphoribosyl-AMP was found to be upregulated in the RMet group respect to the old control animals.

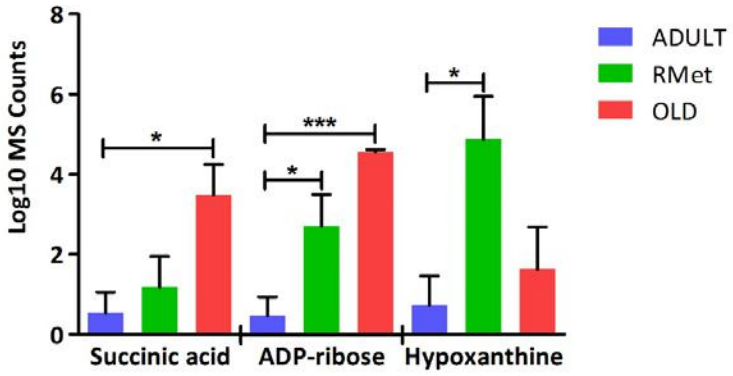

Figure 63. Intensities of different metabolites from heart samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

As it has been discussed before, the more polar lipids are well detected with the untargeted metabolomic analysis. In cardiac tissue, between the statistically different metabolites, a set of acyl carnitines was identified. All of them were previously identified as metabolites upregulated in old control rats respect to adult animals when the effect of aging was being studied in section

4.2.4. RMet animals showed a significant decreased in acyl carnitine levels respect to old control animals. Intensity levels of four of the acyl carnitine species identified are represented in Figure 64. In this illustration it can be appreciated how acyl carnitine levels in RMet old animals presented levels more similar to the adult control animals than old control group. On the other hand, a set of derivatives of AA were identified such as leukotriene C4 and 10-F2-dihomo isoprostane, which intensity levels are illustrated in Figure 65. Finally, a few LPG were identified to be upregulated in RMet old animals respect to old control animals except for the lipid specie LPG(19:0) downregulated respect both control groups. Two of the lysophosphatylglycerol lipids are represented in Figure 65. In both of them it can be seen how the trend regulation in RMet group was to be in between both experimental control groups.

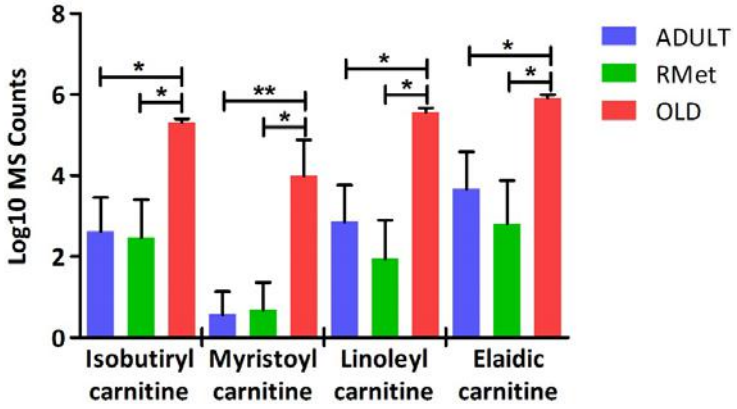

Figure 64. Intensities of different acyl carnitine species from heart samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

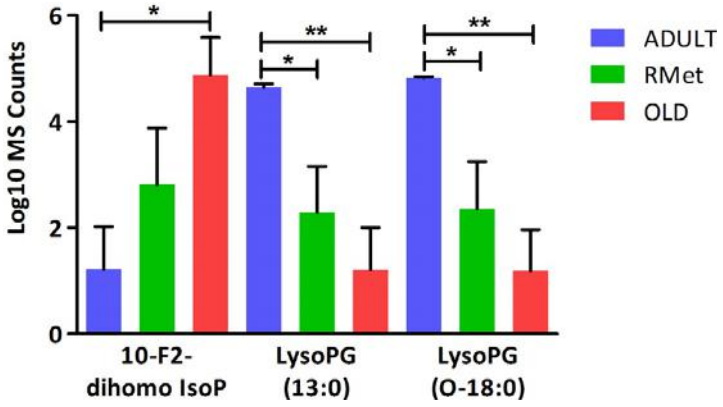

Figure 65. Intensities of a F2 isoprostane and two phosphatidylglycerol species from heart samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

4.3.5. Liver

In order to evaluate the effect of the RMet diet in the liver samples of the rats, untargeted metabolomic and lipidomic analyses were performed and results are described below. First, it have been described the results obtain with the untargeted lipidomic analysis. The unsupervised approach in the multivariate statistical analysis showed clear differences between RMet animals and both control groups. This fact can be appreciated in both angles of the principal component analysis illustrated in Figure 66. RMet animals were mostly differentiated from both of the control groups by the second principal component and thus, the influence of the RMet diet in the lipidome can explained approximately a 7.4% of the variability across the hepatic tissue samples of the experimental groups. On the other hand, age-related changes in the lipidome did not seem to be an important factor for explaining the variability across samples. Nevertheless, in the other PCA angle showed in the same figure it can be seen how in the third component both control groups, adults and old animals, were clustered individually.

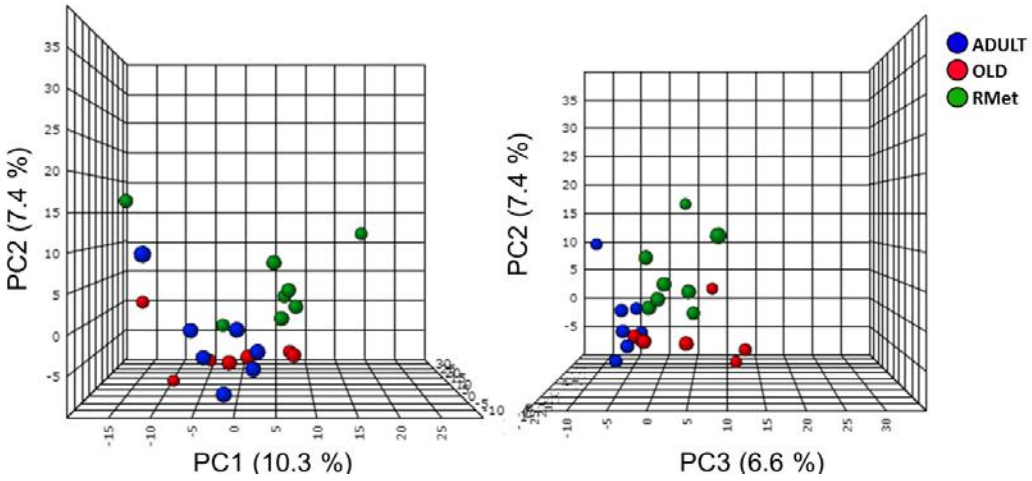

Figure 66. Multivariate statistics revealed different lipid profiles for heart samples of restricted animals and adult and old control animals. Two viewing angles of the unsupervised PCA are showed. PC2 revealed differences mainly between the restriction animals and both control groups, adult and old rats. Data was obtained by untargeted lipidomic analysis with positive polarity of electrospray ionization.

Analyzing the lipidome with a hierarchical clustering algorithm did not show a clear separation between the experimental group with the whole set of detected and filtered lipid species. However, when the most statistically different compounds are used to perform the analysis, each experimental group was clustered together being the RMet animals in between both control groups although more closed to the old animals because the first division put off the adult control group from the old groups (Figure 67). In order to identify those entities

responsible for a specific lipid profile for each experimental group, a one-way ANOVA test was performed with a post hoc Tukey to compare all of the groups between them.

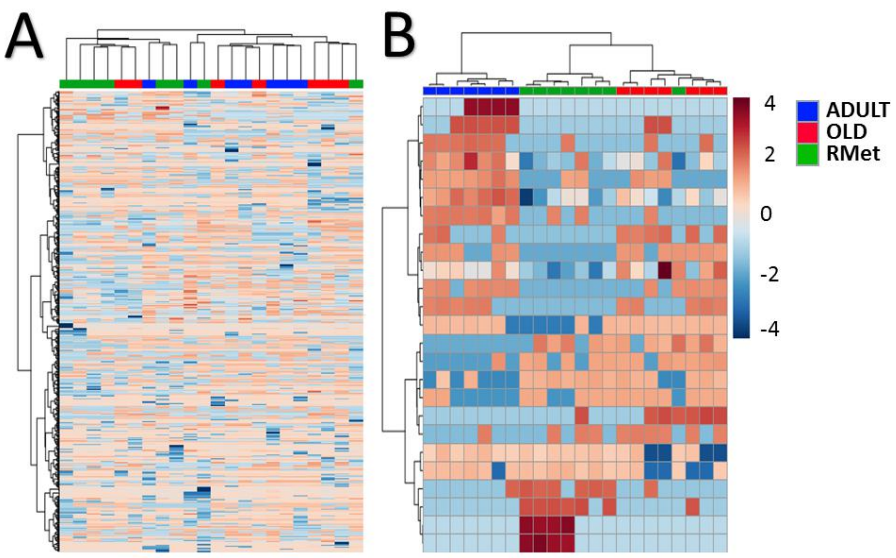

Figure 67. Lipid species distribution in liver samples of restricted animals, control old and adult animals. A) Heat map representation of 629 metabolites found in liver samples in positive ESI polarity. B) Heat map representation of the 43 most statistically different metabolites obtained one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units**.**

From the 629 lipid species detected and filtered in the untargeted lipidomic analysis, forty three were significantly different between groups and sixteen of them were identified. All of the non-identified compounds obtained by untargeted lipidomic analysis are in Table S43 of annex. Table 33 contains all of the identified lipids and the regulation of these compounds in the RMet animals respect to both control groups. Between the lipid species identified there were GPs, GLs, SPs and Pr species. From the GP category, PEs were the most abundant lipid species identified. The trend in the regulation of these lipid subclass was to be downregulated in the restricted animals respect to both experimental control groups. Nevertheless, in the case of PE(36:5), represented in Figure 68, the intensity of this lipid in the restricted animals was lower respect to adult control. Although PE(36:5) in the RMet animals was higher than the age-matched control, this difference was not statistically significant. In the same figure, it also has been represented the intensity of a phosphoric acid ether lipid, PA(P-30:1), significantly upregulated in the RMet group respect to both control groups. Thus, the RMet effect on the GP category seems to be specific for each individual lipid specie. Among the SP species, two different types of HexCer were identified, one of them conjugated with a glucose molecule and the other with two

molecules of galactose. Both of them were upregulated in the restricted old animals compared to old animals with control diet.

Table 33. Liver lipid species statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity**.**

Compound	m/z	RT	p value	Log FC RMet vs OLD	RMet vs OLD	Log FC RMet vs ADULT	RMet vs ADULT
PA(P-30:1)	585,4219	6,41	9,79E-03	10,09	up	10,08	up
PC(34:2)	758,5625	7,33	2,17E-03	-0,01	down	-11,82	down
LysoPE(18:1)	444,2904	0,84	2,12E-02	-9,33	down	-2,31	down
PE(36:5)	738,5068	6,83	2,91E-04	1,86	up	-13,17	down
PE(34:1)	740,5147	6,81	9,97E-03	-2,08	down	10,52	up
PE(34:2)	716,5163	6,88	1,67E-04	-0,35	down	-1,10	down
PE(36:1)	768,5477	7,34	4,01E-02	-7,41	down	-7,77	down
PE(36:2)	766,5328	6,87	1,07E-02	-7,95	down	-13,20	down
Glucosylceramide (d38:1)	794,613	8,88	9,15E-03	9,01	up	9,07	up
Galabiosylceramide (d43:1)	1010,7737	8,51	2,40E-02	1,85	up	-6,64	down
DAG(36:6)	613,463	8,55	7,64E-03	-4,87	down	-12,03	down
TAG(42:1)	738,6608	9,22	8,44E-03	-7,53	down	3,97	up
TAG(48:5)	814,6781	8,91	1,08E-03	10,22	up	12,66	up
TAG(52:4)	893,7064	9,76	9,08E-03	8,41	up	8,47	up
TAG(66:6)	1064,9312	10,82	4,87E-04	-0,63	down	12,62	up
Ubiquinone 9	812,6496	9,17	2,74E-02	-0,99	down	-0,57	down

Concerning the lipid species identified from the GL category, almost all of the identified species were TAGs, except for DAG(36:6) downregulated by RMet diet compared to both control groups. Regulation in the RMet animals compared to both control groups was heterogeneous and no pattern was found between the identified lipid subclasses. Finally, belonging to the Pr category, ubiquinone 9 was identified, being downregulated in the restricted animals respect to both, old

and adult, experimental control groups. The intensity levels of ubiquinone 9 are also represented in Figure 68.

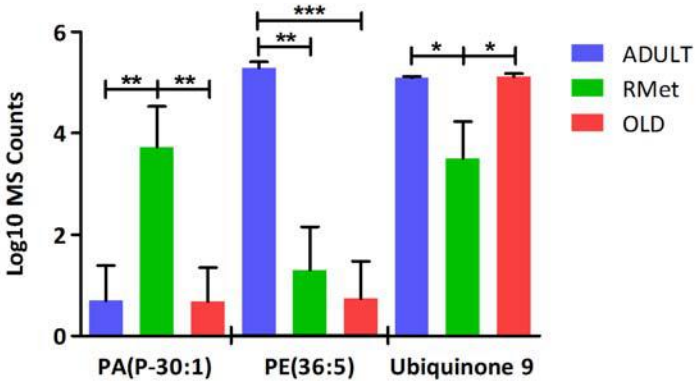

Figure 68. Intensities of lipid species from liver samples of rats. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

Regarding to the results of the untargeted metabolic analysis, equally to the results obtained in the lipidomic analysis, the unsupervised approach in the multivariate statistical analysis showed clear differences between RMet animals and both control groups. This fact can be appreciated in both angles of the principal component analysis illustrated in Figure 69. RMet animals were mostly differentiated from the control groups by the second principal component, being diet the most important factor to classify the experimental groups. Unlike the lipid profile, metabolites of both control groups, adults and old animals, were mixed together even in the angle of the third component. Hierarchical clustering algorithm with the whole set of detected and filtered metabolites showed a difference between RMet animals and both control groups, just like in the PCA. Moreover, when the most statistically different compounds are used to analyze the samples, the heat map showed a clear difference between each experimental group being both experimental control groups clustered together and the RMet animals a part from both of them (Figure 70). In order to identify those entities responsible for a specific lipid profile for each experimental group, a one-way analysis of variance test was performed with a post hoc Tukey to compare all of the groups between them. From the 1136 lipid species detected and filtered in the untargeted lipidomic analysis, one hundred and forty two were significantly different between groups and twenty seven of them were identified. All of the non-identified compounds obtained by untargeted lipidomic analysis are in Table S44 of annex. Table 34 contains all of the identified metabolites and the regulation of these compounds in the RMet animals respect to both control groups.

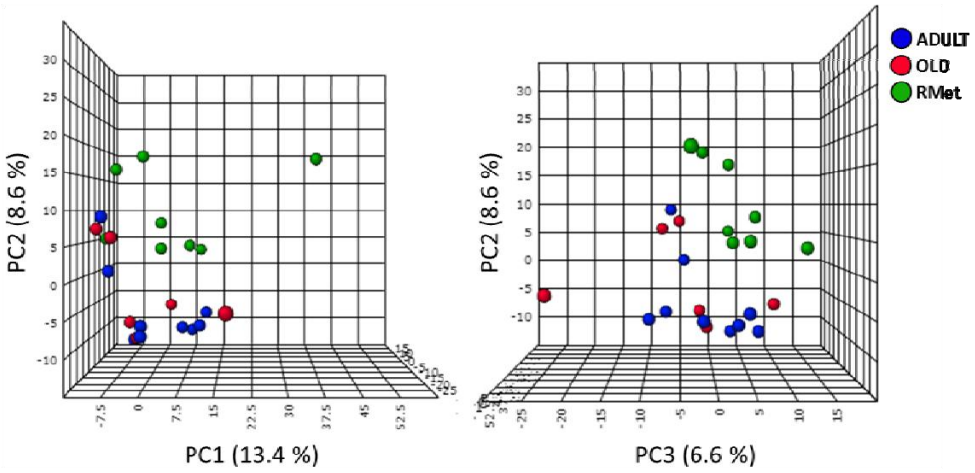

Figure 69. Multivariate statistics revealed different metabolic profiles for liver samples of restricted animals and adult and old control animals. Two viewing angles of the unsupervised PCA are showed. PC 2 revealed differences mainly between the restriction animals and both control groups, adult and old rats. Data was obtained by untargeted lipidomic analysis with positive polarity of electrospray ionization.

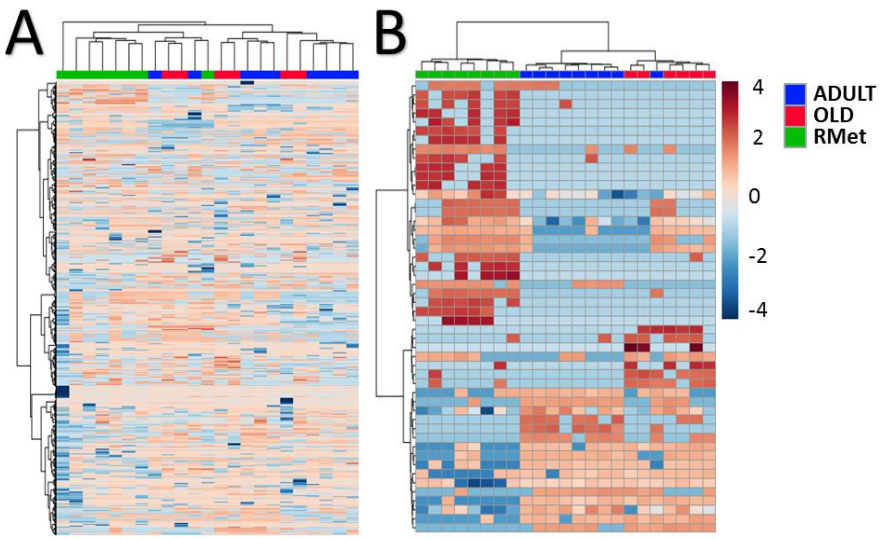

Figure 70. Metabolites distribution in liver samples of restricted animals, control old and adult animals. A) Heat map representation of 1136 metabolites found in liver samples in positive ESI polarity. B) Heat map representation of the 50 most statistically different metabolites obtained one-way anova in positive ESI polarity. Each line of this graphic represents an accurate mass ordered by retention time, colored by its abundance intensity normalized to internal standard and baselining to mean across the samples. The scale from -3 (blue) to 3 (red) represents this normalized abundance in arbitrary units.

Between the compounds identified, ADP-ribose was downregulated in the restricted animals. ADP-ribose was significantly different between the experimental groups also in gluteus, heart and renal cortex. In all the organs, ADP-ribose was downregulated in RMet animals but no in the gluteus samples. Moreover, the amino acid proline was identified to be upregulated in the

restricted animals respect to both control groups. 10-F2-dihomo isoprostane, already identified in cardiac samples, was as well downregulated in RMet animals respect to the old control group.

Table 34. Liver metabolites statistically different between adult control, old control and RMet old animals. Results were obtained by a one-way ANOVA with a Tukey's post hoc of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs OLD	RMet vs OLD	LogFC RMet vs ADULT	RMet vs ADULT
2',3'-Cyclic UMP	307,0762	0,59	2,23E-07	-5,39	down	-5,07	down
ADP-ribose	542,059	0,89	3,65E-02	-1,76	down	-1,84	down
Biotin amide	261,138	1,48	9,78E-04	2,91	up	2,99	up
dGMP	348,0627	0,52	2,96E-02	-2,26	down	-2,34	down
Proline	116,052	0,41	9,08E-04	3,35	up	3,42	up
10-F2-dihomo IsoP	397,2882	10,44	4,35E-02	-2,03	down	-2,94	down
C17 SPA-1P	385,2853	10,36	3,42E-02	-0,25	down	-2,91	down
MG(18:1)	339,2816	13,30	3,94E-02	-2,02	down	0,64	up
LysoPA(18:0)	439,2831	10,94	4,93E-02	1,83	up	0,05	up
LysoPE(16:0)	471,325	10,18	2,14E-02	-2,34	down	-2,25	down
LysoPE(17:2)	446,2787	10,93	2,06E-02	-1,53	down	-3,14	down
LysoPE(18:1)	480,3016	10,72	1,31E-02	-2,18	down	-2,23	down
LysoPE(18:2)	478,2865	10,31	4,48E-02	-1,47	down	-1,62	down
LysoPI(16:1)	593,2641	8,88	7,88E-03	2,14	up	2,21	up
LysoPS(16:0)	480,271	8,35	2,04E-02	-3,33	down	-1,44	down
LysoPS(16:1)	496,2665	8,47	1,39E-02	-2,90	down	-3,19	down
PG(O-20:0)	509,3554	8,06	3,25E-02	1,55	up	2,40	up
Oxalyl-CoA	822,08	13,49	5,73E-03	-3,04	down	-2,45	down
Cholic acid	446,2884	8,06	5,47E-03	3,06	up	3,41	up
Glycochenodeoxycholic Acid	450,3163	9,68	1,92E-05	3,87	up	3,94	up
Glycocholic Acid	466,3105	9,11	3,86E-04	3,08	up	3,15	up
Glycoursodeoxycholic acid	432,3038	9,59	2,68E-05	3,88	up	3,96	up
Sulfolithocholylglycine	514,2764	8,47	2,11E-04	-4,09	down	-3,32	down
Taurocholic acid	533,3248	9,45	2,37E-02	-2,67	down	-2,01	down
Taurocholic acid 3-sulfate	578,234	8,05	6,39E-03	2,60	up	3,18	up
Taurolithocholic acid	448,3	8,49	4,81E-04	2,90	up	2,98	up
Tauroursodeoxycholic acid	520,2332	8,88	5,34E-03	2,02	up	3,72	up

Concerning the rest of the metabolites most of them are or GPs or bile acids. On one hand, the GPs are mostly LGP species. The PE as well as PS species were downregulated in the restricted animals respect to both control groups while the LPA and PI were upregulated. An ether lipid of phosphoglycerol was also identified to be upregulated in RMet animals compared to both

experimental control groups. The bile acids identified were both primary and secondary bile acids and all of them were upregulated in the restricted animals except for the taurocholic acid and the sulfolithocholylglycine. Cholic acid and its conjugated form with glycine, glycocholic acid, were both of them upregulated in the restricted animals respect both control groups. From the rest of the primary bile acids only the glycochenodeoxycholic acid was identified and it was also upregulated in the RMet group respect both control animals, old and adults. About the secondary bile acids, neither the deoxycholic acid nor their conjugates were identified. Three secondary bile acids product of the chenodeoxycholic were also identified. One of them, derivative from the lithocholic acid and conjugated with taurine, taurolithocholic acid was, as most of the bile acids, upregulated in the restricted animals respect to both control groups. The other two secondary bile acids were tauroursodeoxycholic acid and glycoursodeoxycholic acid. Both products of ursodeoxycholic acid, which was not either identified or detected in the metabolomic analysis. Main bile acids are represented in Figure 71, both primary and secondary, identified or not. Only the sulfated bile acids identified, taurocholic acid 3-sulfate and sulfolithocholylglycine, are missing in the illustration. Regulation was different for each other, taurocholic acid 3-sulfate was upregulated in the restricted animals respect both control groups while sulfolithocholylglycine was downregulated in the RMet group respect the old and adults animals with control diet.

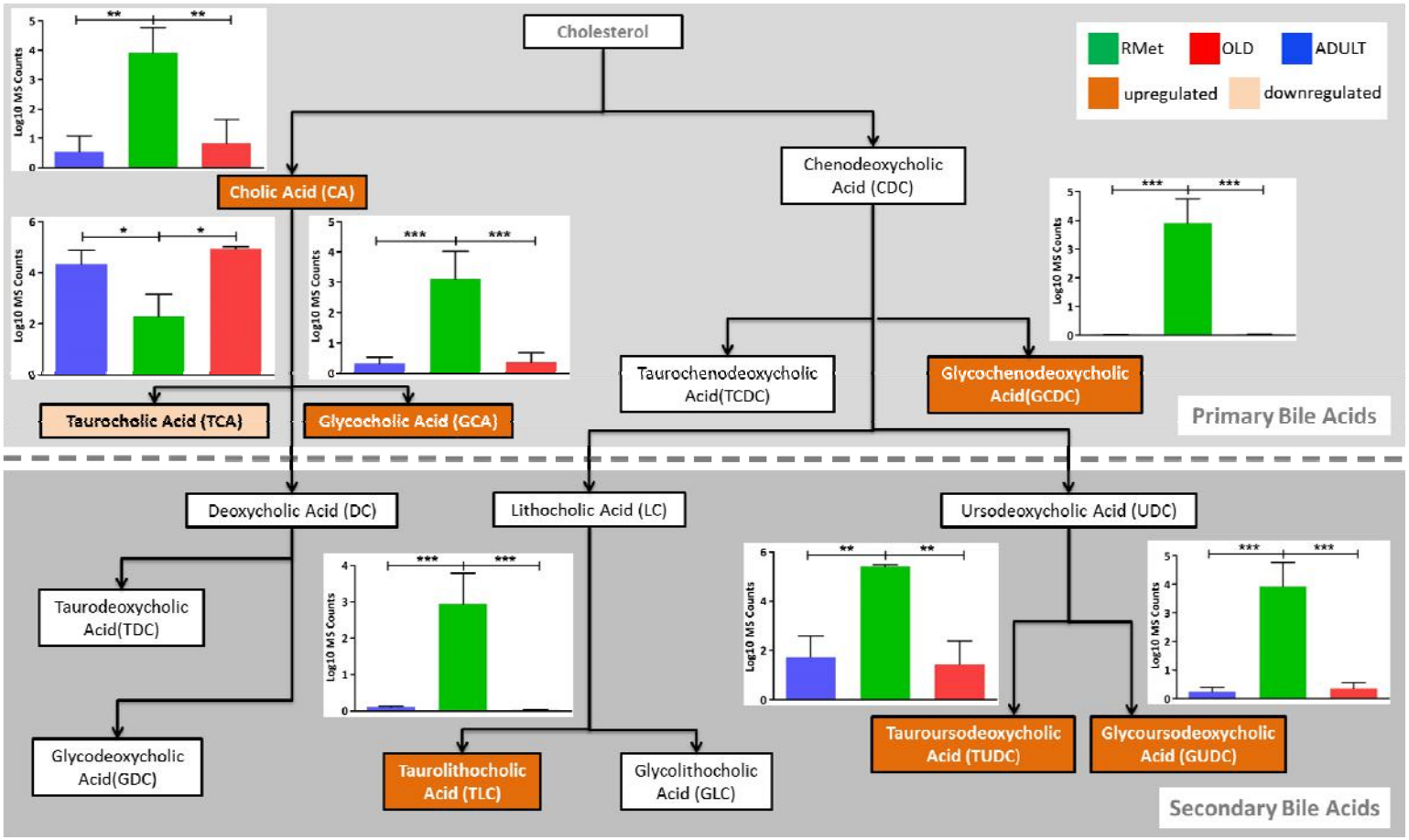

Figure 71. Intensities of bile acids identified from liver samples of restricted animals, control old and adult animals. Bile acids detected and identified are colored in dark orange if they were upregulated in RMet animals respect to both control or light orange in the case of Taurocholic Acid because it was downregulated in RMet animals. The rest of bile acids of the scheme were not either detected or identified in the untargeted metabolomic analysis. Represented values in this graph indicate changes in lipid species MS counts intensity of the experimental groups expressed as median ± standard error of the mean of eight animals per group. Significance between groups was calculated with the multiple comparison test Tukey. *p<0.05, **p<0.01 and ***p<0.001**.**

Once detected significant differences in bile acid levels between the experimental groups, the expression of several proteins related to lipogenesis was analyzed. Lipogenesis is mainly controlled through transcriptional regulation of glycolytic genes and lipogenic genes. These genes are activated by different transcription regulators, some of them also can regulate other genes involved in the regulation of lipid uptake, trafficking, and/or storage. Between them, SREBP family (SREBP-1a, SREBP-1c and SREBP-2) are master regulators of lipid metabolism. These proteins are located in the membrane of the endoplasmic reticulum and they are translocated to the Golgi and cleaved sequentially by SIP1 and SIP2 proteases to release a transcriptionally active SREBP. In this work, we have analyzed this active form of the SREBP-1c. Other protein analyzed was the Farnesoid X receptor (FXR), a nuclear receptor family member that is activated by bile acids, suppresses bile acid synthesis in a negative feedback way. FXR, at the same time, stimulates the expression of Small heterodimer partner (SHP), which suppresses the expression of SREBP-1 and by consequence, causing the inhibition on the lipogenesis process (*Lefebvre et al. 2009*; *Rui 2014*).

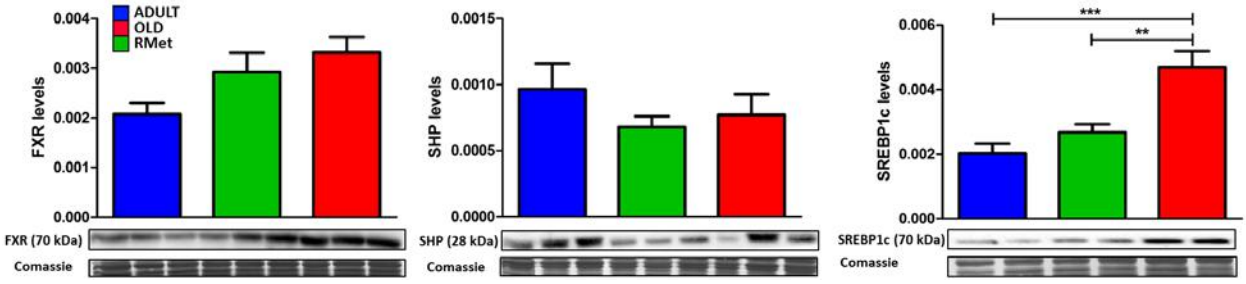

Figure 72. Expression of proteins related to the lipogenesis and bile acid metabolism in rats liver. The analyzed proteins were FXR, SHP and SREBP1c. Data are the means ± SEM of 6 animals per group. Protein levels are expressed as a percentage of the value of total protein represented by comassie blue. *P<0.05, **P<0.01, *** P<0.001 by one-way ANOVA post hoc Tuckey's**.**

DISCUSSION

5. DISCUSSION

5.1 Metabolomic and lipidomic profiles reflect tissues physiology

Metabolomic and lipidomic techniques have allowed to rapidly measure thousands of metabolites or lipid species simultaneously from only a minimal amount of sample, opening a new pathway in the understanding of the biology and physiology of the organisms (*Patti et al. 2012*). In order to know how aging could affect different metabolic pathways in an animal model, there is a need to establish the metabolomic profile of a healthy mature organism. The metabolomic profile of a tissue is expected to reflect its biological functions; hence, each tissue should present a specific metabolome (Ma et al. 2015). Moreover, biology of systems and computational biology have demonstrated how metabolism is characterized by its functional plasticity and ability of the metabolic networks to respond to endogenous and exogenous variations (*Almaas et al. 2005*; *Güell et al. 2014*).

In the present thesis, the metabolomic and lipidomic profiles of healthy adult male Wistar rats have been studied. The evaluated tissues in this work were cardiac, renal cortex, hepatic tissue, two types of skeletal muscle (gluteus and soleus) and two types of WAT (visceral, VAT and subcutaneous, SAT). In the skeletal muscle, gluteus was chosen because is mainly formed by type II fibers and as consequence, it is an appropriate muscle to act as representation of glycolytic fibers of skeletal muscle. On the other hand, soleus presents predominance of type I fibers and therefore it is an ideal muscle as a representation of oxidative fibers of skeletal muscle (Díaz-Herreral et al. 2001; Silva Cornachione et al. 2011). In regard to WAT, SAT and VAT depots are anatomically, metabolically and physiologically different and it has been reported that inadequate SAT stores result in lipid overflow into VAT and other non-adipose tissues being therefore VAT a possible marker of ectopic fat (*Danforth 2000*; *Lafontan 2013*).

In order to achieve the maximum coverage of the metabolome different methodologies were chosen. First, an untargeted metabolomic approach was performed allowing the detection of polar metabolites including some lipid species such as acyl-CoA, acylcarnitines, LGP and bile acids. Both types of WAT were excluded from the metabolomic analysis due to their high amount of hydrophobic lipid species. Second, an untargeted lipidomic approach was performed for the detection of non-polar lipids and third a targeted lipidomic analysis was executed permitting the quantification of 652 different lipids species.

Beginning with the untargeted metabolomic analysis, the results revealed clear differences in the metabolome of each tissue, showing common and tissue-specific metabolites. Among the identified compounds purine metabolism was common for all the tissues while they differed in the abundance of cyclic adenosine diphosphate ribose (cADPR) and branched-chain amino acids (BCAA). In addition, the metabolomic profile of each tissue was comprised of several polar lipid species most of them involved in signaling pathways. For example, N-acyl amines and oxylipin species were common for all the tissues while LGP, ether lipid and bile acids presented tissue-specific abundances. Finally, several acylcarnitines and MAG were differential across tissues reflecting difference in energy metabolism.

The resulting metabolome of each tissue was analyzed using different unsupervised multivariate statistical analysis and the PCA demonstrated that 48.9% of the variability across tissues is due to their metabolomes. These results are supported by the hierarchical clustering analysis that was performed on one hand with the whole set of metabolites and on the other hand with the top 100 metabolites obtained by the univariate statistical analysis, one-way ANOVA, from all the tissues analyzed. The heat maps from both analyses clustered each type of tissue perfectly but skeletal muscle showed differences between gluteus and soleus when the analysis was performed with the top 100 metabolites. Despite differences in fiber composition of each type, their metabolomes were similar when comparing with cardiac, renal and hepatic tissue. For this reason, in the study of the metabolomic profiles of each tissue, gluteus and soleus were analyzed and studied together as skeletal muscle.

Metabolomics field is still growing and the main disadvantage of the untargeted approach is the difficulty in spectrum identification. In fact, in the determination of tissue specific metabolomic profiles only a 12.6% of the significantly different metabolites were identified in the best-case scenario. However, the identified metabolites of the present study, some presented a tissue-specific distribution while others showed a common distribution amongst the analyzed tissues.

For example, metabolites belonging to the purine metabolic pathway were described in all the tissues analyzed. Several components of this pathway were identified in skeletal and cardiac muscle, hepatic and renal tissues. Purine and pyrimidine nucleotides are major energy carriers, subunits of nucleic acids and precursors for the synthesis of nucleotide cofactors such as NAD and SAM (*Moffatt and Ashihara 2002*). Furthermore, in 1970 a purinergic signaling using ATP as transmitter substance was discovered in the gut of guinea-pigs (*Burnstock et al. 1970*). Since its discovery many studies have demonstrated that extracellular nucleotides, signaling via purinergic receptors, participate in numerous biological processes in most tissues (*Burnstock*

2009). Identified purinergic receptors are classified in two big groups: those that are selective for adenosine named P1, and those activated by purines and some pyrimidines called P2. Inside P1 groups there are different subtypes named A1, A2a, A2b and A3. In turn, P2 receptors can be both, ligand-gated ion channel receptors, called P2X or G protein-coupled receptors, known as P2Y (*Burnstock 2007*). ATP is well known for its role as an intracellular energy source and physiology. Although the regulation of purinergic signaling is still relatively unknown the number of studies is increasing and it has been demonstrate that A1 receptor regulates lipolysis and lipogenesis as well as leptin secretion from adipocytes (*Johansson et al. 2008*; *Gharibi et al. 2012*). All 4 subtypes of P1 receptors and some P2X receptors are expressed in cardiomyocytes being thought to mediate cardio protection and apoptosis (*Shen et al. 2014*; *Burnstock and Pelleg 2015*; *Burnstock 2017*). At renal level, P2X and P2Y receptors seem to be involved in the control of renin release and electrolyte transport and a decrease in the availability of nucleotides in hepatic tissue affects insulin regulation and glucose metabolism through P2 receptors (*Gonzales et al. 2007*; *Enjyoji et al. 2008*; *Burnstock et al. 2014*). Finally, several studies have shown that extracellular ATP can regulate myoblast proliferation and the differentiation of mammalian skeletal muscle (*Ryten et al. 2002*; *Martinello et al. 2011*; *Burnstock et al. 2013*). Adenosine monophosphate (AMP) and adenosine biphosphate (ADP) were found in every tissue analyzed but unfortunately, adenosine triphosphate (ATP) was not. Metabolites like ATP are challenging to measure due to their susceptibility to hydrolyze into more stable low energy compounds like ADP or AMP (*Alves et al. 2015*). As it has been reported, skeletal muscle is thus a major site of *de novo* purine production in the mammalian body. In this line, higher levels of adenine and its precursor inosine 5' monophosphate were found in skeletal muscle supporting previous published results (*Brosh et al. 1982*). Approximately 90% of the free purines are recycled through the salvage pathways, which plays a critical role in the purine economy of mammals (*Kim et al. 1992*). In that sense, in the present study adenosine was found in kidney and liver, inosine, xanthosine were found in liver and guanosine was present in heart suggesting a different metabolic regulation or flux in each tissue. Furthermore, the evidences of the expression of purinergic receptors in all the tissues analyzed open a new line of possibilities for the study of purine and pyrimidine signaling and its physiological implications in each tissue.

Differences among tissues were found in terms of cADPR and BCAA abundances. Higher levels of cADPR were found in skeletal muscle and renal tissue when comparing with heart and liver, which presented higher levels of BCAA. On one hand, cADPR, originally isolated from sea urchins in 1987, is a potent intracellular calcium-mobilizing second messenger (*Clapper et al. 1987*). The

cADPR calcium signaling system is active in diverse tissues including smooth, skeletal and cardiac muscle, brain, pancreas and kidney. In the skeletal muscle, calcium ions had a particularly important function in muscle contraction (*Guse 2004*). In kidney, the regulatory properties of cADPR has been hypothesized to be involved in intracellular signaling pathways by which renal cells modulate activity of cotransporting sodium and phosphate (*Dousa 1996*). These studies explain the importance and function of cADPR in skeletal muscle and renal cortex but the differences between those tissues and cardiac and hepatic tissue remain unknown, notwithstanding cADPR biosynthesis have been reported in both heart and liver from rats (*Walseth et al. 1991*). On the other hand, BCAA -leucine, isoleucine and valine- shared structural features in their side-chain and a common catabolic pathway. The final catabolic products of BCAA are acetyl-CoA and succinyl-CoA, which are consumed in mitochondria through tricarboxylic acid cycle (TCA) for the production of reduced NAD for respiration. Additionally, BBCA have a role as key building blocks for peptide synthesis and are demonstrated to be significant sources for biosynthesis of sterol, keto bodies, and glucose (*Baquet et al. 1991*). Furthermore, BCAA, especially leucine, have potent nutrient signaling activity in cells promoting protein synthesis, cellular metabolism, and cell growth through mTOR signaling (*Lynch and Adams 2014*). These physiological functions of BBCA along with published studies that demonstrate the importance of BCAA catabolism for correct cardiac physiology and apoptosis and regeneration of hepatocytes could explain the higher abundances of BBCA found in heart and liver (*Huang et al. 2011*; *Tajiri and Shimizu 2013*).

As discussed at the beginning, the untargeted metabolomic analysis allows the detection of small polar metabolites including several lipid species. Among the identified lipid species most of them were involved in signaling pathways and a few in energy metabolism (MAG and FAC). Amongst the second messenger, N-acyl amines and oxylipin species were found in common for all the tissues whilst LGP, ether lipid and bile acids abundances were tissue-specific.

Regarding signaling molecules, N-acyl amines and oxylipins were found in all the tissues analyzed. N-acyl amines belong to class fatty amides inside the fatty acyl category according to LIPIDMAPS (*Fahy et al. 2005*). N-acyl amines contain one fatty acid and an amine or one amino acid linked by an amide bond (*Tan et al. 2009*). This subclass of compound was firstly identified in plants in 1995, but few years ago different studies identified several N-acyl amines in brain of adult male Sprague-Dawley rats (*Cartwright 1955*; *Tan et al. 2009*, *2010*). However, for many of these molecules, relatively little is known so far about their biological significance or distribution across tissues. In that sense, this thesis demonstrates the presence of N-palmitoyl serine, N-

stearoyl tryptophan and N-stearoyl tyrosine in skeletal muscle while N-oleoyl tyrosine was found in both cardiac and renal tissue. Concerning the oxylipins, it can be defined as a family of oxygenated natural products that are formed from fatty acids by both enzymatic and non-enzymatic reactions (*Gurr et al. 2002*). Although a vast literature on PUFA in mammals exists, comparable data on their oxidized products is lacking. In the present study, oxylipins were found in all the tissues analyzed; however, differences in the type of oxylipins detected were observed across tissues. In muscular tissues, leukotrienes and hydroxyzed forms of dihomo-γ-linoleic acid and linoleic acid were found in skeletal muscle and heart, respectively. Conversely, hepatic and renal cortex present protectins derived from docosahexaenoic acid (DHA) and a hydroperoxide from AA. Globally, the recent identification of both N-acyl amines and oxylipins implies that the number of published studies about their physiological functions is limited; however, their ubiquitous presence as part of the metabolome of each tissue suggest a role in common cellular mechanisms. On the other hand, to the best of our knowledge this is the first time that N-palmitoyl serine, N-stearoyl tryptophan and N-stearoyl tyrosine have been identified in skeletal muscle as well as N-oleoyl tyrosine in both cardiac and renal tissue of adult male Wistar rats.

Among tissue-specific lipid species identified, several LGPs were found. LGPs are synthetized from their corresponding GPs by the action of phospholipases or acyltransferases and therefore they act as precursors of GP synthesis (*Gurr et al. 2002*; *Hishikawa et al. 2014*). However, LGPs act as well as second messenger through specific G-protein-coupled receptors. Specific signaling functions have been reported for several LGP species and the biological role of each specie will depend on the nature of the phosphate head group, the positional distribution of the fatty acids on the glycerol moiety and the chain-length and degree and position of saturation of the fatty acyl chains (Makide et al. 2014). In that sense, LGP are involved in the regulation of cell proliferation, cell migration, eicosanoids metabolism, immune response and calcium ion mobilization (*van Corven et al. 1989*; *Ridley et al. 2003*; *Makide et al. 2009*, *2014*; *Andradas et al. 2011*; *Sevastou et al. 2013*; *Grzelczyk and Gendaszewska-Darmach 2013*). Furthermore, LGP species can present ether or ester linkages to the glycerol backbone. Ether lipids are a subclass of LGPs that have an alkyl chain attached by an ether bond at the *sn-1* position of the glycerol backbone (*Dean and Lodhi 2017*). The biosynthesis of LGP ether lipids remains unclear, being possible the generation through the remodeling of GP acyl chains by the regulated activity of different enzymes like phospholipase As, acyl-CoA synthases, transacylases, and lysophospholipid acyltransferases or through the formation of the alkyl bond using the LGP as precursor (*de Vet et al. 1999*; *Hishikawa et al. 2014*). In the present study, both LGP and ether

LGP species were detected in all tissues excluding the presence of ether LGP in hepatic tissue. Since LGP serve as precursors for GP biosynthesis, the ubiquitous presence of LPGs in all the tissues analyzed could be a possible pool of LGP species for generating GP due to their main role as structural lipid species in the biological membranes (*Van Meer et al. 2008*). On the other hand, although LGPs were found in all the tissues, the LGP individual species vary across tissues. The greatest number and diversity of LGP was found in liver, followed by kidney and then the muscular tissues. In addition, liver and kidney shared several LGP species, especially LPC and LPE with 18:0 and 20:4 acyl chains. In skeletal muscle, LPA, LPG and LPC with SFA chain were detected along with several ether lipids. The marked differences in the abundance of ether lipids between liver and skeletal muscle suggest a specific role for these molecules in the skeletal muscle. Finally, LPC(18:0) and LPC(22:6) species found in skeletal muscle are in agreement with the lipid profiling in soleus and gastrocnemius of mice published last year where both of them along with LPC(16:0) are the most concentrated LPC species in skeletal muscle (*Park et al. 2017b*). Hence, this difference in individual LGP and ether LGP species across tissues supports the idea of their physiological function as second messenger regulating the metabolic pathways depending on the needs of the tissue.

Several bile acids were found in the hepatic tissue, as it could be expected since primary bile acids are synthesized by hepatocytes from cholesterol. Although predominantly bile acids are localized in the enterohepatic circulation some of them are also present in the systemic circulation at low concentrations that depend on the fed status (*Iguchi et al. 2010*). In the present study, lithocholic acid was found in cardiac tissue and several studies have demonstrated the importance of TGR5, a G protein-coupled receptor that is activated by bile acids, in the cardiovascular function (*Iguchi et al. 2010*; *Khurana et al. 2011*; *Porez et al. 2012*). Therefore, may be the function of the bile acids is not only limited to participating tissues in enterohepatic circulation, but also in the whole body as signaling molecules.

To end with the untargeted metabolomic analysis, the metabolite profile of the skeletal muscle largely reflected its energy demand. Skeletal muscle was enriched with fatty acylcarnitines (FAC) and MAG. FAC help transport fatty acids across mitochondrial inner membranes, whereas carnitine acts as an acetyl group acceptor, maintaining the pool of CoA and preventing inhibition of pyruvate dehydrogenase, especially in skeletal muscle tissues with type I fiber predominance, which depend on beta-oxidation (*Vaz and Wanders 2002*; *Hoppel 2003*). Alternatively, MAG species, within tissues are produced by lipolysis and its catabolism leads to the formation of free fatty acids and glycerol (*Vance and Vance 2008*). However, the species of MAG found in skeletal

muscle could be also involved in glucose metabolism and insulin sensitivity, as it has been described in other tissues (*Shi and Cheng 2009*; *Hansen et al. 2012*; *Poursharifi et al. 2017*). Globally, the results in the present thesis showed that lipid species involved in bioenergetic metabolism are especially important in skeletal muscle.

In order to complete the information obtained about the specific lipid profile of each tissue an untargeted lipidomic approach was chosen for the evaluation of non-polar lipid species. In this lipidomic analysis both types of WAT, VAT and SAT, were included along with the rest of tissues discussed in the metabolomic analysis. Unsupervised multivariate statistical analysis were used to evaluate the influence of the lipidome in each tissue. The lipidomic analysis was performed for both ESI polarities, positive and negative, because one ionization mode cannot cover all the types of molecules since some lipid species are better ionized in the positive mode while other are ionized more efficiently in the negative mode (*Cajka and Fiehn 2014*). For example, CE and acylglycerols are only effectively ionize in ESI(+) using the methodology of the present thesis. Both PCAs, ESI(+) and ESI(-), clustered each type of tissue separately suggesting the existence of a specific lipidome for WAT, skeletal muscle, liver, heart and kidney. The ESI(-) PCA explained almost a 45% of the variability across samples and approximately 33% was the variability explained by the lipid species detected in the ESI(+). In this last PCA, the principal component 1 clearly separated both types of WAT from the other tissues mainly because of the abundance of CE and TAG detected in the ESI(+) and highly abundant in VAT and SAT. The unsupervised multivariate analysis with all the tissue did not allow observing differences in the lipidomic profile of gluteus and soleus as well as between both types of WAT. However, individual multivariate analysis of skeletal muscle clustered gluteus and soleus perfectly explaining a 30.6% of the variability across samples while surprisingly, the same analysis of both types of WAT although clustered separately VAT from SAT only explained a 24.2% of the variability across samples. In summary, the untargeted lipidomic analysis provided the existence of a tissue specific organization of lipids, which may be because of the specific metabolic adaptations of each tissue.

In view of these findings, lipid species comprises an important part of the specific metabolome of tissues. For this reason, a targeted lipidomic analysis was performed in order to define quantitative and qualitatively the lipidome across mammalian tissues. In biological systems, the primary function of lipids is to generate membranes (*Tanford 1978*; *Lombard et al. 2012*). It was later during evolution that this property was extended to new functions such as cell signaling and energy storage (*Hulbert et al. 2014*). To do this, a wide diversity of molecular lipid species

emerged and their biosynthesis pathways incorporated to the general cell metabolism (*Sud et al. 2007*). This lipid diversity was also expressed at compositional level in cell membranes and organelles (*Van Meer et al. 2008*; *Klose et al. 2013*). In this thesis, the existence of a tissue specific organization of lipids, which may be because of the specific metabolic adaptations of each tissue, has been demonstrated. The discussion has been summarized according to the biological function of the lipid species; structural, signaling and energetic. However, although the lipid species will be discussed in one function it is important to mention that other functional properties ascribed to them cannot be discarded.

The major structural lipids in membranes from eukaryotic cells are GPs: PC, PE, PS, and PI (*Van Meer et al. 2008*). In accordance with this general idea, the results of this thesis confirm their quantitative relevance in all the tissues. PC and PE were the most abundant species in all tissues, analogously to most eukaryotic membranes. Differences in their concentrations across tissues may reflect the differences in the complexity of cellular metabolism and the relative abundance and traffic of organelles and membranes between tissues. The most abundant PC and PE molecular species shared by all tissues are PC(16:0/18:1), PC(16:0/18:2), PE(16:0/18:2) and PE(16:0/22:6), which are primary molecular species in the *de novo* synthesis of PC and PE (*Schmid et al. 1995*); as well as PC(16:0/16:0), PC(18:0/18.2), PC(16:0/20:4), PE(16:0/20:4) and PE(18:0/20:4), which are produced by remodeling at both *sn-1* and *sn-2* positions and are not further remodeled (*Schmid et al. 1995*). For PI and PS, the most significant molecular species are PI(16:0/20:4), PI(18:0/20:4) and PS(38:4), likely also resulting from a remodeling activity and with AA as the most predominant acyl chain found in the *sn-2* position. The remaining molecular species are the result of remodeling processes and their concentration is in a lower range showing a wide diversity of incorporated PUFA. In this sense, there are differences among GPs in terms of chain length (number of carbon atoms) and degree of unsaturation (number of double bonds) in their fatty acid composition, the major factors determining the geometric properties of lipids which, in turn, have major consequences on the membrane functional properties (*Piomelli et al. 2007*). The major diversity in number of carbon atoms and unsaturation degree among tissues was observed for PE and PS, both subclasses showed the greatest diversity in the PUFA composition and clear differences among tissues. GP acyl chains are remodeled by the regulated activity of different enzymes like phospholipase As, acyl-CoA synthases, transacylases, and lysophospholipid acyltransferases (*Hishikawa et al. 2014*). The result is the generation of a pool of LGPs. The relative abundance of LGPs is, as expected, lower than GPs in at least 1.5 orders of magnitude, and maintain the relation among them in an identical way to GPs. Thus, LPC > LPE >

LPI > LPS; and by tissues: liver > heart > kidney > soleus > gluteus > SAT > VAT, that express tissue specific differences is the rate of remodeling according to the GP classes, but also the diversity of molecular GPs species generate, being highest for LPC, then LPE, and finally LPI and LPS.

Inside the GPs subclass, ether lipids that have an alkyl chain attached by an ether bond at the *sn-1* position of the glycerol backbone (*Dean and Lodhi 2017*) were also studied. Most ether lipids are presented as PC and PE molecular species. The present study demonstrates that ether lipids of PE and PC have a heterogeneous distribution depending on the tissue being more abundant in muscular tissues and less in liver. The main molecular species of PE(P-) shared by all tissues are: PE(P-16:0/20:4), PE(P-16:0/22:5n3), PE(P-16:0/22:6), PE(P-18:0/20:4), PE(P-18:0/22:6) and PE(P-18:1/20:4). These molecular species confirm that in PE(P-) the long chain fatty acid in *sn-1* consists exclusively of SFA and MUFA groups, while *sn-2* position is esterified with SFA or MUFA acids, but also and predominantly with n-6 and n-3 PUFA (*Wallner and Schmitz 2011*). Interestingly, this fatty acid profile confers a higher unsaturation degree and average chain length to ether lipids present as PE than as PC. In contrast to PE(P-), the PC(P-) percentage of total amount of PC is in a low range for all the tissue but higher than the alkyl and alkenyl forms of LPC and LPE. The physiological role of plasmalogens are essentially linked to their function as membrane components playing an important role in membrane properties such as fluidity, formation of lipid raft microdomains, and source of second messengers. Other specific functions where plasmalogens are involved are transmembrane protein function, cholesterol transport, vesicular function, membrane fusion events, and G-protein mediated signal transduction (*Dean and Lodhi 2017*). Interestingly, an antioxidant effect has also been ascribed to plasmalogens that, like a scavenger, could protect unsaturated membrane lipids. Consequently, it is proposed that the heterogeneous presence of plasmalogens in tissues is an adaptive response to offer stability and protection against oxidative stress conditions to lipid membranes, and particularly lipid rafts, in a tissue-dependent way.

Another lipid that it seems to have also a potential antioxidant role is ubiquinone (*Wang and Hekimi 2016*). This lipid, as well named coenzyme Q, is a prenol lipid primarily present in mitochondria as a component of the electron transport chain where participates in aerobic cellular respiration. Ubiquinone show the highest concentrations in those tissues with the highest energy requirements —such as heart, kidney, and liver—, decreasing their content in one order of magnitude in skeletal muscle, and 2 orders for WAT. Similarly to ubiquinone content, is the concentration of the PG, which is a precursor of CL, a very special and unique GP which is found at mitochondrial level (*Van Meer 2005a*; *Van Meer et al. 2008*). In this thesis, PG

is detected in all tissues, being its relative abundance especially lower in both WATs, slightly higher in skeletal muscle tissues, kidney and liver, and showing the highest level in heart, clearly expressing the mitochondrial enrichment of this tissue. In all tissues, PG(16:0/18:1) and PG(16:0/18:2) predominates, probably expressing molecular species from *de novo* synthesis; followed by PG(18:1/18:1), resulting from remodeling. This lipid specie is the chemical form used for CL synthesis since it has been demonstrated that only fatty acids with 18 carbon atoms, and low unsaturation degrees (1 or 2 double bonds) are present in mitochondrial CL from rat tissues (*Schlame et al. 2000*; *Horvath and Daum 2013*).

Several SPs and cholesterol have also important functions as structural lipids (*Van Meer et al. 2008*). The data of this thesis confirm that the major SP in mammalian tissues is SM, especially in the renal cortex. For all of SP, the distribution follows a heterogeneous and non-shared pattern. For glycosphingolipids, the tissue amount expresses, for all tissues, a gradient being highest for the MHC forms, followed by DHC, and finally THC with the lowest content. Among types of skeletal muscle, difference between soleus and gluteus exist in almost of SP subclasses but it is remarkable the exceptional amount of MHC showed by soleus (30%). Globally, all SP are formed by SFA and MUFA that confer to SPs a geometry that contributes, jointly with cholesterol, to lipid microdomain formation. Cholesterol and SP shared the same gradient in concentration across tissues, likely as expression of the close interaction between cholesterol and SP species to maintain the optimal properties of membrane. Cholesterol metabolism was enhanced in liver being the concentration of its biosynthetic precursor and also metabolites higher in the hepatic tissue.

The hydrolysis of GL and SP species produces a series of messenger lipids which play a key role in cell signaling. In the present study, it can be considered as messenger lipids: LGPs, DAGs, Sph, Sph1P, Cer1P, dhCer and Cer. However, it is important to mention that these lipid species could have other functional properties ascribed to them such as precursor of other lipid classes and/or structural role in membranes. In any case, for all tissues, in terms of relative abundance, the highest amounts correspond to DAGs, followed by Cer, LGPs, Sph, dhCer, Sph1Ps and Cer1P. More in detail, DAGs are particularly relevant in WAT (SAT > VAT) where is present the highest amount along with liver, then kidney, and finally the muscular tissues (heart > soleus > gluteus). For Cer, and their precursor dhCer, the highest amount is present in liver and kidney, being their amount lower and identical for the rest of tissues. Sph were higher in heart, kidney and liver while no differences across tissues were observed for Sph1P and Cer1P. Focusing on the LGPs species with the highest concentrations in the tissues, two groups can be discerned. The first one

is made up by LGPs with the fatty acid in *sn-1* position, generated by the activity of a phospholipase A2. LPC(16:0), LPE(16:0), LPE(18:0) and LPS(16:0) are the main molecular species of this group sharing all of them the presence of a SFA chain. They are likely generated within the remodeling process of GPs. In contrast, the second group is made up by LGPs with the fatty acid in *sn-2* position. The more abundant molecular species in tissues of this group are LPC(18:2), LPC(20:4), LPE(18:2), LPE(20:4), LPE(22:6), and LPI(20:4). Interestingly, the systematic presence of highly UFA suggests that all of them are generated from remodeled GPs previously obtained by *de novo* synthesis. Furthermore, their generation implies the activity of a phospholipase A1, which has to be present in all tissues, suggesting that the resulting LGPs are not transition species in the remodeling process, but the result of a specific pathway to generate a new subclass of compounds. In fact, recently it has been described that LGPs *sn-2* are substrates for a new lipid signaling pathway based on the generation and activity of specific lipid species named eicosanoids-lysolipids (*Liu et al. 2016*) and, we additionally also propose, docosanoids-lysolipids.

Finally, lipids are used for energy storage as TAGs and CEs, in lipid droplets, and energy source principally as fatty acylcarnitines (FACs). For FACs, the highest levels were detected in skeletal muscle. TAGs are the main form of energy storage. As expected, the highest content is present in WATs, showing SAT higher amount of TAGs than the VAT. TAG abundance in decreasing order by tissues was after WAT, kidney, liver and muscular tissues being heart TAG concentration lower in an order of magnitude. In line with this distribution, and described for the first time, we have detected the presence in significant amounts of ether lipids-TAGs (TAG(O-)). Considering that ether lipids have, among others, antioxidants properties, we propose that the present of this form of TAGs and their distribution across tissues is a molecular adaption to protect lipid droplets from cellular oxidative conditions. In addition to TAG, the other chemical form of energy storage is as CE. Liver is, by far, the tissue with the highest content in CE, followed by kidney and heart, and showing the lowest content and with a similar amount the skeletal muscle and WATs. Interestingly, the content of oxCE species is also higher in liver, and lower and not different in the other tissues.

All in all, this findings suggest the presence of general rules and patterns shared by tissues about lipid distribution as a result of a phylogenetic and ontogenetic process to cover three basic cellular processes: formation of membranes, signaling and bioenergetics. The first rule is the preferential structural presence of GPs with a specific weight for PCs and PEs followed by PI and PS; and, in a minor amount, the presence of SP with a predominant use of SMs. Interestingly, the important presence of ether lipid forms and fatty acids with a low unsaturation degree, both

traits conferring antioxidant and protective properties to membranes, could be the expression of an evolutionary adaption to oxidative stress to confer a resistance to damage in order to maintain membrane integrity (*Pamplona 2008*). A second general rule is the predominance of molecular species obtained by *de novo* synthesis along with a minor presence of a wide variety of other lipid species which offer diversity in the fatty acid profile (particularly to ensure a diversity in the PUFA content). It is suggested that lipid species are built on the basis of a resistance to oxidative stress since SFA and MUFA are the primary lipid used for their synthesis. It is a remodeling process who generates a diversity of lipid species and, consequently, changes in the susceptibility to oxidative damage. And as a third rule, the differences among tissues can be ascribed to quantitative rather than qualitative differences in the lipid species used that could be interpreted as an adaption to the specific metabolic and physiological needs which are tissue-dependent. In summary, this lipidomic approach demonstrates the existence of a specific lipid distribution among tissues. Additional 'omics' studies such as proteomics and transcriptomics should be done for a more complete metabolic network description which support the differential lipid distribution among tissues.

5.2 Metabolome remodeling during aging

The physiological aging process demands adaptation for the maintenance of metabolic homeostasis at every biological level (molecular, cellular, organic and systemic), henceforth supporting an imbalance or shift in the metabolism that self-intensifies and ultimately becomes clinically manifest (*Hulbert et al. 2007*). As it has been discussed in the previous section, tissues have enhanced or diminished a set of metabolic pathways providing a specific metabolome for each one and therefore the age-related changes can vary from one tissue to another.

In the last years, several studies have performed an untargeted metabolomic analysis of plasma and serum to elucidate the metabolic changes produced with advancing age in both humans and rodents, demonstrating alterations in the lipid homeostasis and one carbon metabolism (*Houtkooper et al. 2011*; *Yu et al. 2012*; *Gonzalez-Covarrubias et al. 2013*; *Tomás-Loba et al. 2013*; *De Guzman et al. 2013*; *Lee et al. 2014*; *Cheng et al. 2015*; *Jové et al. 2017*). Regarding lipid homeostasis, studies performed in 23 and 26-month old C57BL/6 mice demonstrate the existence of a metabolomic signature associated with aging that involves changes in acylcarnitines and a decrease in plasma levels of LPC, SM and cholesterol derivatives

(*Houtkooper et al. 2011*; *De Guzman et al. 2013*) while cholesterol plasma levels are significantly increased by aging process in 26-month old male Wistar rats (*Cabré 2015*). Further metabolomic studies in 117 wild-type mice of different genetic backgrounds ranging from 8-129 weeks of age demonstrate a decrease in LPC and SM species and define PE(16:0/18.2) and PE(16:0/22:6) as biomarkers that increase with the aging process while PE(P-) plasma levels decrease (*Tomás-Loba et al. 2013*). Metabolomic studies on human plasma support that SP and GP species including LGP and ether lipid species could be critical candidate metabolites in the aging process (*Yu et al. 2012*; *Gonzalez-Covarrubias 2013*; *Lee et al. 2014*; *Cheng et al. 2015*; *Jové et al. 2017*). In addition, these studies point the importance of acylcarnitine and the β-oxidation process due to an age-related increment of their plasma levels (*Yu et al. 2012*; *Lee et al. 2014*)

Notwithstanding the valuable contribution of plasma metabolomic analyses, these studies represent one part of age-related changes in the lipid metabolism but the lipidome of the each tissue can vary in a specific manner during the physiological process of aging. However, the number of metabolomic studies of aged tissues without any associated pathology is limited. Hence, there is a lack of specific tissue biomarkers of aging, which considerably complicates the assessment of metabolic interventions consequences on the aging process. As it has been discussed the primary function of lipids in biological systems is to generate membranes, being GP, SP and cholesterol the major structural lipids in membranes from eukaryotic cells (*Tanford 1978*; *Van Meer et al. 2008*; *Lombard et al. 2012*). Studies performed in different tissues of rodents show an increase in either PUFA content or PI of membranes with age, an increase in both in vitro and in vivo membrane lipid peroxidation with age, as well as age-related changes in physicochemical membrane properties of different tissues (see reviews *Pamplona 2008*). In concordance with previous published results, the metabolomics analyses in rodents report an increased in the PUFA content of the skeletal muscle but not in brain tissue (*Garvey et al. 2014*; *Zheng et al. 2016*). These metabolomic studies have been focused on the age-related changes in brain, liver and skeletal muscle of rodents (*Houtkooper et al. 2011*; *Garvey et al. 2014*; *Zheng et al. 2016*). All of them reported differences in the GP and SP metabolism and propose fatty acids, acylcarnitines and GP species as the best metabolites to predict age in an animal model. In addition, the aging process is related to a decrease in the bile acid metabolism in these tissues (*Houtkooper et al. 2011*; *Garvey et al. 2014*; *Zheng et al. 2016*). Globally, these studies support a relevant role for lipid metabolism changes in the aging process.

In this line, the untargeted metabolomic and lipidomic analysis performed in WAT, skeletal muscle, heart, kidney and liver in this thesis demonstrate specific changes associated with the

aging process in the metabolome and lipidome of the analyzed tissues being the lipid metabolism especially relevant. Differences in structural lipids (GP, SP and cholesterol), bioactive lipids (Sph1P and oxylipins) and lipid species involved in the energy metabolism (acylglycerol and acylcarnitines) have been found across tissues.

The unsupervised multivariate statistics applied to the results of the untargeted metabolomic and lipidomic analysis showed that the age-related changes of the metabolome and the lipidome are different across mammalian tissues. In kidney and liver the unsupervised multivariate did not showed differences due to the aging process neither in their metabolome or lipidome, although the supervised multivariate, PLS-DA, in both methodologies clustered separately the adults and old animals. These results demonstrate that although the variability across renal and hepatic samples can not be explained by the aging process, the age-related changes in their metabolome and lipidome are important enough to differentially group old and adult animals. The obtained results from the analysis of the heart showed that a 26.1% of the variability across samples can be explained by the detected metabolites and a 16.7% is due to age-related changes in the cardiac metabolome. For both types of skeletal muscle (gluteus and soleus) and WAT (VAT and SAT), the hierarchical clustering and the variability explain by the PCA clustered firstly the samples according to the types of tissues and after that according to their age. Thus, for these tissues age factor was secondary to explain the differences between them. However, inside each type differences in the lipidome of adult and age animals were observed. In fact, an univariate statistical analysis was performed to identify metabolites displaying differences between adult and old animals and the percentage of significantly altered metabolites was 7.54% for the lipidome of the skeletal muscle and higher than 6% for the lipidomes of WAT and liver. For cardiac tissue, the age-related changes were observed above all to those more polar lipid species and metabolites being 8.4% of them significantly affected by the aging process. Finally, kidney was among the tissues analyzed the one less affected by aging though approximately 4% of polar and non-polar metabolites were significantly different between the experimental groups. In summary, these results demonstrate that age-related changes in the metabolome and the lipidome are tissue-specific. For cardiac tissue, main compounds modified by aging comprise the polar fraction of the metabolome while for liver, skeletal muscle and WAT age-related changes disturb predominantly non-polar lipid species. Renal tissue metabolome and lipidome were the ones showing less age-related modifications.

The identification of the significantly different lipid species between adults and old animals revealed the implication of several structural lipids. The GP species identified support that the

effect of aging is not only tissue-specific but also specific for individual GP species more than for subclasses of GP. All the GP species found in skeletal muscle were decrease with aging while in WAT all the GP identified, PE and PA species with PUFA chains, were increase. The aging process in renal tissue did not affect any GP species or at least none of them were identified in the present study. In the hepatic tissue age-related changes affect every individual in a specific manner being some PE species with PUFA chains increase and other decrease by aging. In heart, the old animals presented higher levels of PC(38:6), which is reported to be increased by aging in human plasma (*Cheng et al. 2015*). Amongst the GP species identified, several ether lipids were found in the different tissues and their regulation with advancing age it seems to be also tissue-specific. More specifically, PC(O-) were increased in kidney while PE(P-) were decreased in skeletal muscle. This regulation of ether lipids in aging is in agreement with previous metabolomic studies performed in plasma of mice and humans (*Gonzalez-Covarrubias et al. 2013*; *Tomás-Loba et al. 2013*). As it has been discussed in the previous section of this chapter, the physiological role of plasmalogens are essentially linked to their function as membrane components although other specific functions as second messenger and antioxidant components have been ascribed to them (Dean and Lodhi 2017). Thus, the age-related changes in ether lipids in kidney and skeletal muscle could be affecting to their role in the biological membranes or to their functions as antioxidant and bioactive lipids. In summary, the results from the present study demonstrate that GP species in skeletal muscle are decreased by aging while PA, PE and PC with PUFA chains were increased in WAT, liver and heart. In addition, the effects of aging in ether lipids of specifically kidney and skeletal muscle point to the imperative for greater understanding of the functions of ether lipids individually and in combination in the context of tissue specific profiles, as our understanding of the functions and relative bioactivities of many ether lipids is still limited.

Other structural lipid species identified amongst the significantly different compounds between adult and old animals were several SP. The obtained results showed that the effect of aging in the SP metabolism was tissue-specific. Cer and SM were increase in skeletal muscle of old animals while in WAT levels of Cer and GM were decreased by aging. Different HexCer were found in WAT, heart in liver. In WAT and liver, MHC and DHC species were decreased respectively while in heart DHC(d44:1) was increased. Finally, in the kidney any of the identified compounds belong to the SP category. The changes observed in Cer levels could affect all the SP metabolism due to Cer are the central axis of the SP biosynthesis. Cer can be obtained either by the *de novo* synthesis based on the degradation of complex SPs or by the salvage pathway

consisting in reacylation of sphingoid long chain basis, and act as precursor of SM, HexCer, which are the main precursors of most glycosphingolipids such as GM (*Mencarelli and Martinez–Martinez 2013*). Thus, the modifications of SM and GM observed in skeletal muscle and WAT could be due to Cer are as well affected by the aging process in these tissues. A previous study in rodents has revealed that the activities and levels of SP catabolic enzymes, such as sphingomyelinase and ceramidase, increased during aging and therefore explaining the imbalance of Cer and SM in tissues (*Sacket et al. 2009*). However, there are no studies about the activity of glucosylceramide synthase or lactosylceramide synthase in aging; that could explained the dysregulation of HexCer in heart, WAT and liver, although in the view of these results the activity of these enzymes will be possible to decay with advancing age in adipose and hepatic tissue. The role of SP, along with cholesterol, in the biological membranes is the formation of lateral lipid clusters, denominated lipid rafts, in which particular molecules are concentrated and participate in membrane-mediated signaling events. The high affinity of SM and cholesterol locates them together in this microdomains, where SM concentration seems to control the cholesterol distribution, and on the surface of the lipoproteins (*Milhas et al. 2010*). Furthermore, HexCer help to stabilize the membranes and their complex products, gangliosides modulate the charge density at the membrane surface (*D'Angelo et al. 2013*; *Russo et al. 2016*). In this sense, the age-related changes in the composition of the SP could influence their role in relation to their physical properties and function in membranes.

As it has been discussed, cholesterol plays an important role in biological membranes. The two major pathways for cholesterol synthesis, Bloch and Kandutsch–Russell, were described more than 50 years ago (Kandutsch and Russell, 1960b; Bloch, 1965). A study based on the flux analysis of cholesterol biosynthesis in mice demonstrated that tissues with low rates of cholesterol synthesis, such as heart and skeletal muscle, predominantly used the K–R pathway. However, in this thesis the 4,4-Dimethyl-5a-cholesta-8,24-dien-3b-ol, an intermediate in the conversion of lanosterol to zymosterol, was upregulated in the cardiac tissue of old animals suggesting a possible switch to the Bloch pathway with advancing age. Another intermediate in the Bloch pathway; 4α-Hydroxymethyl-4β-methyl-5α-cholesta-8,24-dien-3β-ol, was downregulated this time in WAT, being possible a change in cholesterol synthesis flux in the WAT with aging . Hence, it would be interesting to study the enzymatic activity of C-4 methylsterol oxidase, necessary for the intermediate formation and which activity can be dietary modulated (*Kwon et al. 2015*). Neither cholesterol or bile acids were found significantly different between old and adults male Wistar rats in liver though it has been reported an increase of

cholesterol in old Wistar rats (*Uchida et al. 1978*). A targeted approach for their quantification could be interesting because it has been postulated that reduced conversion of cholesterol to bile acids may be one explanation of the age-related increase of plasma cholesterol seen in 24-month-old male Sprague-Dawley rats (*Stahlberg et al. 1991*). To end with the cholesterol metabolism, old animals of the present study presented higher levels of 26-hydroxycholesterol sulfate in cardiac tissue than adult rats. Previous published results have linked the accumulation of oxidized cholesterol in cardiomyocytes with higher risk of heart failure (*Tang et al. 2018*). Furthermore, Seneff and collaborators have proposed a novel theory that postulate an explanation for atherosclerosis due to cholesterol sulfate deficiency (*Seneff et al. 2015*). In view of these results, higher levels of oxysterol sulfate in the cardiac tissue of old animals compared to adults maybe the cholesterol sulfate deficiency it is due to an imbalance with the oxidized species of cholesterol sulfate. To sum up, cholesterol derivatives were found in WAT and heart dysregulated in old animals when comparing with the adults. These changes along with those in GP and SP metabolism could contribute to the disturbances in the physical properties and function in membranes during the aging process.

Several lipid species involve in signaling pathways were found altered in different tissues in the old animals. Sph and Sph1P presented higher levels in the aged skeletal and cardiac muscles respectively. Nor Sph or Sph1P were found to be modified by the aging process in kidney, liver or WAT. Although most of the SP species have been discussed as structural lipid due to their importance in biological membranes, some are considered bioactive lipids. In this sense, Shp1P acts as an intracellular second messenger and extracellular mediator in mammalian cells. In both cardiac and skeletal muscle seems to regulate the apoptosis while its dephosphorylated form act as a mediator in calcium signaling due to its ability to block calcium flux through the dihydropyridine receptor and ryanodine receptor calcium channels (*Sabbadini et al. 1999*). Thus, the altered levels of Sph and Sph1P could be associated with age-related dysfunction in both types of muscles. Along with this SP species, the aging process affected several oxylipins in a tissue-specific manner. Higher levels of these signaling lipids were found in aged hearts while some oxylipins derived from AA were decreased in the aged kidney. There is a lack in the literature about the physiological roles of oxylipins and the effect of aging on their metabolism in mammalian tissues. A recent study provides the first comprehensive profile of oxylipins in kidney, liver and serum of adult healthy rats and it demonstrates that oxylipin profiles can be highly divergent across mammalian tissues (*Leng et al. 2017*). The present study showed that the effect of aging on oxylipins was particularly notorious in cardiac tissue. Amongst the oxylipins

increased in old hearts were: DiHOME, produced by the metabolism of epoxy-octadecenoic acids through cytochrome P450 enzymes, is associated with oxidative stress and inflammation in endothelial cells (*Viswanathan et al. 2003*); Leukotrien B4 (LTB4), produced via the 5-LOX pathway, a chemotactic molecule that stimulates neutrophil lysosomal degranulation of neutrophils (*Mello et al. 1992*) and 10-F2-dihomo-isoprostane (10-F2-dihomo-IsoP). Isoprostanes are non-enzymatically derived oxylipins, F2-isoprostane is formed by the peroxidation of AA and they are excellent biomarkers of oxidative stress (*Morrow et al. 1990*; *Milne et al. 2007*). In fact, the levels of pro-inflammatory oxylipins seem to be increased with age in different tissues (*Caligiuri et al. 2017*). This increase in pro-inflammatory oxylipins agrees with the oxidation-inflammation theory of aging, which postulates a close link between oxidation and inflammation, since excessive or uncontrolled free radical production can induce an inflammatory response and free radicals are inflammation effectors. As a result of the aging process the immune cells show an increase in oxidant and inflammatory compounds and a decrease in antioxidant and anti-inflammatory defenses, explaining several aspects of immunosenescence (*De la Fuente 2008*; *De la Fuente and Miquel 2009*). On the other hand, the results of the present study showed a decrease in AA and its metabolites with age in kidney, which is in agreement with previous published studies (*Omata et al. 1992*; *Hornych 2004*; *Drenjančević et al. 2016*). Thus, the age-related decline in renal function could be due to a decrease in AA and its metabolites that can generate an imbalance between vasodilatory and vasoconstrictive events affecting the renal function in the aging kidneys. In summary, aging affects the levels of SP species that act as second messengers in both skeletal and cardiac muscle while the age-related changes in the oxylipins metabolism is tissue specific. Several pro-inflammatory oxylipins increases in aged heart probably as the vital role of oxidative stress and inflammation in the process of aging, while oxylipins derived from AA are decrease in the aged kidney suggesting an association with the age-related decline in renal function.

Regarding lipid involves in the energy metabolism, this thesis demonstrates that aging affects the levels of certain acylglycerols species in every tissue analyzed. In this sense, aged kidney showed an increased in MAG(18:0) and DAG with PUFA chains as in skeletal muscle and liver. The levels of DAG in WAT were lower in the old animals while no changes for this lipid subclass were found in heart. The levels of several TAG species in WAT were lower in the old animals, although the aging process increased the levels of a few TAG species with PUFA chains. Almost all of the identified TAG species in the skeletal muscle showed and increased in those with PUFA chains along with kidney and liver. However, in renal and hepatic tissues the identified TAG

species were found to be both decreased and increased with aging depending on the individual lipid species. This specific regulation of the TAG species by aging was as well found in cardiac muscle, being some of them increased and other decreased in the old animals. Nevertheless, the aging process in the heart was associated with an increase of several acylcarnitines species. The decrease in DAG and TAG species observed in WAT can be associated with previous published studies that reported a decrease in acetate and palmitate rates of incorporation with advancing age in rats, meaning a possible down regulation of both the *de novo* fat synthesis and synthesis of acylglycerols from preformed fatty acids with aging (*Benjamin et al. 1961*). In skeletal muscle, DAG and TAG accumulation in old rats could be attributed to an increase in TAG synthesis, a decrease in TAG utilization, or both. In any case, the results from this thesis correlate with human studies where an increment in lipids and lipid droplets in skeletal muscle with aging has been reported (*Crane et al. 2010*; *Gueugneau et al. 2015*). In kidney, the increase in acylglycerols with PUFA chains agrees with previous studies in rodents, where an association of higher levels of MAG, DAG and TAG seems to be due to an increase in lipid synthesis, maybe through sterol regulatory element-binding proteins (SREBP) (*Jiang et al. 2005*). The age-associated changes in both DAG and TAG observed in the hepatic tissue of old animals were fully consistent with a previously published survey of the hepatic metabolome comparing 3 and 23 months old C57BL/6N mice (*Houtkooper et al. 2011*). Finally, in the old hearts TAG with PUFA chains were decreased but an increase in Cer species and acylcarnitines was found in agreement with previous studies that blame those lipid species rather than TAG for the cardiac lipotoxicity associated with the age-related lipid accumulation (*Drosatos 2016*). On this wise, several studies performed in human plasma have reported an increase in acylcarnitines levels with aging (*Yu et al. 2012*; *Lee et al. 2014*) and the results of the present study showed as well higher amounts of acylcarnitines in the heart of the old animals. The accumulation of acylcarnitines observed may be indicative of mitochondrial dysfunction and/or defects in cellular fatty acid oxidation. Cardiac fatty acid oxidation is important for lipid metabolism homeostasis and normal cardiac function and an impaired fatty acid oxidation leads to lipid accumulation known as cardiac lipotoxicity. In this sense, the results about the effects of aging in the cardiac tissue are in concordance with model of cardiac fatty acid metabolism and lipotoxicity reported by previous studies (see review *Drosatos 2016*). Moreover, it has been reported that high cardiac tissue levels of acylcarnitine can disrupt biological membranes through nonspecific detergent actions, induce electrophysiological alterations, and inhibit several critical enzyme systems (*Yamada et al. 1994*; *Wu and Corr 1994*; *Son et al. 2010*). Thus, the carnitine shuttle system is considered to be a prominent factor in maintaining mitochondrial performance and cardiac function (*Noland et al.*

2009). To sum up, acylglycerols levels in all the analyzed tissues showed an age-associated effect that is specific not only for tissues but also for lipid species. In this sense, TAG regulation of renal and hepatic tissue during the aging process affect individual lipid species in a determinate manner. TAG with PUFA chain accumulation is particularly notorious in skeletal muscle while high levels of acylcarnitines are representative of aged hearts. These results point to the importance of i) lipid biosynthesis ii) fatty acid oxidation and iii) the individual lipid species in the aging process. Therefore, to generalize about the effects of aging regarding all the lipid species in given class will be unappropriated in some circumstances, being necessary to study lipid species individually in each tissue.

Globally, the present study demonstrate age-associated changes in the metabolome and specially the lipidome of WAT, skeletal muscle, heart, kidney and liver being these effects of the aging process tissue-specific. The renal tissue was the one less affected by the aging process although the decrease observed in oxylipins derived from AA could be crucial in the renal function with advancing age. Liver, skeletal muscle and WAT present differences with advancing age mostly in the non-polar fraction of their lipidomes. The aging process in liver affect mainly to GL species which could lead to a in the lipid biosynthesis and storage. Aging in skeletal muscle produces a decreased in plasmalogens along with an increase in DAG and TAG species with PUFA chains. In WAT, most of the age-related changes affects to the GL metabolism. In cardiac tissue, the aging process affects mainly its metabolome and those polar lipids such as acylcarnitines. Finally, to a greater or lesser extent, all the analyzed tissue present age-associated alterations in GP and SP metabolism that will be reflected in the membrane physicochemical properties and functions with advancing age.

5.3 Effects of the methionine restriction diet on metabolomic and lipidomic profiles

Caloric restriction without malnutrition is the most studied non genetic experimental intervention able to decrease the aging rate, increase maximum longevity in several species and delay the onset of age-related diseases (*Fontana et al. 2004*; *Pamplona and Barja 2006*, *2007*, *2011*; *Meyer et al. 2006*; *Heilbronn et al. 2006*; *Mair and Dillin 2008*; *Colman et al. 2009*; *Barger et al. 2013*; *Mattison et al. 2017*). Although mechanisms through which CR exerts its effects remain unclear, several studies have hypothesized a key role for oxidative stress in CR pro

longevity effects since it has been demonstrated that CR is able to decrease mitochondrial ROS production and macromolecular oxidative damage (*Barja 1993*; *Gredilla and Barja 2005a*; *Pamplona and Barja 2006*; *Sanz et al. 2006d*). Along with CR, both restrictions, RP and RMet, seem to be responsible for half of the effects of CR in prolonging longevity (*Barrows and Kokkonen 1975*; *Leto et al. 1976*; *Goodrick 1978*; *Orentreich et al. 1993*; *Richie et al. 1994*; *Miller et al. 2005*; *López-Torres and Barja 2008*; *Sun et al. 2009*). This thesis project is focused on RMet because numerous studies designate this amino acid as a key agent in the aging process (see reviews *Pamplona and Barja 2006*; *Pamplona 2008*; *Perrone et al. 2013*; *Lee et al. 2016*; *Brown-Borg and Buffenstein 2017*). In truth, methionine is one of the most susceptible amino acids to be oxidized by free radicals in proteins and there are studies that negatively correlates the amount of methionine in proteins with maximum longevity in mammals (*Moskovitz et al. 2001*; *Ruiz et al. 2005*; *Pamplona et al. 2005*). Therefore, isocaloric RMet positives effects in oxidative stress and longevity have been demonstrated in several studies. Also interesting, although much less numerous, are those works in which the RMet has been applied at older ages in order to assess whether its beneficial effects can also be established at these ages or if the deleterious effects of aging are already irreversible. In this regard, Sun et al. and Sánchez-Román et al. have demonstrated that 65% and 40% RMet started at advanced ages (12 and 24 months old respectively) are able to increase longevity in mice and the ability to reduce free radical production is maintained, leading to a decrease in oxidative damage in liver of old rats (*Sanchez-Roman et al. 2012*). However, these effects occur to a lesser extent than when the intervention is 80% of RMet in younger rodents being as well an important factor the restriction time (*Orentreich et al. 1993*; *Richie et al. 1994*; *Miller et al. 2005*; *Sanz et al. 2006a*; *Caro et al. 2008a*). Beneficial effects of this intervention have always been demonstrated in a long-term restriction, one year minimum, or short or near-term depending on the tissue (from 6 weeks to 6 months) (*Gredilla and Barja 2005b*; *Pamplona and Barja 2006*). In this sense, the results from the present thesis have been obtained from 26-months old rats in order to evaluate the effect of a 7-week RMet in the metabolome and particularly in the lipidome of old animals.

CR, PR and RMet not only improves biomarkers of metabolic health and increases longevity in rodents but also produces a highly integrated series of physiological and biochemical responses including remodeling lipid metabolism into a healthier lipid profile (*Anthony et al. 2013*). RMet increases energy expenditure and induces weight loss along with a reduction of fat deposition, especially of visceral and ectopic depots (*Orentreich et al. 1993*; *Zimmerman et al. 2003*; *Malloy et al. 2006*). Several studies have been focused on the effects of the RMet intervention on the

lipid metabolism showing differences across tissues (see review *Zhou et al. 2016*). RMet remodels coordinately lipid metabolism between liver and WAT depots leading to a reduction in circulating and tissue lipids (*Hasek et al. 2013*). The RMet remodeling comprises an increase in lipogenic expression, especially of fatty acid synthase (FAS) and stearoyl-CoA desaturase-1 (SCD-1) in WAT and both a decrease in lipogenic but also an increase in lipolytic gene expression in liver (*Perrone et al. 2012*; *Hasek et al. 2013*; *Lees et al. 2014*). In the liver, the decrease in lipogenesis and the increase in free fatty acid oxidation, along with the reduce in TAG storage and hepatic levels, represents a protection against fatty liver disease not only in young and adult animals but also in old ones (*Anthony et al. 2013*; *Lees et al. 2017*). These changes in the expression of genes and key proteins involved in the lipid metabolism are translate into changes that both restrictions, CR and RMet induce in the fatty acid composition that seems to be tissue-specific. Studies about the effect of CR and RMet on liver skeletal and cardiac muscle, brain and spinal cord show changes in the fatty composition that lead to a decrease of both double bond index and peroxidability, conferring higher resistance to oxidative damage even when the CR applied is as low as 8.5% (*Laganiere and Yu 1987*; *Laganiere and Fernandes 1991*; *Cefalu et al. 2000*; *Sanz et al. 2006a*; *Gómez et al. 2007*; *Jové et al. 2013a*). Nevertheless, the changes in the fatty acid composition in WAT by RMet show an increase in both PUFA and MUFA species, which suggest a tissue-specific RMet effect on lipid metabolism (*Perrone et al. 2012*). This effect on the total fatty acid composition affect as well to chain length and degree of unsaturation of fatty acid from GP, TAG and CE both circulating or from liver, kidney, heart, brain and skeletal muscle under CR suggesting a metabolic reprogramming that involves an up-regulation of β-oxidation and lower levels products of oxidative damage (*Tacconi et al. 1991*; *Jeon et al. 2001*; *Pamplona et al. 2002b*, *c*; *Ward et al. 2005*; *Faulks et al. 2006*; *Selman et al. 2006*; *Perrone et al. 2012*; *Jové et al. 2014*; *Miller et al. 2017*). In addition, lipidomic studies showed that the effects of this dietary restrictions are tissue-specific, defining for example a nervous system-specific lipidomic profile of RMet due to at least 50% of the lipids changed are common in the brain and spinal cord but not in the liver (*Jové et al. 2013a*). Interestingly, RMet affects as well the bile acid metabolism being the levels of glycocholate and glycodeoxycholate increase, but not in taurine-conjugated bile acids, in serum, WAT and liver from young rodents. (*Perrone et al. 2012*; *Ghosh et al. 2017*). Finally, short-term CR and RMet studies in humans revealed an increase in fatty acid oxidation, a decrease in ectopic fat, including intrahepatic and intramyocellular lipids, and a remodeling of both GP and SP metabolism (*Larson-Meyer et al. 2006*; *Plaisance et al. 2011*; *Collet et al. 2017*).

Overall, these studies suggest a key role for lipid metabolic integrity in health and aging. Therefore, the present thesis has evaluated the metabolomic and lipidomic changes caused by RMet in old rats. In this sense, the result from the untargeted metabolomic and lipidomic analysis performed in WAT, skeletal muscle, heart, kidney and liver demonstrate specific changes in the metabolome and lipidome of the analyzed tissue as a consequence of the RMet in the old animals compared to both control groups, adults and old animals. Differences in the purine metabolism, in structural lipids (GP and SP species), signaling lipids (Spa, CerP, MAG and oxylipins), lipid species involved in the energy metabolism (acylglycerol, acyl-CoA and acylcarnitines) and bile acid metabolism have been found across tissues.

The unsupervised multivariate statistics applied to the results of the untargeted metabolomic and lipidomic analysis showed that the RMet changes of the metabolome and the lipidome are different across mammalian tissues. In skeletal and cardiac muscles, while the PCA from both the whole metabolome and lipidome did not showed differences, the hierarchical clustering analysis performed with the top 25 metabolites obtained by one-way ANOVA from all the experimental groups showed that the RMet metabolomic and lipidomic profiles shared more similarities with the adult group than with the age-matched control. For both types of WAT and kidney, the PCA representing the whole metabolome and lipidome did not showed differences; however, both the hierarchical clustering analysis performed with the top 25 metabolites obtained by one-way ANOVA and the supervised multivariate analysis, PLS-DA, showed that the effect of the RMet produces a specific remodeling of the metabolomic and lipidomic profiles of old animals. Finally, the hepatic metabolome and lipidome profiles represented in the PCA show clear differentiation within each diet, being the RMet animals clustered separately from both control groups, old and adults. This highly marked effect of the RMet in the metabolome and lipidome profiles of the old animals was corroborated with the results obtained from the supervised multivariate and univariate analysis. In fact, the percentage of significantly altered metabolites and lipid species supported the tissue-specific results observed in the multivariate analysis. The highest differences was observed between the two types of skeletal muscle where in gluteus 17,27% of the metabolites were significantly affected while for soleus the value was 5.85%. Kidney and heart showed similar values being approximately a 7.5% of their metabolomes different while for both types of WAT was between 8-10% and almost an 11% of the hepatic metabolome showed differences. In summary, these results demonstrate that RMet changes in the metabolome and the lipidome are tissue-specific, being especially notorious in the hepatic tissue and gluteus. For all the muscular tissues analyzed the resulting metabolome and lipidome shared

more similarities with the adults rather than with the old animals without RMet while for WAT and kidney the effect of the diet led to a specific RMet remodeling of their metabolomic and lipidomic profiles. Globally, the differences between old rats with and without RMet strongly indicates that the metabolomic pattern is altered by the diet intervention while the differences found between the profiles of adult animals and RMet old rats suggest that the RMet does not result in complete protection from the aging-associated metabolic state, implicating a remodeling of the metabolome and lipidome profiles.

Several components of the purine metabolism were found to display differences between the experimental groups in skeletal muscle, heart, liver and kidney. As the metabolomic analysis was not performed in any type of WAT, due to their highly hydrophobic nature, no information regarding the purine metabolism was obtained. In skeletal muscle along with liver, the purine pathway was down-regulated in the RMet animals compared to the old control for the skeletal muscle or to both control groups in the hepatic tissue. In kidney, the levels of the different compounds of the pathway identified were increase or decrease compared to the old animals, being more similar to the levels of the adult renal tissue. Finally, cardiac tissue showed and upregulation of the purine metabolism in the RMet animals compared to both control groups for guanosine 3P and hypoxanthine while the ADP-ribose levels were lower in the old animals with RMet than without. In agreement with the results of this thesis, a tissue-specific RMet effect in the purine metabolism has been reported in adults rats on RMet for 3 months (*Perrone et al. 2010*). Furthermore, a transcriptomic analysis show a downregulation of the purinergic receptor P2X, ligand gated ion channel 7 (P2rx7) in the hepatic tissue of adult rats with RMet (*Perrone et al. 2012*). These RMet effects on the purine metabolism could be due to the interaction of the methionine and folate cycles in the one carbon metabolism and its repercussions can go beyond the rearrangement of the nucleotide cofactors of nucleic acid biosynthesis (*Moffatt and Ashihara 2002*; *Locasale 2013b*). The remodeling in purine metabolism caused by RMet could affect several tissue-specific metabolic pathways and functions through the purinergic signaling previously discussed in the first section of this chapter, which has been reported to have a tissue-specific role during development and aging (*Burnstock and Dale 2015*). In summary, the purine metabolism suffers a tissue-specific remodeling by the action of RMet even in 26 months old rats. Although the biological significance of the purine metabolism remodeling is currently unclear it could play a key role in the beneficial effects produced by the RMet.

The identification of the significantly different lipid species between the experimental groups revealed the implication of several structural lipids, mainly GP and SP species. RMet induce

changes in LGPs levels of old animals in every tissue except for both types of WAT. This fact could be due to most of the LPG species are detected with the metabolomic methodology that was not performed in the WAT. In gluteus and soleus, the levels of the LPGs of RMet old animals were found to be both or increase by the RMet respect both control groups or more similar to the adults rather the age-matched control group. However in cardiac tissue, LPGs were or decrease compared to both control by the RMet or as well as the skeletal muscle more similar to the adults. Finally, in renal and hepatic tissues the remodeling caused by the RMet in the LPG metabolism was specific for each lipid species being increase or decrease respect just one or both control groups. LPA species were found in liver, soleus and heart, while LPS(16:0) and (16:1) were only in the hepatic tissue and both presented lower values than the control groups. LPC and LPG changes were restricted to muscular tissues but the regulation did not show a subclass specific pattern and finally LPE and LPI species were altered in all tissues. Since LGP serve as a precursors for GP biosynthesis, changes in the pool levels of LPG species in a tissue-specific manner could directly affect to the biosynthesis of GP. However, the signaling functions ascribed to some of the LGP species could affect other specific processes in each tissue. Regarding other GP species, the subclasses of PC and PE were those that appear most affected by the RMet. Different PC species were altered in gluteus, SAT, kidney and liver while PE species affected by the RMet were in VAT, liver and soleus. PC levels in SAT, liver and kidney follow a remodeling because of the RMet different respect both control groups while the level of PC in gluteus of old RMet animals was more similar to the adults. PE levels in VAT and soleus were decreased by the RMet compared to old animals and the resulting levels were more similar to the adults. In liver, some of the PE species showed the same regulation that the PE species in VAT and soleus, while other decrease as effect of the diet respect to both control groups. PA species found in heart and SAT were lower in the RMet groups respect both control animals and PI(32:4) found in both types of skeletal muscle showed differences between them. In gluteus levels were higher in old animals with RMet than without, while in soleus RMet animals showed lower levels of PI(32:4) respect both control groups. The result obtained in this thesis about the effects of RMet in the GP metabolism supports the previous published hypothesis that RMet induce changes are not equally distributed among all the GP (*Jové et al. 2013a*). In addition, compared to previous studies performed in adult mice, this thesis showed that shorter restriction time in older animals induces as well important changes in GP species in a tissue-specific manner. Globally, GP metabolism showed tissue-specific differences and the effect of the RMet in old animals could lead to reversion of the old phenotype to a younger one for some GP species while for other the change is RMet-specific. Moreover, differences between both types of skeletal muscle (gluteus

and soleus) and WAT (VAT and SAT) were observed in old animals with RMet. The impact of RMet in GP metabolism of the hepatic tissue was higher than the other tissues analyzed, although all of them showed differences due to the RMet.

Concerning SP species, changes in all the analyzed tissues were observed as a result of the RMet. Both types of skeletal muscle showed a decrease in SM respect both control groups while in gluteus lower levels of Cer along with higher levels of HexCer were found in old RMet animals compared to the age-matched control groups. In both types of WAT and kidney SM species were higher in RMet animals compared to both control groups while Cer in WAT and HexCer in kidney presented lower levels in RMet animals, suggesting an increase in SM biosynthesis. Oppositely, in liver higher levels of HexCer were found in RMet animals compared to both groups while in heart, ganglioside GA2 was decrease by the RMet, suggesting different susceptibilities of SP metabolism of each tissue to change induced by nutritional interventions. Most of these changes counteract the modification produced by advancing age in the tissues analyzed. GPs and SPs contribute to membrane lipid asymmetry, whereas cholesterol and SPs define a lipid microdomain, the lipid raft, which serves as key assembly and sorting platforms for cell to cell interactions and signal transduction complexes (*Zheng et al. 2006*; *Van Meer et al. 2008*). In summary, SP metabolism is affected by the RMet in old animals in a tissue-specific manner producing a remodeling that in some cases counteract the age-related changes and in other lead to a specific RMet profile. Globally, the differential effects of RMet in GP and SP species suggest possible changes not only in the membrane composition but also in the lipid raft composition and, therefore, altered signaling pathways in these animals compared to control ones. Interestingly, not all the lipids modified by RMet were the same in skeletal muscle, heart, kidney, WAT and liver, and a tissue specific lipidome profile of RMet for structural lipids could be defined.

Beside a possible altered signaling function of the lipid rafts, the levels of other lipid species that act as second messengers have been found altered by the RMet in the old animals. SP signaling species (Cer1P, Spa and Spa1P) were found in skeletal muscle and liver, fatty acid esters of hydroxy fatty acids (FAHFAs) in heart and gluteus and several oxylipins in in all the muscular tissues, VAT and kidney. In gluteus, levels of Cer1P were increased by the RMet compared to the old animals while Cer levels were decreased. Cer and Cer1P are potent signaling molecules capable of regulating vital cellular functions. While Cer induces cell cycle arrest and promote apoptosis Cer1P acts as an inducer of cell survival by inhibiting the apoptosis (*Gómez-Muñoz 2006*).Therefore, an impaired balance between the levels of these two antagonistic molecules

may result in a metabolic dysfunction. In this sense, RMet effect seems to switch this balance towards levels more similar to the adult animals and perhaps this effect of the RMet helps the coordination of Cer and Cer1P to ensure normal cell functioning and gluteus homeostasis. Regarding Spa and Spa1P, the saturated forms of Sph and Sph1P, old animals with RMet presented higher levels of Spa in soleus while in the hepatic tissue Spa1P was decreased by the RMet. In both tissues, the levels of these lipids were RMet specific and different from both controls suggesting an important role for them in the effects of RMet in soleus and liver. However, the biological function of Spa and Spa1P is poorly characterized compared to Sph or Sph1P. A few studies in fibroblast suggest an antagonistic role for Spa1P compared to Sph1P as lipid mediator in both the tumor necrosis factor (TNF) alpha and beta (*Bu et al. 2006*, *2010*). Hence, the role of this relatively unknown lipid mediators could be crucial for the reported anti-inflammatory effect of the dietary restrictions (*Wanders et al. 2014*; *Miller et al. 2017*).

Other bioactive lipid found altered by RMet was FAHFA(18:0/9-O-18:0) in heart and gluteus, being the resulting levels more similar to adult animals than age-matched controls. FAHFA have been recently identified being their levels in tissues and serum similar to concentrations of signaling lipids such as prostacyclins, prostaglandins, steroids and endocannabinoids (*Yore et al. 2014*). FAHFA can directly bind and activate the cell surface receptor G Protein-Coupled Receptor 120 (GPCR120) and therefore FAHFA have been defined as anti-diabetic and anti-inflammatory effectors (*Yore et al. 2014*). The activation of GPR120 directly or indirectly inhibits inflammation, modulates hormone secretion from the gastrointestinal tract and pancreas, and regulates lipid and/or glucose metabolism in adipose, liver, and muscle tissues (*Zhang and Leung 2014*). Moreover, the expression of different GPR receptors, GPR43 and GPR120, have proved to be dietary-inducible in heart, liver and skeletal muscles, probing their importance in maintaining metabolic health (*Cornall et al. 2011*). Studies in adipocytes have demonstrated that GPR120 activation with FAHFA block inflammatory cytokine production and reduce adipose inflammation, provoke an insulin-induced Glut4 translocation and glucose uptake in adipocytes as well as an increase on glucagon-like peptide 1 (GLP-1) secretion (*Yore et al. 2014*). The results of the present study demonstrated that RMet altered levels of FAHFA(18:0/9-O-18:0) returning them to a younger phenotype. Therefore, it would be interesting to assess the possible role FAHFAs as mediators of both anti-inflammatory effects and the enhance insulin sensitivity that present RMet animals as well as to determine if RMet is able to increase GLP-1 secretion and if so, if it is through FAHFA signaling.

Amongst the bioactive lipid species identified to be altered by the RMet several oxylipins were found in all the muscular tissues, VAT and kidney. Most of them presented levels in the RMet old animals more similar to the levels in the adults than the age-matched control group. Other were upregulated or downregulated by RMet in a specific manner different from both producing a remodeling in the oxylipins of the tissues. Oxylipins derived from AA (leukotrienes, prostaglandins and isoprostanes), from DHA (epoxy-HDHA and DiHDPE) and from LA (HODE) were found across tissues with a regulation specific for each lipid specie. 20-carboxy-LTB4 was found to be highly increase in gluteus and decrease in kidney. Although LTB4 is a potent pro inflammatory effector, this metabolite is less biologically active or even totally inactive compared to its precursor LTB4 (*Ford-Hutchinson et al. 1983*). In heart, RMet presented lower levels of LTC4 that beside its role as pro inflammatory effector has been reported to be a mediator of the reticulum stress-induced ROS production (*Dvash et al. 2015*). In the present thesis, the metabolomic analysis showed that RMet old animals presented lower levels 10-F2-dihomo-IsoP in gluteus, heart and liver. F2-IsoP are non-enzymatically derived oxylipins formed by the peroxidation of AA and they are excellent biomarkers of oxidative stress, which suggest that lower levels of 10-F2-dihomo-IsoP could be translated into lower levels of oxidative stress in gluteus, heart and liver of the RMet old animals. Comparable to this evidence, significantly lower levels of glutamic semialdehyde (GSA) and N-ε -(Carboxyethyl) lysine (CEL), both oxidative stress biomarkers, were reported in liver of RMet old animals (*Cabré 2015*). In summary, the oxylipins metabolism showed differences across tissues by the effect of RMet in old animals, particularly in skeletal muscle, heart and kidney. For some lipid species the RMet modification led to levels more similar to a younger phenotype while other suffer a remodeling completely different from adult or old animals, mainly in the renal cortex. Overall, these changes could be related the previously reported beneficial effects of the RMet in terms of oxidation and inflammation, which are the main biological responses accountable for the aging process (*Sanz et al. 2006a*; *De la Fuente and Miquel 2009*; *Wanders et al. 2014*).

Related to the effects of RMet in the oxidative stress and redox systems, GSSG and ubiquinone 9 were found altered in gluteus, kidney and liver. GSSG levels were regulated by the RMet in a specific manner for each tissue. In gluteus, GSSG was upregulated compared to both control animals while the opposite situation was found in kidney. Glutathione-related redox pathway have been studied in male F-344 rats with a 80% RMet for up to six months, where a decrease in oxidative stress biomarkers along with higher levels of free GSH in blood were reported (*Maddineni et al. 2013*). Thus, RMet decreases oxidative levels providing higher resistance to

oxidative damage and the reason for these findings could be due to enzymatic changes produced by the diet. However, in that same study, GSH peroxidase activity decreases in liver and increased in kidney while no changes in the activity of GSH reductase is observed as a result of RMet. The decrease in GSSG in the old kidney of RMet animals seem contradictory to enzymatic activity reported by Maddineni and collaborators, although their final conclusion is that oxidative stress is reduced by RMet in rats, but this effect cannot be explained by changes in the activity of antioxidant enzymes (*Maddineni et al. 2013*). In summary, it is uncertain if the observed changes in the glutathione-related redox pathway are adaptive changes to the new oxidative stress level or are produced by the RMet itself.

Ubiquinone 9 levels were found to be lower in hepatic tissue of old rats after 7-week RMet compared to both old and adult animals under control diet. This same observation was published after performed an untargeted lipidomic analysis on 80% RMet during 6 months in young mice (*Jové et al. 2013a*). Despite differences between the animal model in terms of age and restriction time, ubiquinone levels respond equally in both interventions. Ubiquinone 9 is a redox active lipid primarily found in the mitochondrial inner membrane of rodents, although it is also located in plasma membrane (*Wang and Hekimi 2016*). In addition to its function as an indispensable link in mitochondrial electron transport chain from complexes I and II to complex III, the reduced form of ubiquinone acts as a free radical scavenger, while the partially oxidized semiquinone can generate the superoxide free radical (*Hyun et al. 2007*). Subsequently, ubiquinone is highly concentrated in mitochondria, but it is also found at significant levels in all the other cellular membranes, where the cycle between reduced and oxidized states of ubiquinone continues. Maintenance of the redox cycle of ubiquinone in extra-mitochondrial membranes is based on several different enzymes that show ubiquinone-reductase activities, such as NAD(P)H dehydrogenase quinone 1 (NQO1) (*López-Lluch et al. 2010*). According to the effects of aging on ubiquinone levels, it has been reported a significantly decrease at 25−28 months in heart, kidney and muscle, and also in mitochondria of liver, heart and kidney in rats (*Beyer et al. 1985*; *Kamzalov and Sohal 2004*). On the other hand, the skeletal muscle ubiquinone levels in the mitochondria were reported to decrease, whereas in the kidney, brain or heart ubiquinone levels remain unchanged during aging in mice (*Lass et al. 1999*). Thus, differences in tissues and animal models must be taken into consideration in order to understand the role of ubiquinone in aging. Jové and collaborators explain the decrease in the ubiquinone 9 levels of the hepatic tissue in young RMet mice through the nuclear factor-E2-related factor 2 (Nrf2), which is the principal regulator of the phase II cellular antioxidant

defense system (*Jové et al. 2013a*). They proposed that lower levels of lipid peroxidation in RMet animals lead to lower Nrf2 activation and therefore a down regulation of antioxidant enzymes, such as NQO1, membrane protein involved in the ubiquinone redox system. They suggest that common ubiquinone changes and Nrf2-dependent responses may be part of a general aging protective system in rodents. Globally, the results of the present study have demonstrated a change in the redox system in a tissue-specific manner that could be as a result of an adaptive change to the lower oxidative stress produced by the RMet. In any case, 7-week RMet in old animals reproduce the observed effects in younger animals under longer restriction time, suggesting that the lipid plasticity remains and responses to diet interventions despite aging.

Regarding the lipid species involved in the energy metabolism, the results of the present study demonstrated that RMet affects the levels of different acylglycerol species, acyl-CoA and acylcarnitines in the analyzed tissues. TAG species were affected by the RMet in all the tissues in a specific manner. Skeletal and cardiac muscles showed a decrease in TAG abundances compared just to the age-matched control for some lipid species or to both control groups for other TAG species. In hepatic and renal tissues TAG levels were specific for each lipid species being some of them upregulated compared to both control groups while other presented levels more similar to the adult group. Finally, TAG composition of both types of WAT suffered a marked remodeling being some species up- or down-regulated compared to the control groups and other TAG species were more similar to the adults rather than the age-matched control group. In addition, Acyl-CoA levels were altered by the RMet in a tissue-specific manner being higher in the skeletal muscle, lower in WAT and liver and more similar to the adult control group in kidney. Finally, acylcarnitines were altered in all the muscular tissues where their levels were lower than the old control or lower than both control groups. As it has been discussed before, published studies have demonstrated that the effect of RMet in lipid biosynthesis or fatty oxidation was tissue-specific (*Perrone et al. 2012*; *Hasek et al. 2013*; *Lees et al. 2014*, *2017*). Moreover, the decrease observed in the acylcarnitines levels in the cardiac tissue counteracts the increase produced by the aging process. In skeletal muscle, no differences in acylcarnitines were found associated with aging, hence the decrease in the acylcarnitines levels could explained as well the higher levels of acyl-CoA found in the skeletal muscle but not in the heart. Globally, a 7-week RMet in old animals produces a remodeling in the lipid content by affecting the levels of TAG, acyl-CoA and acylcarnitines in a different manner for each tissue. In this thesis, the analyzed tissue can be clustered in three groups according the changes observed in the lipid species involved in energy metabolism i) VAT and SAT, both present the greater number of TAG

species altered by the RMet where some TAG species return to the levels of the adult control group, giving an adult-like lipid profile to the old animals while other TAG species did not follow a rejuvenation pattern but a specific pattern of the RMet; ii) muscular tissues, gluteus, soleus and heart showed a decrease in TAG, acylcarnitines and only for skeletal muscle an increase in acyl-CoA and iii) kidney and liver, where most of the TAG and acyl-CoA species showed similar levels to a younger phenotype. To sum up, a tissue-specific remodeling of GL metabolism was observed in RMet old animals despite the advancing age of the animals and the restriction time.

Interestingly, an upregulation of bile acid metabolism was observed in the RMet old group respect both controls. Most of the bile acids were found in liver although not exclusively because deoxycholic was higher in gluteus of RMet animals and glycocholic in kidney. The results of the present study showed a difference in taurocholic and glycolic acid regulation being the taurocholic levels decrease in the liver of RMet old animals. This fact may be because glycine conjugation with cholic is favored since taurine availability has reported to be decreased in rodents under RMet as a result of a limited production from methionine (*Perrone et al. 2012*). The presence of higher levels of certain bile acids in gluteus and kidney of RMet old animals suggest that the effects of the upregulation of the bile metabolism as a consequence of the RMet can have repercussion not only to those tissues involved in enterohepatic circulation. In concordance with the results of the present thesis, a metabolomic study published by Perrone and collaborators reported an upregulation in the hepatic bile acid (BA) metabolism of 6-week old F344 rats after 3 months of RMet. Their results showed an increase in glycocholate and glycodeoxycholate in liver and serum but accompanied by a decrease in taurocholate and taurodeoxycholate in both liver and serum (*Perrone et al. 2012*). In this sense, it is advisable that RMet is able of induce changes in bile acid metabolism independently of both animals age and restriction time. On the other hand, it has been reported that BAs synthesis and bile flow decreases markedly during aging (*Bertolotti et al. 2007*). The role of bile acids in aging process has been previously discussed as result of the chemical genetic screen performed by Goldberg and collaborators were lithocholic acid (LC) was found as one of the most potent anti-aging compounds identified, able to extend the chronological life span of a short-lived yeast mutant (*Goldberg et al. 2010*). The finding that LC modulates yeast life span is however, surprising, given the fact that yeast does not synthesize LC or any related compound (*Ferbeyre 2010*). In this study on yeast models, they suggest that LC modulates housekeeping longevity assurance pathways, in a TOR-independent manner, by suppressing lipid-induced necrosis, attenuating mitochondrial fragmentation, suppressing mitochondria-controlled apoptosis, altering redox homeostasis in

mitochondria, enhancing resistance to oxidative and thermal stresses, and enhancing stability of nuclear and mitochondrial DNA (*Goldberg et al. 2010*). However, the most known role of BAs is in absorption of dietary lipids and fat-soluble vitamins from the small intestine as well as for TAG and cholesterol homeostasis in the liver. BA synthesis, metabolism and transport in the enterohepatic circulation are strictly controlled by BAs themselves via activation of FXR. A previous study has demonstrated that activation of FXR, by natural and synthetic agonists, increases SHP levels, which in turn reduces SREBP-1c expression, which controls the expression of genes involved in lipogenesis, such as acetyl-CoA carboxylase (ACC), FAS, SCD-1, acetyl-CoA synthetase (AceCS) and glycerol-3-phosphate acyltransferase (*Watanabe et al. 2004*). In this sense, the expression of FXR, SHP and SREBP-1c in the hepatic tissue was analyzed. The expression of FXR and SHP did not show significantly differences between the experimental groups but SREBP-1c expression revealed an increase in the liver of old animals with control diet respect to the adult group, which was reversed by the RMet. This fact suggests that the effect of the RMet in the lipid metabolism could involve the participation of SREBP-1c but its regulation is not through SHP inhibition. In concordance, transcriptional studies of rodents showed that RMet induced decrease in expression of hepatic Srebp-1c, consistent with the repressive effect of RMet on lipogenic gene expression (*Hasek et al. 2013*). Although, a previous published study in 10-month-old male C57BL/6 J wild-type mice on 80%RMet for 2 weeks reported a significantly increase in the expression of the gen Srebp1c in WAT of RMet animals but did not report changes for expression of Srebp1c in the liver (*Lees et al. 2017*). However, these results are not contradictory to the results from the present work for two reasons, both of their experimental groups, control and RMet, are young animals and hence, srebp1c levels are not increased since it is an age-related change and/or maybe a 2-week restriction was not enough for achieve these changes. Besides the FXR/SHP regulation, SREBP-1c is also subject to regulation by cholesterol and glucose, and both are decreased by RMet (*Perrone et al. 2008*). However, whether decreases in cholesterol and glucose are the cause or product of transcriptional responses to RMet remains unclear (*Orgeron et al. 2014*). On the other hand, transcriptional studies showed that essential amino acids deprivation limits the charge of tRNAs and amino acids leading to the activation of the protein kinase called general control nondepressible 2 (GNC2), which could be the mediator of RMet decrease of lipogenic genes in the liver. In fact, GCN2-deficient mice developed liver steatosis and exhibited reduced lipid mobilization, caused by unrepressed expression of lipogenic genes, including Srebp-1c and Fas (*Guo and Cavener 2007*). The main role of GCN2 in RMet has been discussed because RMet increases lipogenic gene expression in WAT and muscle, although it could suggest the involvement of additional sensing and signaling

systems in these tissues. In fact, it has been recently probed that FGF21 is a critical mediator of the effects of RMet on lipid metabolism remodeling of WAT, and increased insulin sensitivity but not of its effects on hepatic gene expression, which supports the theory of tissue specific sensing and signaling systems (*Wanders et al. 2017*). In either case, hepatic SREBP-1c appears to be a key target of the mechanism through which RMet reduces hepatic *de novo* lipogenesis, triglyceride synthesis, and lipid content (*Orgeron et al. 2014*; *Zhou et al. 2016*)**.** In these sense, the present study corroborates the decrease in the SREBP-1c expression by the RMet in old animals after 7-weeks of dietary intervention.

Finally, the results from the present thesis showed that RMet alters the metabolomic and lipidomic profiles in a tissue-specific manner. Moreover, RMet produces significantly different responses compared to age-matched control group but also that RMet effect on the metabolome and lipidome of the analyzed tissues is as well different from adults control mice. Thus, RMet does not result in complete protection from the aging-associated metabolomic and lipidomic changes although it restores the levels of certain metabolites towards a younger phenotype. Amongst these changes, several lipids species and therefore their functions in generating membranes, as bioactive lipids or involve in the energy metabolism, especially show the effect of the RMet remodeling, being a tissue-specific lipidome remodeling.

CONCLUSIONS

6. CONCLUSIONS

1. Skeletal muscle, white adipose tissue, renal cortex, liver and heart present a specific metabolome and lipidome, with metabolites and metabolic pathways in common but other tissue-specifics, being 48.9% of the variability across tissues due to their metabolomes.

2. Skeletal muscle, white adipose tissue, renal cortex, liver and heart present common metabolites such as N-acylamines. In this study it has been demonstrated the presence of N-palmitoyl serine, N-stearoyl tryptophan and N-stearoyl tyrosine have been identified in skeletal muscle as well as N-oleoyl tyrosine in both cardiac and renal tissue of adult male Wistar rats.

3. The targeted lipidomics analysis results suggest the presence of general rules and patterns shared by tissues about lipid distribution as a result of a phylogenetic and ontogenetic process to cover three basic cellular processes: formation of membranes, signaling and bioenergetics.

4. The structural lipid species detected in skeletal muscle, white adipose tissue, renal cortex, liver and heart show the existence of a preferential structural presence of GPs with a specific weight for PCs and PEs followed by PI and PS; and, in a minor amount, the presence of SP with a predominant use of SMs.

5. Skeletal muscle, white adipose tissue, renal cortex, liver and heart show a predominance of molecular species obtained by *de novo* synthesis along with a minor presence of a wide variety of other lipid species which offer diversity in the fatty acid profile (particularly to ensure a diversity in the PUFA content), maybe as an adaptive change to resist oxidative stress.

6. The differences among tissues can be ascribed to quantitative rather than qualitative differences in the lipid species used that could be interpreted as an adaption to the specific metabolic and physiological needs which are tissue-dependent.

7. The untargeted metabolomic and lipidomic analysis performed in white adipose tissue, skeletal muscle, heart, kidney and liver demonstrate specific changes associated with the aging process in the metabolome and lipidome of the analyzed tissues of 26 months old male Wistar rats. For cardiac tissue, main compounds modified by aging comprise

the polar fraction of the metabolome while for liver, skeletal muscle and WAT age-related changes disturb predominantly non-polar lipid species. Renal tissue metabolome and lipidome were the ones showing less age-related modifications.

8. The aging process produces changes in: i) structural lipid contributing to age-related disturbances in the physical properties and function in membranes; ii) oxylipins metabolism in a tissue specific manner, probably increasing oxidative stress and inflammation in the aged heart and decreasing the effect of arachidonic metabolites in the renal cortex; iii) lipid biosynthesis and fatty acid oxidation being those age-related changes specific for individual lipid species.

9. The untargeted metabolomic and lipidomic analysis performed in white adipose tissue, skeletal muscle, heart, kidney and liver demonstrate specific changes in the metabolome and lipidome of the analyzed tissue as a consequence of the 7-week RMet in 26 months old male Wistar rats, reproducing some of the changes observed in younger rodents with longer restrictions time. Shorter interventions in older animals could achieve a younger healthier phenotype due to metabolic plasticity remains and responds to RMet.

10. Differences in the metabolomic and lipidomic profile by the RMet in old animals are tissue-specific and especially marked in the hepatic tissue. However, in all the analyzed tissues the differences between old rats with and without RMet strongly indicates that the metabolomic and lipidomics patterns are altered by the diet intervention while the differences found between the profiles of adult animals and RMet old rats suggest that the RMet does not result in complete protection from the aging-associated metabolic state, implicating a remodeling of the metabolome and lipidome profiles.

11. Purine metabolism suffers a tissue-specific remodeling by the action of 7 weeks RMet even in 26 months old rats. Although the biological significance of the purine metabolism remodeling is currently unclear it could play a key role in the beneficial effects produced by the RMet through purinergic signaling in the analyzed tissues.

12. The RMet in old animals produces changes in: i) structural lipid suggesting a remodeling in the physical properties and function in membranes; ii) signaling lipid species that regulates apoptosis and inflammation producing a specific RMet profiles or switching to a younger phenotype; iii) the redox-pathway through the modulation of GSSG and ubiquinone 9 levels; iv) lipid biosynthesis and fatty acid oxidation in a tissue-specific

manner observing three different patterns for WAT, muscular tissues and finally for renal and hepatic tissue.

13. RMet up-regulates the bile acid metabolism independently of both animals age and restriction time in liver, gluteus and kidney, suggesting a role of bile acids as signaling mediators of the RMet beneficial effects.

14. SREBP-1c expression in the hepatic tissue increases with advancing age and 7-weeks of RMet restores the levels of this protein by lowering them, being therefore more similar to a younger phenotype. The regulation of the SREBP-1c expression by RMet is FXR/SHP independent.

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ANNEX

8. ANNEX

8.1 Annex 1

Below in Table S1 it has been described the conditions for the LC/MS analysis for the entire set of lipid detected and quantified. In all of them, the ion polarity of the electrospray ionization was positive and the fragmentor was set at 380 volts. Retention time window was 10% and the accuracy mass 20%.

Table S1. Conditions for tandem mass spectrometry quantification of all the lipid species detected by targeted lipidomic analysis

Lipid Name	Internal Standard	Transition	RT	TS	CE	CAV
AcylCarnitine 12:0	LPC 13:0	344.3 -> 85.1	1,28	1	30	5
AcylCarnitine 13:0	LPC 13:0	358.3 -> 85.1	1,459	1	30	5
AcylCarnitine 14:0	LPC 13:0	372.3 -> 85.1	1,871	1	30	5
AcylCarnitine 14:1	LPC 13:0	370.3 -> 85.1	1,489	1	30	5
AcylCarnitine 14:2	LPC 13:0	368.3 -> 85.1	1,235	1	30	5
AcylCarnitine 15:0(a)	LPC 13:0	386.3 -> 85.1	1,94	1	30	5
AcylCarnitine 15:0(b)	LPC 13:0	386.3 -> 85.1	2,12	1	30	5
AcylCarnitine 16:0	LPC 13:0	400.4 -> 85.1	2,562	1	30	5
AcylCarnitine 16:1	LPC 13:0	398.3 -> 85.1	2,054	1	30	5
AcylCarnitine 17:0(a)	LPC 13:0	414.4 -> 85.1	2,64	1	30	5
AcylCarnitine 17:0(b)	LPC 13:0	414.4 -> 85.1	2,78	1	30	5
AcylCarnitine 18:0	LPC 13:0	428.4 -> 85.1	3,224	1	30	5
AcylCarnitine 18:1	LPC 13:0	426.4 -> 85.1	2,702	1	30	5
AcylCarnitine 18:2	LPC 13:0	424.3 -> 85.1	2,291	1	30	5
CE 14:0	CE 18:0-d6	614.6 -> 369.3	11,447	1	10	5
CE 15:0	CE 18:0-d6	628.6 -> 369.3	11,678	1	10	5
CE 16:0	CE 18:0-d6	642.6 -> 369.3	11,76	1	10	5
CE 16:1	CE 18:0-d6	640.6 -> 369.3	11,52	1	10	5
CE 16:2	CE 18:0-d6	638.6 -> 369.3	11,373	1	10	5
CE 17:0	CE 18:0-d6	656.6 -> 369.3	11,873	1	10	5
CE 17:1	CE 18:0-d6	654.6 -> 369.3	11,656	1	10	5
CE 18:0	CE 18:0-d6	670.7 -> 369.3	12,016	1	10	5
CE 18:1	CE 18:0-d6	668.6 -> 369.3	11,831	1	10	5
CE 18:2	CE 18:0-d6	666.6 -> 369.3	11,561	1	10	5
CE 18:3	CE 18:0-d6	664.6 -> 369.3	11,382	1	10	5
CE 20:1	CE 18:0-d6	696.7 -> 369.3	12,014	1	10	5
CE 20:2	CE 18:0-d6	694.7 -> 369.3	11,84	1	10	5
CE 20:3	CE 18:0-d6	692.6 -> 369.3	11,611	1	10	5
CE 20:4	CE 18:0-d6	690.6 -> 369.3	11,444	1	10	5
CE 20:5	CE 18:0-d6	688.6 -> 369.3	11,203	1	10	5
CE 22:0	CE 18:0-d6	726.7 -> 369.3	12,336	1	10	5
CE 22:1	CE 18:0-d6	724.7 -> 369.3	12,165	1	10	5
CE 22:4	CE 18:0-d6	718.7 -> 369.3	11,674	1	10	5
CE 22:5(a)	CE 18:0-d6	716.6 -> 369.3	11,443	1	10	5
CE 22:5(b)	CE 18:0-d6	716.6 -> 369.3	11,57	1	10	5
CE 22:6	CE 18:0-d6	714.6 -> 369.3	11,317	1	10	5
CE 24:0	CE 18:0-d6	754.7 -> 369.3	12,432	1	10	5
CE 24:1	CE 18:0-d6	752.7 -> 369.3	12,324	1	10	5
CE 24:4	CE 18:0-d6	746.7 -> 369.3	11,91	1	10	5
CE 24:5	CE 18:0-d6	744.7 -> 369.3	11,714	1	10	5
CE 24:6	CE 18:0-d6	742.7 -> 369.3	11,527	1	10	5
Cer(d16:1/16:0)	Cer 17:0	510.6 -> 236.3	6,69	1	29	5
Cer(d16:1/18:0)	Cer 17:0	538.6 -> 236.3	7,832	1	29	5
Cer(d16:1/20:0)	Cer 17:0	566.6 -> 236.3	9,099	1	29	5
Cer(d16:1/22:0)	Cer 17:0	594.6 -> 236.3	10,045	1	29	5
Cer(d16:1/23:0)	Cer 17:0	608.6 -> 236.3	10,112	1	29	5
Cer(d16:1/24:0)	Cer 17:0	622.6 -> 236.3	10,25	1	29	5
Cer(d16:1/24:1)	Cer 17:0	620.6 -> 236.3	10,043	1	29	5
Cer(d17:1/16:0)	Cer 17:0	524.6 -> 250.3	7,173	1	29	5
Cer(d17:1/18:0)	Cer 17:0	552.6 -> 250.3	8,44	1	29	5
Cer(d17:1/20:0)	Cer 17:0	580.6 -> 250.3	9,74	1	29	5

Cer(d17:1/22:0)	Cer 17:0	608.6 -> 250.3	10,135	1	29	5
Cer(d17:1/23:0)	Cer 17:0	622.6 -> 250.3	10,226	1	29	5
Cer(d17:1/24:0)	Cer 17:0	636.6 -> 250.3	10,295	1	29	5
Cer(d17:1/24:1)	Cer 17:0	634.6 -> 250.3	10,144	1	29	5
Cer(d18:1/14:0)	Cer 17:0	510.5 -> 264.3	6,702	1	29	5
Cer(d18:1/16:0)	Cer 17:0	538.5 -> 264.3	7,785	1	29	5
Cer(d18:1/18:0)	Cer 17:0	566.6 -> 264.3	9,056	1	29	5
Cer(d18:1/19:0)	Cer 17:0	580.6 -> 264.3	9,707	1	29	5
Cer(d18:1/20:0)	Cer 17:0	594.6 -> 264.3	10,022	1	29	5
Cer(d18:1/21:0)	Cer 17:0	608.6 -> 264.3	10,124	1	29	5
Cer(d18:1/22:0)	Cer 17:0	622.6 -> 264.3	10,226	1	29	5
Cer(d18:1/23:0)	Cer 17:0	636.6 -> 264.3	10,318	1	29	5
Cer(d18:1/24:0)	Cer 17:0	650.6 -> 264.3	10,42	1	29	5
Cer(d18:1/24:1)	Cer 17:0	648.6 -> 264.3	10,224	1	29	5
Cer(d18:1/26:0)	Cer 17:0	678.6 -> 264.3	10,574	1	29	5
Cer(d18:1x/18:0)	dhCer 8:0	566.6 -> 282.3	9,73	1	31	4
Cer(d18:1x/20:0)	dhCer 8:0	594.6 -> 282.3	10,299	1	31	4
Cer(d18:1x/22:0)	dhCer 8:0	622.6 -> 282.3	10,48	1	31	4
Cer(d18:1x/24:0)	dhCer 8:0	650.7 -> 282.3	10,644	1	31	4
Cer(d18:1x/24:1)	dhCer 8:0	648.6 -> 282.3	10,501	1	31	4
Cer(d18:2/14:0)	Cer 17:0	508.5 -> 262.3	5,9	1	23	5
Cer(d18:2/16:0)	Cer 17:0	536.5 -> 262.3	6,951	1	23	5
Cer(d18:2/17:0)	Cer 17:0	550.5 -> 262.3	7,494	1	23	5
Cer(d18:2/18:0)	Cer 17:0	564.6 -> 262.3	8,105	1	23	5
Cer(d18:2/20:0)	Cer 17:0	592.6 -> 262.3	9,347	1	23	5
Cer(d18:2/21:0)	Cer 17:0	606.6 -> 262.3	9,929	1	29	5
Cer(d18:2/22:0)	Cer 17:0	620.6 -> 262.3	10,054	1	23	5
Cer(d18:2/23:0)	Cer 17:0	634.6 -> 262.3	10,214	1	29	5
Cer(d18:2/24:0)	Cer 17:0	648.6 -> 262.3	10,259	1	23	5
Cer(d18:2/24:1)	Cer 17:0	646.6 -> 262.3	10,063	1	23	5
Cer(d18:2/26:0)	Cer 17:0	676.6 -> 262.3	10,395	1	23	5
Cer(d19:1/16:0)	Cer 17:0	552.6 -> 278.3	8,195	1	29	5
Cer(d19:1/18:0)	Cer 17:0	580.6 -> 278.3	9,348	1	29	5
Cer(d19:1/20:0)	Cer 17:0	608.6 -> 278.3	10,09	1	29	5
Cer(d19:1/22:0)	Cer 17:0	636.6 -> 278.3	10,272	1	29	5
Cer(d19:1/23:0)	Cer 17:0	650.6 -> 278.3	10,351	1	29	5
Cer(d19:1/24:0)	Cer 17:0	664.6 -> 278.3	10,407	1	29	5
Cer(d19:1/24:1)	Cer 17:0	662.6 -> 278.3	10,28	1	29	5
Cer(d19:1/26:0)	Cer 17:0	692.6 -> 278.3	10,595	1	29	5
Cer(d20:1/22:0)	Cer 17:0	650.6 -> 292.3	10,374	1	29	5
Cer(d20:1/23:0)	Cer 17:0	664.6 -> 292.3	10,441	1	29	5
Cer(d20:1/24:0)	Cer 17:0	678.6 -> 292.3	10,519	1	29	5
Cer(d20:1/24:1)	Cer 17:0	676.6 -> 292.3	10,372	1	29	5
Cer(d20:1/26:0)	Cer 17:0	706.6 -> 292.3	10,737	1	29	5
Cer1P(d18:1/16:0)	Cer 17:0	618.4 -> 264.3	5,521	1	29	4
COH (161)	COH-d7 (161)	369.4 -> 161.2	6,351	1	23	5
Desmosterol 16:0	CE 18:0-d6	640.8 -> 367.4	11,541	1	12	4
Desmosterol 18:1	CE 18:0-d6	666.8 -> 367.4	11,634	1	12	4
Desmosterol 18:2	CE 18:0-d6	664.8 -> 367.4	11,267	1	12	4
Desmosterol 20:4	CE 18:0-d6	688.8 -> 367.4	11,16	1	12	4
Desmosterol 20:5	CE 18:0-d6	686.8 -> 367.4	10,973	1	12	4
Desmosterol 22:6	CE 18:0-d6	712.8 -> 367.4	11,086	1	12	4
DG 30:0 -(14:0)	DG 15:0 15:0	558.5 -> 313.3	8,751	1	21	5
DG 32:0 -(16:0)	DG 15:0 15:0	586.5 -> 313.2	9,919	1	21	5
DG 32:1 -(16:1)	DG 15:0 15:0	584.5 -> 313.2	8,958	1	21	5
DG 32:2 -(18:2)	DG 15:0 15:0	582.5 -> 285.2	8,093	1	21	5
DG 34:1 -(18:1)	DG 15:0 15:0	612.6 -> 313.3	10,02	1	21	5
DG 34:2 -(16:1)	DG 15:0 15:0	610.5 -> 339.2	9,152	1	21	5
DG 34:2 -(18:2)	DG 15:0 15:0	610.5 -> 313.2	9,314	1	21	5
DG 36:1 -(18:1)	DG 15:0 15:0	640.6 -> 341.3	10,132	1	21	5
DG 36:2 -(18:1)	DG 15:0 15:0	638.6 -> 339.3	10,063	1	21	5
DG 36:2 -(18:2)	DG 15:0 15:0	638.6 -> 341.3	10,086	1	21	5
DG 36:3 -(18:2)	DG 15:0 15:0	636.6 -> 339.3	9,53	1	21	5
DG 36:4 -(18:2)	DG 15:0 15:0	634.5 -> 337.2	8,662	1	21	5
DG 36:4 -(18:3)	DG 15:0 15:0	634.5 -> 339.2	8,88	1	21	5
DG 36:4 -(20:4)	DG 15:0 15:0	634.5 -> 313.2	9,151	1	21	5
DG 38:4 -(20:3)	DG 15:0 15:0	662.6 -> 339.3	9,879	1	21	5
DG 38:4 -(20:4)	DG 15:0 15:0	662.6 -> 341.3	10,05	1	21	5
DG 38:5 -(20:4)	DG 15:0 15:0	660.6 -> 339.3	9,333	1	21	5
DG 38:5 -(22:5)	DG 15:0 15:0	660.6 -> 313.3	9,54	1	21	5
DG 38:6 -(20:4)	DG 15:0 15:0	658.5 -> 337.2	8,517	1	21	5
DG 38:6 -(22:6)	DG 15:0 15:0	658.5 -> 313.2	8,967	1	21	5
dhCer 16:0	dhCer 8:0	540.5 -> 284.3	8,3	1	30	5

dhCer 18:0	dhCer 8:0	568.6 -> 284.3	9,6	1	30	5
dhCer 20:0	dhCer 8:0	596.6 -> 284.3	10,033	1	30	5
dhCer 22:0	dhCer 8:0	624.6 -> 284.3	10,284	1	30	5
dhCer 24:0	dhCer 8:0	652.7 -> 284.3	10,453	1	30	5
dhCer 24:1	dhCer 8:0	650.6 -> 284.3	10,281	1	30	5
GM1(d18:1/16:0)	Hex3Cer(d18:1/17:0)	760.1 -> 366.2	4,692	1	9	3
GM3(d18:1/16:0)	Hex3Cer(d18:1/17:0)	1153.7 -> 264.3	4,849	1	57	5
GM3(d18:1/18:0)	Hex3Cer(d18:1/17:0)	1181.8 -> 264.3	5,458	1	57	5
GM3(d18:1/20:0)	Hex3Cer(d18:1/17:0)	1209.8 -> 264.3	6,237	1	57	5
GM3(d18:1/22:0)	Hex3Cer(d18:1/17:0)	1237.8 -> 264.3	7,645	1	57	5
GM3(d18:1/24:0)	Hex3Cer(d18:1/17:0)	1265.8 -> 264.3	8,106	1	57	5
GM3(d18:1/24:1)	Hex3Cer(d18:1/17:0)	1263.8 -> 264.3	7,161	1	57	5
GM3(d18:2/24:1)	Hex3Cer(d18:1/17:0)	1261.8 -> 262.3	6,49	1	57	5
Hex1Cer(d16:1/18:0)	Hex2Cer(d18:1/16:0)d3	700.6 -> 236.3	6,419	1	33	5
Hex1Cer(d16:1/20:0)	Hex2Cer(d18:1/16:0)d3	728.6 -> 236.3	7,412	1	33	5
Hex1Cer(d16:1/22:0)	Hex2Cer(d18:1/16:0)d3	756.7 -> 236.3	8,802	1	33	5
Hex1Cer(d16:1/24:0)	Hex2Cer(d18:1/16:0)d3	784.7 -> 236.3	9,878	1	33	5
Hex1Cer(d18:1/16:0)	Hex2Cer(d18:1/16:0)d3	700.6 -> 264.3	6,396	1	33	5
Hex1Cer(d18:1/18:0)	Hex2Cer(d18:1/16:0)d3	728.6 -> 264.3	7,515	1	33	5
Hex1Cer(d18:1/20:0)	Hex2Cer(d18:1/16:0)d3	756.6 -> 264.3	8,56	1	33	5
Hex1Cer(d18:1/22:0)	Hex2Cer(d18:1/16:0)d3	784.7 -> 264.3	9,923	1	33	5
Hex1Cer(d18:1/24:0)	Hex2Cer(d18:1/16:0)d3	812.7 -> 264.3	10,139	1	33	5
Hex1Cer(d18:1/24:1)	Hex2Cer(d18:1/16:0)d3	810.7 -> 264.3	9,945	1	33	5
Hex1Cer(d18:2/18:0)	Hex2Cer(d18:1/16:0)d3	726.6 -> 262.3	6,712	1	33	5
Hex1Cer(d18:2/20:0)	Hex2Cer(d18:1/16:0)d3	754.6 -> 262.3	7,651	1	33	5
Hex1Cer(d18:2/22:0)	Hex2Cer(d18:1/16:0)d3	782.7 -> 262.3	8,964	1	33	5
Hex1Cer(d18:2/24:0)	Hex2Cer(d18:1/16:0)d3	810.7 -> 262.3	9,956	1	33	5
Hex2Cer(d16:1/16:0)	Hex2Cer(d18:1/16:0)d3	834.6 -> 236.3	5,161	1	53	5
Hex2Cer(d16:1/24:1)	Hex2Cer(d18:1/16:0)d3	944.7 -> 236.3	7,993	1	53	5
Hex2Cer(d18:1/16:0)	Hex2Cer(d18:1/16:0)d3	862.6 -> 264.3	5,867	1	53	5
Hex2Cer(d18:1/18:0)	Hex2Cer(d18:1/16:0)d3	890.7 -> 264.3	7,553	1	53	5
Hex2Cer(d18:1/20:0)	Hex2Cer(d18:1/16:0)d3	918.7 -> 264.3	7,879	1	53	5
Hex2Cer(d18:1/22:0)	Hex2Cer(d18:1/16:0)d3	946.7 -> 264.3	9,08	1	53	5
Hex2Cer(d18:1/24:0)	Hex2Cer(d18:1/16:0)d3	974.8 -> 264.3	9,989	1	53	5
Hex2Cer(d18:1/24:1)	Hex2Cer(d18:1/16:0)d3	972.7 -> 264.3	9,111	1	53	5
Hex2Cer(d18:2/16:0)	Hex2Cer(d18:1/16:0)d3	860.6 -> 262.3	5,321	1	53	5
Hex2Cer(d18:2/24:1)	Hex2Cer(d18:1/16:0)d3	970.7 -> 262.3	8,229	1	53	5
Hex3Cer(d18:1/16:0)	Hex3Cer(d18:1/17:0)	1024.7 -> 264.3	5,588	1	57	5
Hex3Cer(d18:1/18:0)	Hex3Cer(d18:1/17:0)	1052.7 -> 264.3	6,421	1	57	5
Hex3Cer(d18:1/20:0)	Hex3Cer(d18:1/17:0)	1080.7 -> 264.3	7,438	1	57	5
Hex3Cer(d18:1/22:0)	Hex3Cer(d18:1/17:0)	1108.8 -> 264.3	8,576	1	57	5
Hex3Cer(d18:1/24:0)	Hex3Cer(d18:1/17:0)	1136.8 -> 264.3	9,785	1	57	5
Hex3Cer(d18:1/24:1)	Hex3Cer(d18:1/17:0)	1134.8 -> 264.3	8,62	1	57	5
LPC 14:0(a)	LPC 13:0	468.3 -> 184.1	1,805	1	21	5
LPC 14:0(b)	LPC 13:0	468.3 -> 184.1	2,009	1	21	5
LPC 15:0(a)	LPC 13:0	482.3 -> 184.1	2,171	1	21	5
LPC 15:0(b)	LPC 13:0	482.3 -> 184.1	2,355	1	21	5
LPC 16:0(a)	LPC 13:0	496.3 -> 184.1	2,495	1	21	5
LPC 16:0(b)	LPC 13:0	496.3 -> 184.1	2,71	1	21	5
LPC 16:1(a)	LPC 13:0	494.3 -> 184.1	1,997	1	21	5
LPC 16:1(b)	LPC 13:0	494.3 -> 184.1	2,235	1	21	5
LPC 17:0(a)	LPC 13:0	510.4 -> 184.1	2,72	1	21	5
LPC 17:0(b)	LPC 13:0	510.4 -> 184.1	2,895	1	21	5
LPC 17:0(b) [104_sn1]	LPC 13:0	510.4 -> 104.1	2,862	1	21	5
LPC 17:0(c)	LPC 13:0	510.4 -> 184.1	3,036	1	21	5
LPC 17:1(a)	LPC 13:0	508.4 -> 184.1	2,343	1	21	5
LPC 17:1(b)	LPC 13:0	508.4 -> 184.1	2,526	1	21	5
LPC 17:1(b) [104_sn1]	LPC 13:0	508.4 -> 104.1	2,515	1	21	5
LPC 17:1(c)	LPC 13:0	508.4 -> 184.1	2,731	1	21	5
LPC 18:0(a)	LPC 13:0	524.4 -> 184.1	3,199	1	21	5
LPC 18:0(b)	LPC 13:0	524.4 -> 184.1	3,38	1	21	5
LPC 18:1(a)	LPC 13:0	522.4 -> 184.1	2,676	1	21	5
LPC 18:1(b)	LPC 13:0	522.4 -> 184.1	2,873	1	21	5
LPC 18:2(a)	LPC 13:0	520.3 -> 184.1	2,211	1	21	5
LPC 18:2(b)	LPC 13:0	520.3 -> 184.1	2,417	1	21	5
LPC 18:3(a)	LPC 13:0	518.3 -> 184.1	1,835	1	21	5
LPC 18:3(b)	LPC 13:0	518.3 -> 184.1	1,952	1	21	5
LPC 18:3(b) [104_sn1]	LPC 13:0	518.3 -> 104.1	1,931	1	21	5
LPC 18:3(c)	LPC 13:0	518.3 -> 184.1	2,115	1	21	5
LPC 19:0(a)	LPC 13:0	538.4 -> 184.1	3,389	1	21	5
LPC 19:0(b)	LPC 13:0	538.4 -> 184.1	3,526	1	21	5
LPC 19:0(b) [104_sn1]	LPC 13:0	538.4 -> 104.1	3,505	1	21	5
LPC 19:0(c)	LPC 13:0	538.4 -> 184.1	3,695	1	21	5

LPC 19:1(a)	LPC 13:0	536.4 -> 184.1	2,98	1	21	5
LPC 19:1(b)	LPC 13:0	536.4 -> 184.1	3,198	1	21	5
LPC 19:1(c)	LPC 13:0	536.4 -> 184.1	3,4	1	21	5
LPC 20:0(a)	LPC 13:0	552.4 -> 184.1	3,758	1	21	5
LPC 20:0(b)	LPC 13:0	552.4 -> 184.1	3,929	1	21	5
LPC 20:1(a)	LPC 13:0	550.4 -> 184.1	3,303	1	21	5
LPC 20:1(b)	LPC 13:0	550.4 -> 184.1	3,515	1	21	5
LPC 20:2(a)	LPC 13:0	548.4 -> 184.1	2,87	1	21	5
LPC 20:2(b)	LPC 13:0	548.4 -> 184.1	3,077	1	21	5
LPC 20:3(a)	LPC 13:0	546.4 -> 184.1	2,491	1	21	5
LPC 20:3(c)	LPC 13:0	546.4 -> 184.1	2,641	1	21	5
LPC 20:4(a)	LPC 13:0	544.3 -> 184.1	2,21	1	21	5
LPC 20:4(b)	LPC 13:0	544.3 -> 184.1	2,383	1	21	5
LPC 20:5(a)	LPC 13:0	542.3 -> 184.1	1,823	1	21	5
LPC 20:5(b)	LPC 13:0	542.3 -> 184.1	1,994	1	21	5
LPC 22:0(a)	LPC 13:0	580.4 -> 184.1	4,272	1	21	5
LPC 22:0(b)	LPC 13:0	580.4 -> 184.1	4,463	1	21	5
LPC 22:1(a)	LPC 13:0	578.4 -> 184.1	3,821	1	21	5
LPC 22:1(b)	LPC 13:0	578.4 -> 184.1	4,001	1	21	5
LPC 22:4(a)	LPC 13:0	572.4 -> 184.1	2,76	1	21	5
LPC 22:4(b)	LPC 13:0	572.4 -> 184.1	2,902	1	21	5
LPC 22:5(a)	LPC 13:0	570.4 -> 184.1	2,371	1	21	5
LPC 22:5(b)	LPC 13:0	570.4 -> 184.1	2,522	1	21	5
LPC 22:5(b) [104_sn1]	LPC 13:0	570.4 -> 104.1	2,501	1	21	5
LPC 22:5(c)	LPC 13:0	570.4 -> 184.1	2,706	1	21	5
LPC 22:6(a)	LPC 13:0	568.3 -> 184.1	2,124	1	21	5
LPC 22:6(b)	LPC 13:0	568.3 -> 184.1	2,307	1	21	5
LPC 24:0(a)	LPC 13:0	608.5 -> 184.1	4,887	1	21	5
LPC 24:0(b)	LPC 13:0	608.5 -> 184.1	5,123	1	21	5
LPC 26:0(a)	LPC 13:0	636.5 -> 184.1	5,663	1	21	5
LPC 26:0(b)	LPC 13:0	636.5 -> 184.1	5,942	1	21	5
LPC(P-16:0)	LPC 13:0	480.3 -> 104.1	2,951	1	21	5
LPC(P-17:0)(a)	LPC 13:0	494.3 -> 104.1	3,135	1	21	5
LPC(P-17:0)(b)	LPC 13:0	494.3 -> 104.1	3,307	1	21	5
LPC(P-18:0)	LPC 13:0	508.3 -> 104.1	3,602	1	21	5
LPC(P-18:1)	LPC 13:0	506.3 -> 104.1	3,146	1	21	5
LPC(P-20:0)	LPC 13:0	536.3 -> 104.1	4,099	1	21	5
LPE 16:0(a)	LPE 14:0	454.3 -> 313.3	2,604	1	17	5
LPE 16:0(b)	LPE 14:0	454.3 -> 313.3	2,822	1	17	5
LPE 17:0(a)	LPE 14:0	468.3 -> 327.3	2,984	1	17	5
LPE 17:0(b)	LPE 14:0	468.3 -> 327.3	3,148	1	17	5
LPE 18:0(a)	LPE 14:0	482.3 -> 341.3	3,307	1	17	5
LPE 18:0(b)	LPE 14:0	482.3 -> 341.3	3,487	1	17	5
LPE 18:1(a)	LPE 14:0	480.3 -> 339.3	2,755	1	17	5
LPE 18:1(b)	LPE 14:0	480.3 -> 339.3	2,973	1	17	5
LPE 18:2(a)	LPE 14:0	478.3 -> 337.3	2,301	1	17	5
LPE 18:2(b)	LPE 14:0	478.3 -> 337.3	2,517	1	17	5
LPE 20:4(a)	LPE 14:0	502.3 -> 361.3	2,332	1	17	5
LPE 20:4(b)	LPE 14:0	502.3 -> 361.3	2,472	1	17	5
LPE 22:6(a)	LPE 14:0	526.3 -> 385.3	2,265	1	17	5
LPE 22:6(b)	LPE 14:0	526.3 -> 385.3	2,405	1	17	5
LPE(P-16:0)	LPE 14:0	438.3 -> 266.4	3,083	1	19	5
LPE(P-18:0)	LPE 14:0	466.3 -> 294.4	3,71	1	19	5
LPE(P-18:1)	LPE 14:0	464.3 -> 292.4	3,213	1	19	5
LPE(P-20:0)	LPE 14:0	494.3 -> 322.4	4,226	1	19	5
LPI 18:0(a)	LPE 14:0	618.3 -> 341.3	2,727	1	17	5
LPI 18:0(b)	LPE 14:0	618.3 -> 341.3	2,88	1	17	5
LPI 18:1(a)	LPE 14:0	616.3 -> 339.3	2,219	1	17	5
LPI 18:1(b)	LPE 14:0	616.3 -> 339.3	2,338	1	17	5
LPI 18:2(a)	LPE 14:0	614.3 -> 337.3	1,822	1	17	5
LPI 18:2(b)	LPE 14:0	614.3 -> 337.3	1,971	1	17	5
LPI 20:4(a)	LPE 14:0	638.3 -> 361.3	1,768	1	17	5
LPI 20:4(b)	LPE 14:0	638.3 -> 361.3	1,971	1	17	5
LPS(16:0)	PS 17:0 17:0	498.5 -> 313.5	2,645	2	20	5
LPS(18:0)	PS 17:0 17:0	526.5 -> 341.5	3,326	2	20	5
LPS(18:1)	PS 17:0 17:0	524.5 -> 339.5	2,806	2	20	5
LPS(18:2)	PS 17:0 17:0	522.5 -> 337.5	2,352	2	20	5
OHC 18:0	CE 18:0-d6	686.8 -> 367.4	11,151	2	12	4
OHC 18:1 (a)	CE 18:0-d6	684.8 -> 367.4	10,716	2	12	4
OHC 18:1 (b)	CE 18:0-d6	684.8 -> 367.4	10,963	2	12	4
OHC 18:2 (a)	CE 18:0-d6	682.8 -> 367.4	10,267	2	12	4
OHC 18:2 (b)	CE 18:0-d6	682.8 -> 367.4	10,428	2	12	4
OHC 18:2 (c)	CE 18:0-d6	682.8 -> 367.4	10,596	2	12	4

OHC 18:2 (d)	CE 18:0-d6	682.8 -> 367.4	10,781	2	12	4
OHC 18:2 (e)	CE 18:0-d6	682.8 -> 367.4	11,099	2	12	4
OHC 20:4 (a)	CE 18:0-d6	706.8 -> 367.4	10,506	2	12	4
OHC 20:4 (b)	CE 18:0-d6	706.8 -> 367.4	10,736	2	12	4
oxCE 18:2 +2O NH4	CE 18:0-d6	698.6 -> 369.4	10,405	1	10	5
oxCE 18:2 +O NH4	CE 18:0-d6	682.6 -> 369.4	10,585	1	10	5
PC 28:0	PC 13:0 13:0	678.5 -> 184.1	5,218	1	21	5
PC 30:0	PC 13:0 13:0	706.5 -> 184.1	6,009	1	21	5
PC 31:0(a)	PC 13:0 13:0	720.6 -> 184.1	6,337	1	21	5
PC 31:0(b)	PC 13:0 13:0	720.6 -> 184.1	6,337	1	21	5
PC 32:0	PC 13:0 13:0	734.6 -> 184.1	6,854	1	21	5
PC 32:1	PC 13:0 13:0	732.6 -> 184.1	6,176	1	21	5
PC 32:2	PC 13:0 13:0	730.5 -> 184.1	5,551	1	21	5
PC 33:0(a)	PC 13:0 13:0	748.6 -> 184.1	7,307	1	21	5
PC 33:0(b)	PC 13:0 13:0	748.6 -> 184.1	7,479	1	21	5
PC 33:1	PC 13:0 13:0	746.6 -> 184.1	6,662	1	21	5
PC 33:2	PC 13:0 13:0	744.6 -> 184.1	6,006	1	21	5
PC 34:0	PC 13:0 13:0	762.6 -> 184.1	7,918	1	21	5
PC 34:1	PC 13:0 13:0	760.6 -> 184.1	7,11	1	21	5
PC 34:2	PC 13:0 13:0	758.6 -> 184.1	6,45	1	21	5
PC 34:3(a)	PC 13:0 13:0	756.6 -> 184.1	5,704	1	21	5
PC 34:3(b)	PC 13:0 13:0	756.6 -> 184.1	5,871	1	21	5
PC 34:3(c)	PC 13:0 13:0	756.6 -> 184.1	5,894	1	21	5
PC 34:4	PC 13:0 13:0	754.5 -> 184.1	5,54	1	21	5
PC 34:5	PC 13:0 13:0	752.5 -> 184.1	5,099	1	21	5
PC 35:1(a)	PC 13:0 13:0	774.6 -> 184.1	7,373	1	21	5
PC 35:1(b)	PC 13:0 13:0	774.6 -> 184.1	7,556	1	21	5
PC 35:2(a)	PC 13:0 13:0	772.6 -> 184.1	6,839	1	21	5
PC 35:2(b)	PC 13:0 13:0	772.6 -> 184.1	6,957	1	21	5
PC 35:3(a)	PC 13:0 13:0	770.6 -> 184.1	5,96	1	21	5
PC 35:3(b)	PC 13:0 13:0	770.6 -> 184.1	6,184	1	21	5
PC 35:4	PC 13:0 13:0	768.6 -> 184.1	5,96	1	21	5
PC 35:5	PC 13:0 13:0	766.5 -> 184.1	5,463	1	21	5
PC 36:0	PC 13:0 13:0	790.6 -> 184.1	9,526	1	21	5
PC 36:1	PC 13:0 13:0	788.6 -> 184.1	8,155	1	21	5
PC 36:2(a)	PC 13:0 13:0	786.6 -> 184.1	7,245	1	21	5
PC 36:2(b)	PC 13:0 13:0	786.6 -> 184.1	7,578	1	21	5
PC 36:3(a)	PC 13:0 13:0	784.6 -> 184.1	6,39	1	21	5
PC 36:3(b)	PC 13:0 13:0	784.6 -> 184.1	6,636	1	21	5
PC 36:3(c)	PC 13:0 13:0	784.6 -> 184.1	7,002	1	21	5
PC 36:4(a)	PC 13:0 13:0	782.6 -> 184.1	5,882	1	21	5
PC 36:4(b)	PC 13:0 13:0	782.6 -> 184.1	6,39	1	21	5
PC 36:5(a)	PC 13:0 13:0	780.6 -> 184.1	5,636	1	21	5
PC 36:5(b)	PC 13:0 13:0	780.6 -> 184.1	5,904	1	21	5
PC 36:6(a)	PC 13:0 13:0	778.5 -> 184.1	5,174	1	21	5
PC 36:6(b)	PC 13:0 13:0	778.5 -> 184.1	5,409	1	21	5
PC 37:4(a)	PC 13:0 13:0	796.6 -> 184.1	6,765	1	21	5
PC 37:4(b)	PC 13:0 13:0	796.6 -> 184.1	6,765	1	21	5
PC 37:6	PC 13:0 13:0	792.6 -> 184.1	5,803	1	21	5
PC 38:2	PC 13:0 13:0	814.6 -> 184.1	8,454	1	21	5
PC 38:3	PC 13:0 13:0	812.6 -> 184.1	7,74	1	21	5
PC 38:4(a)	PC 13:0 13:0	810.6 -> 184.1	6,966	1	21	5
PC 38:4(b)	PC 13:0 13:0	810.6 -> 184.1	6,966	1	21	5
PC 38:4(c)	PC 13:0 13:0	810.6 -> 184.1	7,382	1	21	5
PC 38:5(a)	PC 13:0 13:0	808.6 -> 184.1	6,552	1	21	5
PC 38:5(b)	PC 13:0 13:0	808.6 -> 184.1	6,813	1	21	5
PC 38:6(a)	PC 13:0 13:0	806.6 -> 184.1	5,847	1	21	5
PC 38:6(b)	PC 13:0 13:0	806.6 -> 184.1	6,195	1	21	5
PC 38:7(a)	PC 13:0 13:0	804.6 -> 184.1	5,43	1	21	5
PC 38:7(b)	PC 13:0 13:0	804.6 -> 184.1	5,571	1	21	5
PC 38:7(c)	PC 13:0 13:0	804.6 -> 184.1	5,825	1	21	5
PC 39:5(a)	PC 13:0 13:0	822.6 -> 184.1	6,8	1	21	5
PC 39:5(b)	PC 13:0 13:0	822.6 -> 184.1	6,988	1	21	5
PC 39:6(a)	PC 13:0 13:0	820.6 -> 184.1	6,469	1	21	5
PC 39:6(b)	PC 13:0 13:0	820.6 -> 184.1	6,704	1	21	5
PC 40:4(a)	PC 13:0 13:0	838.6 -> 184.1	8,141	1	21	5
PC 40:4(b)	PC 13:0 13:0	838.6 -> 184.1	8,51	1	21	5
PC 40:5(a)	PC 13:0 13:0	836.6 -> 184.1	7,473	1	21	5
PC 40:5(b)	PC 13:0 13:0	836.6 -> 184.1	7,845	1	21	5
PC 40:6	PC 13:0 13:0	834.6 -> 184.1	7,209	1	21	5
PC 40:7(a)	PC 13:0 13:0	832.6 -> 184.1	6,137	1	21	5
PC 40:7(b)	PC 13:0 13:0	832.6 -> 184.1	6,376	1	21	5
PC 40:7(c)	PC 13:0 13:0	832.6 -> 184.1	6,527	1	21	5

PC 40:8	PC 13:0 13:0	830.6 -> 184.1	5,756	1	21	5
PC(O-16:0/0:0)	LPC 13:0	482.4 -> 104.1	2,983	1	21	5
PC(O-18:0/0:0)	LPC 13:0	510.4 -> 104.1	3,644	1	21	5
PC(O-18:1/0:0)	LPC 13:0	508.4 -> 104.1	3,146	1	21	5
PC(O-20:0/0:0)	LPC 13:0	538.4 -> 104.1	4,171	1	21	5
PC(O-20:1/0:0)	LPC 13:0	536.4 -> 104.1	3,738	1	21	5
PC(O-22:0/0:0)	LPC 13:0	566.5 -> 104.1	4,793	2	21	5
PC(O-22:1/0:0)	LPC 13:0	564.4 -> 104.1	4,242	2	21	5
PC(O-24:0/0:0)	LPC 13:0	594.5 -> 104.1	5,575	2	21	5
PC(O-24:1/0:0)	LPC 13:0	592.5 -> 104.1	4,898	2	21	5
PC(O-24:2/0:0)	LPC 13:0	590.5 -> 104.1	4,356	2	21	5
PC(O-32:0)	PC 13:0 13:0	720.6 -> 184.1	7,62	2	21	5
PC(O-32:1)	PC 13:0 13:0	718.5 -> 184.1	6,7	2	21	5
PC(O-32:2)	PC 13:0 13:0	716.6 -> 184.1	6,031	2	21	5
PC(O-34:1)	PC 13:0 13:0	746.6 -> 184.1	7,805	2	21	5
PC(O-34:2)	PC 13:0 13:0	744.6 -> 184.1	7,1	2	21	5
PC(O-34:4)	PC 13:0 13:0	740.6 -> 184.1	5,984	2	21	5
PC(O-35:4)	PC 13:0 13:0	754.5 -> 184.1	6,52	2	21	5
PC(O-36:0)	PC 13:0 13:0	776.6 -> 184.1	9,946	2	21	5
PC(O-36:1)	PC 13:0 13:0	774.6 -> 184.1	9,008	2	21	5
PC(O-36:2)(a)	PC 13:0 13:0	772.6 -> 184.1	8,054	2	21	5
PC(O-36:2)(b)	PC 13:0 13:0	772.6 -> 184.1	8,054	2	21	5
PC(O-36:3)(a)	PC 13:0 13:0	770.6 -> 184.1	7,27	2	21	5
PC(O-36:3)(b)	PC 13:0 13:0	770.6 -> 184.1	7,27	2	21	5
PC(O-36:4)	PC 13:0 13:0	768.6 -> 184.1	6,993	2	21	5
PC(O-36:5)	PC 13:0 13:0	766.5 -> 184.1	6,368	2	21	5
PC(O-38:4)	PC 13:0 13:0	796.6 -> 184.1	8,154	2	21	5
PC(O-38:5)	PC 13:0 13:0	794.6 -> 184.1	7,141	2	21	5
PC(O-38:6)	PC 13:0 13:0	792.6 -> 184.1	6,837	2	21	5
PC(O-40:5)	PC 13:0 13:0	822.6 -> 184.1	8,005	2	21	5
PC(O-40:6)	PC 13:0 13:0	820.6 -> 184.1	7,926	2	21	5
PC(O-40:7)(a)	PC 13:0 13:0	818.6 -> 184.1	6,988	2	21	5
PC(O-40:7)(b)	PC 13:0 13:0	818.6 -> 184.1	7,74	2	21	5
PC(P-30:0)	PC 13:0 13:0	690.4 -> 184.1	6,443	2	21	5
PC(P-32:0)	PC 13:0 13:0	718.5 -> 184.1	7,448	2	21	5
PC(P-32:1)	PC 13:0 13:0	716.6 -> 184.1	6,688	2	21	5
PC(P-34:0)	PC 13:0 13:0	746.6 -> 184.1	8,605	2	21	5
PC(P-34:1)	PC 13:0 13:0	744.6 -> 184.1	7,699	2	21	5
PC(P-34:2)	PC 13:0 13:0	742.5 -> 184.1	6,948	2	21	5
PC(P-34:3)	PC 13:0 13:0	740.6 -> 184.1	6,347	2	21	5
PC(P-35:2)(a)	PC 13:0 13:0	756.6 -> 184.1	7,26	2	21	5
PC(P-35:2)(b)	PC 13:0 13:0	756.6 -> 184.1	7,558	2	21	5
PC(P-35:4)(a)	PC 13:0 13:0	752.6 -> 184.1	6,221	2	21	5
PC(P-35:4)(b)	PC 13:0 13:0	752.6 -> 184.1	6,369	2	21	5
PC(P-36:2)(a)	PC 13:0 13:0	770.6 -> 184.1	7,767	2	21	5
PC(P-36:2)(b)	PC 13:0 13:0	770.6 -> 184.1	8,066	2	21	5
PC(P-36:3)	PC 13:0 13:0	768.5 -> 184.1	7,259	2	21	5
PC(P-36:4)	PC 13:0 13:0	766.5 -> 184.1	6,828	2	21	5
PC(P-36:5)	PC 13:0 13:0	764.6 -> 184.1	6,265	2	21	5
PC(P-37:4)(a)	PC 13:0 13:0	780.5 -> 184.1	7,234	2	21	5
PC(P-37:4)(b)	PC 13:0 13:0	780.5 -> 184.1	7,395	2	21	5
PC(P-38:4)	PC 13:0 13:0	794.6 -> 184.1	7,927	2	21	5
PC(P-38:5)(a)	PC 13:0 13:0	792.6 -> 184.1	7,025	2	21	5
PC(P-38:5)(b)	PC 13:0 13:0	792.6 -> 184.1	7,349	2	21	5
PC(P-38:6)	PC 13:0 13:0	790.6 -> 184.1	6,611	2	21	5
PC(P-40:4)	PC 13:0 13:0	822.6 -> 184.1	9,081	2	21	5
PC(P-40:5)	PC 13:0 13:0	820.6 -> 184.1	7,926	2	21	5
PC(P-40:6)	PC 13:0 13:0	818.6 -> 184.1	7,67	2	21	5
PC(P-40:7)	PC 13:0 13:0	816.6 -> 184.1	6,894	2	21	5
PE 32:0	PE 17:0/17:0	692.5 -> 551.5	7,172	2	17	5
PE 32:1	PE 17:0/17:0	690.5 -> 549.5	6,454	2	17	5
PE 34:1	PE 17:0/17:0	718.5 -> 577.5	7,402	2	17	5
PE 34:2	PE 17:0/17:0	716.5 -> 575.5	6,689	2	17	5
PE 34:3(a)	PE 17:0/17:0	714.5 -> 573.5	6,043	2	17	5
PE 34:3(b)	PE 17:0/17:0	714.5 -> 573.5	6,043	2	17	5
PE 34:3(c)	PE 17:0/17:0	714.5 -> 573.5	6,177	2	17	5
PE 35:1(a)	PE 17:0/17:0	732.6 -> 591.5	7,677	2	17	5
PE 35:1(b)	PE 17:0/17:0	732.6 -> 591.5	7,876	2	17	5
PE 35:2(a)	PE 17:0/17:0	730.5 -> 589.5	7,08	2	17	5
PE 35:2(b)	PE 17:0/17:0	730.5 -> 589.5	7,28	2	17	5
PE 36:0	PE 17:0/17:0	748.6 -> 607.6	9,539	2	17	5
PE 36:1	PE 17:0/17:0	746.6 -> 605.6	8,56	2	17	5
PE 36:2(a)	PE 17:0/17:0	744.6 -> 603.5	7,536	2	17	5

PE 36:2(b)	PE 17:0/17:0	744.6 -> 603.5	7,875	2	17	5
PE 36:3(a)	PE 17:0/17:0	742.5 -> 601.5	6,972	2	17	5
PE 36:3(b)	PE 17:0/17:0	742.5 -> 601.5	6,972	2	17	5
PE 36:4	PE 17:0/17:0	740.5 -> 599.5	6,628	2	17	5
PE 36:5(a)	PE 17:0/17:0	738.5 -> 597.5	5,839	2	17	5
PE 36:5(b)	PE 17:0/17:0	738.5 -> 597.5	5,984	2	17	5
PE 37:4 (a)	PE 17:0/17:0	754.6 -> 613.5	6,959	2	17	5
PE 37:4 (b)	PE 17:0/17:0	754.6 -> 613.5	7,249	2	17	5
PE 38:3(a)	PE 17:0/17:0	770.6 -> 629.6	8,246	2	17	5
PE 38:3(b)	PE 17:0/17:0	770.6 -> 629.6	8,592	2	17	5
PE 38:4	PE 17:0/17:0	768.6 -> 627.5	7,696	2	17	5
PE 38:5(a)	PE 17:0/17:0	766.5 -> 625.5	6,768	2	17	5
PE 38:5(b)	PE 17:0/17:0	766.5 -> 625.5	7,075	2	17	5
PE 38:6	PE 17:0/17:0	764.5 -> 623.5	6,438	2	17	5
PE 39:6(a)	PE 17:0/17:0	778.5 -> 637.5	6,755	2	17	5
PE 39:6(b)	PE 17:0/17:0	778.5 -> 637.5	7,05	2	17	5
PE 40:4(a)	PE 17:0/17:0	796.6 -> 655.6	8,655	2	17	5
PE 40:4(b)	PE 17:0/17:0	796.6 -> 655.6	8,655	2	17	5
PE 40:5(a)	PE 17:0/17:0	794.6 -> 653.6	7,916	2	17	5
PE 40:5(b)	PE 17:0/17:0	794.6 -> 653.6	8,321	2	17	5
PE 40:6	PE 17:0/17:0	792.6 -> 651.5	7,498	2	17	5
PE 40:7(a)	PE 17:0/17:0	790.5 -> 649.5	6,565	2	17	5
PE 40:7(b)	PE 17:0/17:0	790.5 -> 649.5	6,802	2	17	5
PE(O-34:1)	PE 17:0/17:0	704.6 -> 563.5	8,171	2	17	5
PE(O-34:2)	PE 17:0/17:0	702.5 -> 561.5	7,368	2	17	5
PE(O-36:3)(a)	PE 17:0/17:0	728.6 -> 587.5	7,65	2	17	5
PE(O-36:3)(b)	PE 17:0/17:0	728.6 -> 587.5	7,689	2	17	5
PE(O-36:4)	PE 17:0/17:0	726.5 -> 585.5	7,424	2	17	5
PE(O-36:5)	PE 17:0/17:0	724.5 -> 583.5	6,75	2	17	5
PE(O-38:4)(a)	PE 17:0/17:0	754.6 -> 613.6	8,258	2	17	5
PE(O-38:4)(b)	PE 17:0/17:0	754.6 -> 613.6	8,615	2	17	5
PE(O-38:5)(a)	PE 17:0/17:0	752.6 -> 611.5	7,387	2	17	5
PE(O-38:5)(b)	PE 17:0/17:0	752.6 -> 611.5	7,885	2	17	5
PE(O-38:6)	PE 17:0/17:0	750.6 -> 609.5	7,076	2	17	5
PE(O-40:5)	PE 17:0/17:0	780.6 -> 639.6	8,711	2	17	5
PE(O-40:6)	PE 17:0/17:0	778.5 -> 637.5	8,367	2	17	5
PE(O-40:7)	PE 17:0/17:0	776.6 -> 635.5	7,35	2	17	5
PE(P-15:0/20:4)(a)	PE 17:0/17:0	710.5 -> 361.3	6,54	2	17	5
PE(P-15:0/20:4)(b)	PE 17:0/17:0	710.5 -> 361.3	6,7	2	17	5
PE(P-15:0/22:6)(a)	PE 17:0/17:0	734.5 -> 385.3	6,35	2	17	5
PE(P-15:0/22:6)(b)	PE 17:0/17:0	734.5 -> 385.3	6,55	2	17	5
PE(P-16:0/18:1)	PE 17:0/17:0	702.5 -> 339.3	7,98	2	17	5
PE(P-16:0/18:2)	PE 17:0/17:0	700.5 -> 337.3	7,241	2	17	5
PE(P-16:0/18:3)	PE 17:0/17:0	698.5 -> 335.3	6,678	2	17	5
PE(P-16:0/20:3)(a)	PE 17:0/17:0	726.5 -> 363.3	7,67	2	17	5
PE(P-16:0/20:3)(b)	PE 17:0/17:0	726.5 -> 363.3	7,8	2	17	5
PE(P-16:0/20:4)	PE 17:0/17:0	724.5 -> 361.3	7,148	2	17	5
PE(P-16:0/20:5)	PE 17:0/17:0	722.5 -> 359.3	6,617	2	17	5
PE(P-16:0/22:4)	PE 17:0/17:0	752.6 -> 389.3	8,1	2	17	5
PE(P-16:0/22:5)(a)	PE 17:0/17:0	750.5 -> 387.3	7,41	2	17	5
PE(P-16:0/22:5)(b)	PE 17:0/17:0	750.5 -> 387.3	7,399	2	17	5
PE(P-16:0/22:6)	PE 17:0/17:0	748.5 -> 385.3	6,924	2	17	5
PE(P-17:0/20:4)(a)	PE 17:0/17:0	738.6 -> 361.3	7,653	2	17	5
PE(P-17:0/20:4)(b)	PE 17:0/17:0	738.6 -> 361.3	7,653	2	17	5
PE(P-17:0/22:6)(a)	PE 17:0/17:0	762.6 -> 385.3	7,443	2	17	5
PE(P-17:0/22:6)(b)	PE 17:0/17:0	762.6 -> 385.3	7,443	2	17	5
PE(P-18:0/18:1)	PE 17:0/17:0	730.6 -> 339.3	9,214	2	17	5
PE(P-18:0/18:2)	PE 17:0/17:0	728.6 -> 337.3	8,315	2	17	5
PE(P-18:0/18:3)	PE 17:0/17:0	726.5 -> 335.3	7,527	2	17	5
PE(P-18:0/20:3)(a)	PE 17:0/17:0	754.5 -> 363.3	8,748	2	17	5
PE(P-18:0/20:3)(b)	PE 17:0/17:0	754.5 -> 363.3	8,911	2	17	5
PE(P-18:0/20:4)	PE 17:0/17:0	752.6 -> 361.3	8,224	2	17	5
PE(P-18:0/20:5)	PE 17:0/17:0	750.5 -> 359.3	7,535	2	17	5
PE(P-18:0/22:4)	PE 17:0/17:0	780.6 -> 389.3	9,147	2	17	5
PE(P-18:0/22:5)(a)	PE 17:0/17:0	778.5 -> 387.3	8,2	2	17	5
PE(P-18:0/22:5)(b)	PE 17:0/17:0	778.5 -> 387.3	8,524	2	17	5
PE(P-18:0/22:6)	PE 17:0/17:0	776.6 -> 385.3	7,974	2	17	5
PE(P-18:1/18:1)(a)	PE 17:0/17:0	728.6 -> 339.3	8,182	2	17	5
PE(P-18:1/18:1)(b)	PE 17:0/17:0	728.6 -> 339.3	8,438	2	17	5
PE(P-18:1/18:2)(a)	PE 17:0/17:0	726.5 -> 337.3	7,55	2	17	5
PE(P-18:1/18:2)(b)	PE 17:0/17:0	726.5 -> 337.3	7,725	2	17	5
PE(P-18:1/18:3)	PE 17:0/17:0	724.5 -> 335.3	6,748	2	17	5
PE(P-18:1/20:3)(a)	PE 17:0/17:0	752.5 -> 363.3	7,908	2	17	5

PE(P-18:1/20:3)(b)	PE 17:0/17:0	752.5 -> 363.3	8,022	2	17	5
PE(P-18:1/20:4)(a)	PE 17:0/17:0	750.5 -> 361.3	7,192	2	17	5
PE(P-18:1/20:4)(b)	PE 17:0/17:0	750.5 -> 361.3	7,581	2	17	5
PE(P-18:1/20:5)(a)	PE 17:0/17:0	748.5 -> 359.3	6,794	2	17	5
PE(P-18:1/20:5)(b)	PE 17:0/17:0	748.5 -> 359.3	6,9	2	17	5
PE(P-18:1/22:4)	PE 17:0/17:0	778.5 -> 389.3	8,233	2	17	5
PE(P-18:1/22:5)(a)	PE 17:0/17:0	776.6 -> 387.3	7,556	2	17	5
PE(P-18:1/22:5)(b)	PE 17:0/17:0	776.6 -> 387.3	7,718	2	17	5
PE(P-18:1/22:6)(a)	PE 17:0/17:0	774.5 -> 385.3	7,235	2	17	5
PE(P-18:1/22:6)(b)	PE 17:0/17:0	774.5 -> 385.3	7,293	2	17	5
PE(P-19:0/20:4)(a)	PE 17:0/17:0	766.6 -> 361.3	8,834	2	17	5
PE(P-19:0/20:4)(b)	PE 17:0/17:0	766.6 -> 361.3	9,03	2	17	5
PE(P-20:0/18:1)	PE 17:0/17:0	758.6 -> 339.3	10,026	2	17	5
PE(P-20:0/18:2)	PE 17:0/17:0	756.6 -> 337.3	9,636	2	17	5
PE(P-20:0/20:4)	PE 17:0/17:0	780.6 -> 361.3	9,451	2	17	5
PE(P-20:0/22:6)	PE 17:0/17:0	804.6 -> 385.3	9,287	2	17	5
PE(P-20:1/20:4)	PE 17:0/17:0	778.5 -> 361.3	8,311	2	17	5
PE(P-20:1/22:6)(a)	PE 17:0/17:0	802.6 -> 385.3	8,187	2	17	5
PE(P-20:1/22:6)(b)	PE 17:0/17:0	802.6 -> 385.3	8,309	2	17	5
PG 16:0 18:1	PG 17:0 17:0	766.6 -> 577.5	6,106	2	21	5
PG 18:0 18:1	PG 17:0 17:0	794.6 -> 605.6	7,013	2	21	5
PG 18:1 18:1	PG 17:0 17:0	792.6 -> 603.5	6,389	2	21	5
PG 34:2	PG 17:0 17:0	764.6 -> 575.5	5,604	2	21	5
PI 32:0	PE 17:0/17:0	828.6 -> 551.6	5,712	2	17	5
PI 32:1	PE 17:0/17:0	826.5 -> 549.5	5,172	2	17	5
PI 34:0	PE 17:0/17:0	856.6 -> 579.6	6,503	2	17	5
PI 34:1	PE 17:0/17:0	854.6 -> 577.6	5,845	2	17	5
PI 35:1	PE 17:0/17:0	868.6 -> 591.6	6,25	2	17	5
PI 35:2	PE 17:0/17:0	866.6 -> 589.6	5,7	2	17	5
PI 36:1	PE 17:0/17:0	882.6 -> 605.6	6,787	2	17	5
PI 36:2	PE 17:0/17:0	880.6 -> 603.6	6,079	2	17	5
PI 36:3(a)	PE 17:0/17:0	878.6 -> 601.6	5,4	2	17	5
PI 36:3(b)	PE 17:0/17:0	878.6 -> 601.6	5,52	2	17	5
PI 36:3(c)	PE 17:0/17:0	878.6 -> 601.6	5,844	2	17	5
PI 36:4	PE 17:0/17:0	876.6 -> 599.6	5,342	2	17	5
PI 37:4	PE 17:0/17:0	890.6 -> 613.6	5,644	2	17	5
PI 37:6	PE 17:0/17:0	886.6 -> 609.6	5,611	2	17	5
PI 38:2	PE 17:0/17:0	908.6 -> 631.6	6,964	2	17	5
PI 38:3(a)	PE 17:0/17:0	906.6 -> 629.6	6,135	2	17	5
PI 38:3(b)	PE 17:0/17:0	906.6 -> 629.6	6,467	2	17	5
PI 38:4	PE 17:0/17:0	904.6 -> 627.6	6,09	2	17	5
PI 38:5(a)	PE 17:0/17:0	902.6 -> 625.6	5,469	2	17	5
PI 38:5(b)	PE 17:0/17:0	902.6 -> 625.6	5,577	2	17	5
PI 38:6	PE 17:0/17:0	900.6 -> 623.6	5,213	2	17	5
PI 39:6	PE 17:0/17:0	914.6 -> 637.6	5,523	2	17	5
PI 40:4(a)	PE 17:0/17:0	932.6 -> 655.6	6,787	2	17	5
PI 40:4(b)	PE 17:0/17:0	932.6 -> 655.6	6,787	2	17	5
PI 40:5(a)	PE 17:0/17:0	930.6 -> 653.6	6,226	2	17	5
PI 40:5(b)	PE 17:0/17:0	930.6 -> 653.6	6,526	2	17	5
PI 40:6	PE 17:0/17:0	928.6 -> 651.6	5,955	2	17	5
PS 36:1	PS 17:0 17:0	790.6 -> 605.6	6,978	2	25	5
PS 36:2	PS 17:0 17:0	788.5 -> 603.5	6,378	2	25	5
PS 38:3	PS 17:0 17:0	814.6 -> 629.6	6,575	2	25	5
PS 38:4	PS 17:0 17:0	812.5 -> 627.5	6,366	2	25	5
PS 38:5	PS 17:0 17:0	810.5 -> 625.5	5,658	2	25	5
PS 40:5	PS 17:0 17:0	838.6 -> 653.6	6,319	2	25	5
PS 40:6	PS 17:0 17:0	836.5 -> 651.5	6,182	2	25	5
S1P(d16:1)	Sph(d17:1)	352.2 -> 236.3	1,566	3	16	4
S1P(d17:1)	Sph(d17:1)	366.2 -> 250.3	1,969	3	16	4
S1P(d18:0)	Sph(d17:1)	382.2 -> 284.3	2,735	3	11	4
S1P(d18:1)	Sph(d17:1)	380.2 -> 264.3	2,293	3	16	4
S1P(d18:2)	Sph(d17:1)	378.2 -> 262.3	1,765	3	16	4
SM 31:1	SM 30:1	661.5 -> 184.1	4,789	2	25	5
SM 32:0	SM 30:1	677.6 -> 184.1	5,402	2	25	5
SM 32:1	SM 30:1	675.5 -> 184.1	5,133	2	25	5
SM 32:2	SM 30:1	673.5 -> 184.1	4,661	2	25	5
SM 33:1	SM 30:1	689.6 -> 184.1	5,465	2	25	5
SM 34:0	SM 30:1	705.6 -> 184.1	6,223	2	25	5
SM 34:1	SM 30:1	703.6 -> 184.1	5,874	2	25	5
SM 34:2	SM 30:1	701.6 -> 184.1	5,293	2	25	5
SM 34:3	SM 30:1	699.5 -> 184.1	4,885	2	25	5
SM 35:1(a)	SM 30:1	717.6 -> 184.1	6,121	2	25	5
SM 35:1(b)	SM 30:1	717.6 -> 184.1	6,199	2	25	5

SM 35:2(a)	SM 30:1	715.6 -> 184.1	5,684	2	25	5
SM 35:2(b)	SM 30:1	715.6 -> 184.1	5,907	2	25	5
SM 36:1	SM 30:1	731.6 -> 184.1	6,82	2	25	5
SM 36:2	SM 30:1	729.6 -> 184.1	6,086	2	25	5
SM 36:3	SM 30:1	727.6 -> 184.1	5,496	2	25	5
SM 37:1	SM 30:1	745.6 -> 184.1	7,088	3	25	5
SM 37:2	SM 30:1	743.5 -> 184.1	6,533	2	25	5
SM 38:1	SM 30:1	759.6 -> 184.1	7,953	2	25	5
SM 38:2	SM 30:1	757.6 -> 184.1	7,04	2	25	5
SM 38:3(a)	SM 30:1	755.6 -> 184.1	6,255	3	25	5
SM 38:3(b)	SM 30:1	755.6 -> 184.1	6,358	3	25	5
SM 39:1	SM 30:1	773.7 -> 184.1	8,525	2	25	5
SM 40:0	SM 30:1	789.7 -> 184.1	9,548	2	25	5
SM 40:1	SM 30:1	787.7 -> 184.1	9,114	2	25	5
SM 40:2(a)	SM 30:1	785.7 -> 184.1	8,076	2	25	5
SM 40:2(b)	SM 30:1	785.7 -> 184.1	8,277	2	25	5
SM 40:3(a)	SM 30:1	783.6 -> 184.1	7,223	3	25	5
SM 40:3(b)	SM 30:1	783.6 -> 184.1	7,223	3	25	5
SM 41:0	SM 30:1	803.7 -> 184.1	9,968	3	25	5
SM 41:1(a)	SM 30:1	801.7 -> 184.1	9,911	2	25	5
SM 41:1(b)	SM 30:1	801.7 -> 184.1	9,8	2	25	5
SM 41:2(a)	SM 30:1	799.7 -> 184.1	8,644	2	25	5
SM 41:2(b)	SM 30:1	799.7 -> 184.1	8,886	2	25	5
SM 42:1	SM 30:1	815.7 -> 184.1	10,024	2	25	5
SM 42:2(a)	SM 30:1	813.7 -> 184.1	9,221	2	25	5
SM 42:2(b)	SM 30:1	813.7 -> 184.1	9,221	2	25	5
SM 43:1	SM 30:1	829.7 -> 184.1	10,15	3	25	5
SM 43:2(a)	SM 30:1	827.7 -> 184.1	9,633	3	25	5
SM 43:2(b)	SM 30:1	827.7 -> 184.1	9,633	3	25	5
SM 43:2(c)	SM 30:1	827.7 -> 184.1	10,024	3	25	5
SM 44:1	SM 30:1	843.6 -> 184.1	10,265	3	25	5
SM 44:2	SM 30:1	841.6 -> 184.1	10,092	3	25	5
SM 44:3	SM 30:1	839.6 -> 184.1	9,275	3	25	5
Sph(d16:1)	Sph(d17:1)	272.3 -> 254.3	3,734	3	8	4
Sph(d18:1)	Sph(d17:1)	300.3 -> 282.3	2,402	3	8	4
Sph(d18:2)	Sph(d17:1)	298.3 -> 280.3	1,693	3	8	4
Sulfatide (d18:1:/16:0(OH))	Hex1Cer(d18:1/16:0)d3	796.8 -> 264.3	4,926	2	56	5
Sulfatide (d18:1:/16:0)	Hex1Cer(d18:1/16:0)d3	780.8 -> 264.3	5,055	2	56	5
Sulfatide (d18:1:/24:0(OH))	Hex1Cer(d18:1/16:0)d3	908.8 -> 264.3	8,364	2	56	5
Sulfatide (d18:1:/24:0)	Hex1Cer(d18:1/16:0)d3	892.8 -> 264.3	8,731	2	56	5
Sulfatide (d18:1:/24:1(OH))	Hex1Cer(d18:1/16:0)d3	906.8 -> 264.3	7,335	2	56	5
Sulfatide (d18:1:/24:1)	Hex1Cer(d18:1/16:0)d3	890.8 -> 264.3	7,669	2	56	5
TG 14:0 16:0 18:2	TG 17:0 17:0 17:0	820.8 -> 547.5	11,021	2	21	5
TG 14:0 16:1 18:1	TG 17:0 17:0 17:0	820.8 -> 521.5	11,021	2	21	5
TG 14:0 16:1 18:2	TG 17:0 17:0 17:0	818.8 -> 521.5	10,875	2	21	5
TG 14:0 18:0 18:1	TG 17:0 17:0 17:0	850.8 -> 605.6	11,451	2	21	5
TG 14:0 18:2 18:2	TG 17:0 17:0 17:0	844.8 -> 599.5	10,926	2	21	5
TG 14:1 16:0 18:1	TG 17:0 17:0 17:0	820.8 -> 577.6	11,031	2	21	5
TG 14:1 16:1 18:0	TG 17:0 17:0 17:0	820.8 -> 549.5	11,042	2	21	5
TG 14:1 18:0 18:2	TG 17:0 17:0 17:0	846.8 -> 603.6	11,061	2	21	5
TG 14:1 18:1 18:1	TG 17:0 17:0 17:0	846.8 -> 547.5	11,061	2	21	5
TG 15:0 18:1 16:0	TG 17:0 17:0 17:0	836.8 -> 577.5	11,283	2	21	5
TG 15:0 18:1 18:1	TG 17:0 17:0 17:0	862.8 -> 603.6	11,28	2	21	5
TG 16:0 16:0 16:0	TG 17:0 17:0 17:0	824.8 -> 551.5	11,378	2	21	5
TG 16:0 16:0 18:0	TG 17:0 17:0 17:0	852.8 -> 551.5	11,587	2	21	5
TG 16:0 16:0 18:1	TG 17:0 17:0 17:0	850.8 -> 551.5	11,387	2	21	5
TG 16:0 16:0 18:2	TG 17:0 17:0 17:0	848.8 -> 551.5	11,229	2	21	5
TG 16:0 16:1 18:1	TG 17:0 17:0 17:0	848.8 -> 549.5	11,208	2	21	5
TG 16:0 18:0 18:1	TG 17:0 17:0 17:0	878.8 -> 577.5	11,606	2	21	5
TG 16:0 18:1 18:1	TG 17:0 17:0 17:0	876.8 -> 603.6	11,417	2	21	5
TG 16:0 18:1 18:2	TG 17:0 17:0 17:0	874.8 -> 577.6	11,237	2	21	5
TG 16:0 18:2 18:2	TG 17:0 17:0 17:0	872.8 -> 599.6	11,113	2	21	5
TG 16:1 16:1 16:1	TG 17:0 17:0 17:0	818.8 -> 547.5	10,918	2	21	5
TG 16:1 16:1 18:0	TG 17:0 17:0 17:0	848.8 -> 547.5	11,281	2	21	5
TG 16:1 16:1 18:1	TG 17:0 17:0 17:0	846.8 -> 575.6	11,061	2	21	5
TG 16:1 18:1 18:1	TG 17:0 17:0 17:0	874.8 -> 603.6	11,248	3	21	5
TG 16:1 18:1 18:2	TG 17:0 17:0 17:0	872.8 -> 573.6	11,092	3	21	5

TG 17:0 16:0 16:1	TG 17:0 17:0 17:0	836.8 -> 563.5	11,294	3	21	5
TG 17:0 16:0 18:0	TG 17:0 17:0 17:0	866.8 -> 593.6	11,753	3	21	5
TG 17:0 18:1 14:0	TG 17:0 17:0 17:0	836.8 -> 537.5	11,294	3	21	5
TG 17:0 18:1 16:0	TG 17:0 17:0 17:0	864.8 -> 565.5	11,576	3	21	5
TG 17:0 18:1 16:1	TG 17:0 17:0 17:0	862.8 -> 563.5	11,323	3	21	5
TG 17:0 18:1 18:1	TG 17:0 17:0 17:0	890.8 -> 603.6	11,523	3	21	5
TG 17:0 18:2 16:0	TG 17:0 17:0 17:0	862.8 -> 589.6	11,27	3	21	5
TG 18:0 18:0 18:0	TG 17:0 17:0 17:0	908.9 -> 607.6	12,039	3	21	5
TG 18:0 18:0 18:1	TG 17:0 17:0 17:0	906.9 -> 607.6	11,917	3	21	5
TG 18:0 18:1 18:1	TG 17:0 17:0 17:0	904.9 -> 603.6	11,721	3	21	5
TG 18:0 18:2 18:2	TG 17:0 17:0 17:0	900.8 -> 599.5	11,363	3	21	5
TG 18:1 14:0 16:0	TG 17:0 17:0 17:0	822.8 -> 523.5	11,169	3	21	5
TG 18:1 18:1 18:1	TG 17:0 17:0 17:0	902.9 -> 603.6	11,459	3	21	5
TG 18:1 18:1 18:2	TG 17:0 17:0 17:0	900.9 -> 603.9	11,342	3	21	5
TG 18:1 18:1 20:4	TG 17:0 17:0 17:0	924.9 -> 603.6	11,278	3	21	5
TG 18:1 18:1 22:6	TG 17:0 17:0 17:0	948.9 -> 603.7	11,215	3	21	5
TG 18:1 18:2 18:2	TG 17:0 17:0 17:0	898.9 -> 599.6	11,133	3	21	5
TG 18:2 18:2 18:2	TG 17:0 17:0 17:0	896.9 -> 599.6	11,007	3	21	5
TG 18:2 18:2 20:4	TG 17:0 17:0 17:0	920.9 -> 599.6	10,944	3	21	5
TG(O-50:1)	TG 17:0 17:0 17:0	836.8 -> 563.5	11,692	3	21	5
TG(O-52:0)	TG 17:0 17:0 17:0	866.8 -> 593.6	11,999	3	21	5
TG(O-52:2)	TG 17:0 17:0 17:0	862.8 -> 589.6	11,65	3	21	5
Ubiquinone	Hex3Cer(d18:1/17:0)	880.7 -> 197.0	10,882	3	17	5

RT: retention time (minutes) TS: time segment (arb. unit) CE: collision energy (volts) CAV: cell accelerator voltage (volts)

8.2 Annex 2

This section contains all the information of the unidentified compounds statistically different between tissues in adult animals by a non-parametric t-test of the data obtained in the untargeted lipidomic and metabolomic analysis.

Table S2. Skeletal muscle upregulated unidentified metabolites statistically different from the rest of the studied tissues. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p(Corr)
375.3431@11.64	376.3431	11.64	21.47	2.07E-28
580.2474@11.44	581.2474	11.44	17.69	2.59E-26
669.3145@11.83	670.3145	11.83	16.88	2.59E-26
669.3283@10.70	670.3283	10.7	17.76	6.30E-26
418.3201@10.90	419.3201	10.9	18.3	9.89E-26
667.3544@11.45	668.3544	11.45	17.21	9.89E-26
515.432@12.60	516.432	12.6	17.55	9.89E-26
344.3061@11.35	345.3061	11.35	16.95	1.36E-25
496.4755@11.80	497.4755	11.8	15.91	1.36E-25
313.3127@12.06	314.3127	12.06	16.92	1.72E-25
506.3711@11.03	507.3711	11.03	18.34	1.91E-25
335.1684@5.40	336.1684	5.4	15.09	2.10E-25
506.8734@11.03	507.8734	11.03	17.61	2.21E-25
274.1748@12.20	275.1748	12.2	16.11	2.33E-25
209.1551@7.31	210.1551	7.31	15.21	5.72E-25
681.6301@12.32	682.6301	12.32	15.1	5.72E-25
438.3836@12.39	439.3836	12.39	17.4	7.45E-25
243.1959@7.70	244.1959	7.7	16.88	7.45E-25
484.8567@11.00	485.8567	11	17.73	7.45E-25
379.1948@5.68	380.1948	5.68	14.8	1.58E-24
432.334@11.22	433.334	11.22	16.9	3.33E-24
395.3162@8.98	396.3162	8.98	17.08	3.33E-24
658.9834@12.44	659.9834	12.44	15.39	3.33E-24
361.2561@6.25	362.2561	6.25	17.3	4.23E-24
306.2127@7.25	307.2127	7.25	16.81	5.13E-23
463.3367@8.15	464.3367	8.15	15.96	5.24E-21
319.2797@10.45	320.2797	10.45	17.09	1.47E-20
639.2826@10.51	640.2826	10.51	17.63	4.89E-20
448.8089@10.98	449.8089	10.98	16.07	4.89E-20
435.313@10.95	436.313	10.95	18.35	5.80E-20
293.212@8.87	294.212	8.87	16.02	6.16E-20

325.28@5.87	326.28	5.87	15.78	6.66E-20
655.435@11.21	656.435	11.21	15.37	1.00E-19
552.2553@8.31	553.2553	8.31	15.41	1.43E-19
693.6311@12.28	694.6311	12.28	16.47	1.57E-19
471.3176@8.15	472.3176	8.15	14.29	1.65E-19
106.086@8.31	107.086	8.31	16.47	1.69E-19
239.2332@8.64	240.2332	8.64	17.54	1.77E-19
431.239@8.33	432.239	8.33	2.77	3.50E-19
458.3546@5.87	459.3546	5.87	16.2	4.09E-19
614.9589@12.43	615.9589	12.43	14.84	4.65E-19
414.0438@12.66	415.0438	12.66	13.43	7.37E-19
699.9684@11.06	700.9684	11.06	13.73	7.55E-19
527.3624@7.78	528.3624	7.78	14.31	7.77E-19
725.0233@12.46	726.0233	12.46	14.31	7.77E-19
671.3097@10.51	672.3097	10.51	14.36	8.53E-19
622.2569@10.80	623.2569	10.8	15.46	9.11E-19
619.3697@9.84	620.3697	9.84	14.17	9.11E-19
462.3446@10.97	463.3446	10.97	17.62	9.33E-19
209.1506@5.88	210.1506	5.88	15.33	9.44E-19
407.232@6.84	408.232	6.84	13.47	9.73E-19
412.2942@7.50	413.2942	7.5	14.21	9.73E-19
660.9668@11.20	661.9668	11.2	13.55	9.73E-19
774.3484@11.44	775.3484	11.44	14.94	9.73E-19
743.9968@11.10	744.9968	11.1	12.86	9.98E-19
258.2026@6.85	259.2026	6.85	13.46	9.98E-19
753.3945@11.45	754.3945	11.45	14.49	1.03E-18
666.5687@11.10	667.5687	11.1	15.16	1.22E-18
669.4723@12.45	670.4723	12.45	16.18	1.27E-18
853.428@8.31	854.428	8.31	13.27	1.76E-18
570.9314@12.42	571.9314	12.42	14.57	1.76E-18
592.9453@12.43	593.9453	12.43	14.42	2.20E-18
1014.5795@11.44	1015.5795	11.44	13.06	4.25E-18
134.0809@8.31	135.0809	8.31	17.71	4.05E-17
294.1925@12.31	295.1925	12.31	15.64	4.05E-17
371.3146@10.91	372.3146	10.91	17.45	5.93E-17
414.2118@8.33	415.2118	8.33	2.22	1.78E-16
606.5653@13.58	607.5653	13.58	16.69	1.80E-16
418.819@10.90	419.819	10.9	16	1.81E-16
501.354@11.04	502.354	11.04	18.23	2.32E-16
440.3293@10.94	441.3293	10.94	17.52	2.68E-16
681.364@11.44	682.364	11.44	18.39	4.79E-16
594.9273@11.14	595.9273	11.14	14.96	6.41E-16
741.3555@11.44	742.3555	11.44	15.17	1.33E-15
462.8437@10.97	463.8437	10.97	16.54	1.39E-15
440.8311@10.94	441.8311	10.94	16.4	1.45E-15
652.3041@10.81	653.3041	10.81	15.06	1.73E-15
226.176@2.71	227.176	2.71	1.46	1.93E-15
347.3112@11.12	348.3112	11.12	19.38	3.56E-15
814.174@11.45	815.174	11.45	16.31	3.56E-15
484.3555@11.00	485.3555	11	17.04	3.96E-15
463.839@8.15	464.839	8.15	14.23	3.97E-15
616.4386@11.16	617.4386	11.16	14.39	4.32E-15
638.9536@11.18	639.9536	11.18	13.12	4.35E-15
718.2276@12.68	719.2276	12.68	12.74	4.35E-15
763.4749@7.32	764.4749	7.32	13.04	4.37E-15
660.5048@7.31	661.5048	7.31	11.97	4.37E-15
613.2725@10.11	614.2725	10.11	11.75	4.37E-15
426.7999@10.94	427.7999	10.94	14.36	4.37E-15
834.2379@13.50	835.2379	13.5	14.44	4.37E-15
741.5845@13.50	742.5845	13.5	15.07	4.37E-15
392.0926@11.44	393.0926	11.44	13.47	4.39E-15
316.1978@8.42	317.1978	8.42	13.71	4.39E-15
639.5957@13.47	640.5957	13.47	15.68	4.83E-15
493.2238@6.55	494.2238	6.55	12.43	6.36E-15
306.2024@12.49	307.2024	12.49	13.88	6.36E-15
1049.723@11.42	1050.723	11.42	13.06	6.50E-15
1083.7511@11.09	1084.7511	11.09	13.03	9.42E-15
440.3203@10.53	441.3203	10.53	16.79	9.42E-15
703.0114@12.45	704.0114	12.45	13.68	1.06E-14
526.9122@12.41	527.9122	12.41	13.06	1.07E-14
961.6924@12.17	962.6924	12.17	11.98	1.88E-14
697.4999@12.72	698.4999	12.72	15.08	1.98E-14
572.9141@11.11	573.9141	11.11	14.91	6.72E-14
379.341@10.37	380.341	10.37	16.23	7.21E-14
550.901@11.09	551.901	11.09	15.26	1.36E-13
578.5347@13.44	579.5347	13.44	16.49	1.79E-13
543.3621@8.31	544.3621	8.31	13	3.03E-13

152.0942@10.54	153.0942	10.54	15.1	3.11E-13
503.331@12.73	504.331	12.73	15.16	3.12E-13
559.4165@10.89	560.4165	10.89	15.31	3.65E-13
655.944@11.01	656.944	11.01	13.05	4.48E-13
715.5515@11.56	716.5515	11.56	14.15	5.69E-13
603.4414@10.94	604.4414	10.94	15.68	7.07E-13
335.3154@10.28	336.3154	10.28	13.39	1.35E-12
517.4076@11.75	518.4076	11.75	13.27	1.35E-12
551.492@12.31	552.492	12.31	13.29	1.35E-12
699.9664@11.25	700.9664	11.25	11.56	1.35E-12
220.1254@8.86	221.1254	8.86	12.22	1.37E-12
611.4198@11.17	612.4198	11.17	14.46	1.37E-12
831.2399@13.50	832.2399	13.5	14.99	1.37E-12
553.1792@11.48	554.1792	11.48	12.26	1.37E-12
635.5552@13.22	636.5552	13.22	15.28	1.41E-12
537.3101@5.87	538.3101	5.87	11.38	1.44E-12
499.3076@8.31	500.3076	8.31	13.01	1.44E-12
613.5701@13.45	614.5701	13.45	14.26	1.44E-12
485.826@10.75	486.826	10.75	13.23	1.59E-12
615.1771@8.77	616.1771	8.77	12.07	2.04E-12
281.2795@13.06	282.2795	13.06	13.54	2.08E-12
747.0336@12.47	748.0336	12.47	12.29	2.45E-12
680.9953@12.45	681.9953	12.45	12.81	2.55E-12
539.4515@11.42	540.4515	11.42	14.5	2.55E-12
778.2325@12.57	779.2325	12.57	12.94	2.79E-12
457.3478@10.55	458.3478	10.55	1.27	2.87E-12
580.8913@11.13	581.8913	11.13	12.25	3.13E-12
371.2508@4.41	372.2508	4.41	12.09	3.32E-12
348.2657@5.61	349.2657	5.61	12.62	3.47E-12
616.9357@11.16	617.9357	11.16	13.58	1.31E-11
472.8317@10.72	473.8317	10.72	13.16	1.42E-11
528.887@11.06	529.887	11.06	14.92	1.46E-11
528.3856@11.06	529.3856	11.06	15.42	1.55E-11
426.3914@11.24	427.3914	11.24	14.34	1.67E-11
588.3069@5.87	589.3069	5.87	11.58	2.20E-11
287.2545@9.16	288.2545	9.16	16.14	2.83E-11
877.6388@11.32	878.6388	11.32	12.6	9.13E-11
641.6194@13.60	642.6194	13.6	13.2	9.33E-11
262.1316@8.31	263.1316	8.31	11.24	1.03E-10
819.1684@11.45	820.1684	11.45	11.45	1.03E-10
153.0421@0.41	154.0421	0.41	13.56	1.03E-10
244.1889@1.49	245.1889	1.49	11.25	1.03E-10
1009.7163@11.39	1010.7163	11.39	10.94	1.03E-10
846.1888@11.44	847.1888	11.44	11.87	1.03E-10
787.9795@0.80	788.9795	0.8	10.68	1.03E-10
505.2809@8.25	506.2809	8.25	10.59	1.03E-10
658.4889@12.44	659.4889	12.44	12.22	1.04E-10
589.4272@10.72	590.4272	10.72	0.92	1.12E-10
604.5483@13.47	605.5483	13.47	13.85	1.12E-10
525.3737@8.10	526.3737	8.1	10.5	1.12E-10
618.48@9.39	619.48	9.39	11.76	1.39E-10
789.7162@13.94	790.7162	13.94	13.12	1.46E-10
226.1818@7.32	227.1818	7.32	12.47	1.47E-10
763.6749@13.91	764.6749	13.91	12.69	1.47E-10
579.9239@11.43	580.9239	11.43	11.87	1.76E-10
715.513@11.02	716.513	11.02	11.96	1.82E-10
736.4566@7.32	737.4566	7.32	14.04	1.96E-10
613.4834@11.19	614.4834	11.19	14.44	2.03E-10
363.2034@6.68	364.2034	6.68	11.75	2.46E-10
933.6359@12.41	934.6359	12.41	11.14	2.71E-10
373.3269@11.26	374.3269	11.26	16.27	3.58E-10
622.2573@10.52	623.2573	10.52	12.62	4.22E-10
475.8414@11.00	476.8414	11	12.74	4.50E-10
392.3104@8.91	393.3104	8.91	12.86	7.40E-10
955.6498@11.20	956.6498	11.2	12.55	7.71E-10
274.2239@9.62	275.2239	9.62	13.63	7.80E-10
529.2938@8.32	530.2938	8.32	12.41	2.54E-09
671.5217@11.53	672.5217	11.53	13.11	2.54E-09
446.9157@8.62	447.9157	8.62	12.09	2.79E-09
76.0395@8.31	77.0395	8.31	10.78	3.22E-09
917.6718@12.17	918.6718	12.17	9.84	3.22E-09
478.3549@10.00	479.3549	10	10.3	3.24E-09
669.3315@11.28	670.3315	11.28	11.77	3.24E-09
711.6419@13.84	712.6419	13.84	11.17	3.27E-09
739.6729@13.99	740.6729	13.99	11.18	3.30E-09
367.284@8.09	368.284	8.09	10.83	3.37E-09
777.695@13.98	778.695	13.98	10.69	3.38E-09

366.29@10.14	367.29	10.14	10.97	3.43E-09
152.129@8.60	153.129	8.6	11.41	3.58E-09
737.6873@13.86	738.6873	13.86	11.5	3.58E-09
317.3022@7.60	318.3022	7.6	13.87	3.86E-09
573.398@10.91	574.398	10.91	12.82	4.77E-09
611.9191@10.96	612.9191	10.96	11.54	5.42E-09
373.3734@9.43	374.3734	9.43	12.08	5.88E-09
370.1095@11.48	371.1095	11.48	12.01	5.92E-09
803.5984@11.61	804.5984	11.61	10.9	6.26E-09
578.9299@12.11	579.9299	12.11	10.5	7.33E-09
947.7179@12.39	948.7179	12.39	10.73	9.57E-09
991.7431@12.40	992.7431	12.4	10.24	1.04E-08
558.8802@11.12	559.8802	11.12	12.01	1.11E-08
368.3819@10.27	369.3819	10.27	12.52	1.15E-08
705.4747@11.03	706.4747	11.03	12.5	1.40E-08
545.401@10.67	546.401	10.67	1.01	1.54E-08
550.3133@5.87	551.3133	5.87	11.03	1.67E-08
555.4424@10.66	556.4424	10.66	0.8	1.75E-08
691.4951@11.02	692.4951	11.02	13.88	2.34E-08
647.4666@10.98	648.4666	10.98	13.8	2.55E-08
682.4344@10.82	683.4344	10.82	14.71	2.99E-08
427.3739@10.60	428.3739	10.6	15.22	4.01E-08
470.825@11.01	471.825	11.01	12.37	4.15E-08
487.3589@10.21	488.3589	10.21	1.09	4.21E-08
522.4727@13.09	523.4727	13.09	13.27	4.59E-08
354.0703@12.94	355.0703	12.94	10.65	4.87E-08
759.5739@11.58	760.5739	11.58	10.13	5.23E-08
699.468@11.06	700.468	11.06	10.02	5.27E-08
484.3712@4.92	485.3712	4.92	8.54	5.27E-08
872.1727@11.44	873.1727	11.44	10.05	5.27E-08
879.4262@8.31	880.4262	8.31	8.76	5.28E-08
1011.303@13.42	1012.303	13.42	9.79	5.28E-08
396.39@12.38	397.39	12.38	11.14	5.33E-08
908.2567@13.64	909.2567	13.64	10.81	5.40E-08
369.296@8.63	370.296	8.63	10.67	5.48E-08
457.3261@10.99	458.3261	10.99	14.22	5.50E-08
565.5506@13.07	566.5506	13.07	13.26	5.64E-08
674.6804@12.13	675.6804	12.13	10.55	5.65E-08
650.1494@8.77	651.1494	8.77	9.75	5.77E-08
704.2157@12.28	705.2157	12.28	10.75	5.83E-08
704.5077@13.58	705.5077	13.58	11.58	8.53E-08
454.4061@12.86	455.4061	12.86	11.21	8.86E-08
368.1322@10.10	369.1322	10.1	9.93	1.06E-07
617.4218@10.94	618.4218	10.94	12.33	1.09E-07
636.9767@12.44	637.9767	12.44	10.54	1.13E-07
583.4732@11.47	584.4732	11.47	11.91	1.13E-07
110.047@3.04	111.047	3.04	11.56	1.17E-07
614.4634@12.43	615.4634	12.43	10.86	1.17E-07
238.1523@2.28	239.1523	2.28	10.11	1.22E-07
591.5453@12.81	592.5453	12.81	11.34	1.22E-07
548.9252@12.41	549.9252	12.41	10.28	1.31E-07
539.5463@11.84	540.5463	11.84	10.96	1.31E-07
502.1124@12.66	503.1124	12.66	11.34	1.51E-07
903.6835@12.39	904.6835	12.39	10.15	1.64E-07
213.2544@7.70	214.2544	7.7	11.35	2.29E-07
466.3075@7.28	467.3075	7.28	10.49	2.91E-07
715.2294@12.68	716.2294	12.68	12.24	3.42E-07
786.5722@11.84	787.5722	11.84	10.89	3.86E-07
370.3273@9.72	371.3273	9.72	12.94	3.89E-07
519.8671@11.05	520.8671	11.05	11.45	4.49E-07
585.548@13.29	586.548	13.29	11.36	5.22E-07
679.0684@7.31	680.0684	7.31	10.48	5.95E-07
655.4385@11.01	656.4385	11.01	9.33	5.95E-07
94.086@11.11	95.086	11.11	9.29	5.95E-07
1053.7394@11.42	1054.7394	11.42	8.16	5.95E-07
1085.3226@13.54	1086.3226	13.54	8.61	5.95E-07
805.7196@14.17	806.7196	14.17	9.19	5.95E-07
507.8412@10.79	508.8412	10.79	8.72	5.95E-07
965.3542@12.80	966.3542	12.8	9.1	5.95E-07
600.9481@12.12	601.9481	12.12	8.73	5.95E-07
681.6024@13.62	682.6024	13.62	9.9	5.96E-07
903.4918@13.24	904.4918	13.24	9.26	5.96E-07
791.7073@14.07	792.7073	14.07	10.65	6.15E-07
1035.7684@12.41	1036.7684	12.41	8.26	6.16E-07
441.3535@9.54	442.3535	9.54	12.82	7.05E-07
763.5758@13.58	764.5758	13.58	10.78	9.50E-07
465.1816@9.23	466.1816	9.23	9.49	9.86E-07

369.2959@10.37	370.2959	10.37	12.35	1.05E-06
631.4435@11.77	632.4435	11.77	10.04	1.05E-06
814.4751@7.32	815.4751	7.32	8.02	1.05E-06
576.3704@7.94	577.3704	7.94	9.98	1.09E-06
439.3423@9.08	440.3423	9.08	12.44	1.14E-06
573.418@8.55	574.418	8.55	9.02	1.18E-06
435.8111@10.96	436.8111	10.96	11.49	1.22E-06
461.3508@6.52	462.3508	6.52	8.48	1.29E-06
627.4657@10.95	628.4657	10.95	9.52	1.30E-06
339.2015@5.12	340.2015	5.12	8.84	1.37E-06
749.5476@11.26	750.5476	11.26	9.7	1.39E-06
699.5817@13.09	700.5817	13.09	11.7	1.48E-06
644.9713@12.14	645.9713	12.14	9.12	1.54E-06
658.5189@10.67	659.5189	10.67	10.74	1.67E-06
356.2435@6.34	357.2435	6.34	8.66	1.90E-06
415.3422@9.27	416.3422	9.27	12.08	2.16E-06
547.2964@10.26	548.2964	10.26	9.58	2.20E-06
336.2746@13.18	337.2746	13.18	10.11	2.31E-06
567.3886@11.13	568.3886	11.13	11.69	2.37E-06
494.4405@12.89	495.4405	12.89	11.38	2.40E-06
452.3481@8.15	453.3481	8.15	10.9	2.65E-06
633.9286@11.10	634.9286	11.1	10.18	2.71E-06
840.2016@11.44	841.2016	11.44	11.3	3.93E-06
249.0872@10.83	250.0872	10.83	10.46	3.95E-06
653.3328@11.45	654.3328	11.45	14.22	4.46E-06
858.3873@8.31	859.3873	8.31	7.12	4.47E-06
244.2247@10.91	245.2247	10.91	8.21	4.47E-06
743.497@11.10	744.497	11.1	7.98	4.47E-06
486.846@11.19	487.846	11.19	8.43	4.47E-06
755.3725@11.44	756.3725	11.44	8.4	4.47E-06
711.0124@12.16	712.0124	12.16	7.79	4.47E-06
852.2511@12.80	853.2511	12.8	8.01	4.47E-06
789.2483@12.92	790.2483	12.92	9.15	4.47E-06
729.2496@13.06	730.2496	13.06	8.68	4.47E-06
396.3072@10.87	397.3072	10.87	9.16	4.47E-06
553.377@11.08	554.377	11.08	7.98	4.47E-06
539.4345@12.31	540.4345	12.31	8.91	4.47E-06
789.574@13.37	790.574	13.37	10.24	4.47E-06
833.7516@14.39	834.7516	14.39	8.45	4.47E-06
699.5303@13.00	700.5303	13	9.25	4.48E-06
489.4303@13.05	490.4303	13.05	8.16	4.48E-06
653.5718@13.50	654.5718	13.5	8.81	4.52E-06
817.729@14.12	818.729	14.12	9.77	4.73E-06
118.0913@8.31	119.0913	8.31	12.27	4.94E-06
730.6057@13.25	731.6057	13.25	11.88	5.69E-06
685.556@13.13	686.556	13.13	9.71	5.78E-06
567.8938@11.13	568.8938	11.13	10.73	6.50E-06
641.2107@12.38	642.2107	12.38	10.55	8.22E-06
325.2723@10.26	326.2723	10.26	10.09	8.42E-06
431.2469@8.02	432.2469	8.02	9.06	8.53E-06
550.5106@13.28	551.5106	13.28	11.77	9.13E-06
738.6064@11.63	739.6064	11.63	8.46	9.51E-06
667.9749@11.47	668.9749	11.47	8.38	9.53E-06
199.2377@7.70	200.2377	7.7	9.28	9.92E-06
787.5232@12.81	788.5232	12.81	11.26	1.00E-05
570.4323@12.42	571.4323	12.42	9.14	1.00E-05
535.1661@12.66	536.1661	12.66	12.44	1.02E-05
318.1419@5.41	319.1419	5.41	8.21	1.08E-05
667.6195@12.23	668.6195	12.23	11.58	1.13E-05
787.6105@12.02	788.6105	12.02	8.3	1.16E-05
271.2234@9.63	272.2234	9.63	11.5	1.16E-05
497.8545@11.03	498.8545	11.03	10.59	1.19E-05
238.2367@11.13	239.2367	11.13	10.09	1.24E-05
749.0159@12.46	750.0159	12.46	8.06	1.30E-05
313.2206@7.88	314.2206	7.88	9.19	1.37E-05
358.1704@0.51	359.1704	0.51	8.69	1.48E-05
978.0425@11.45	979.0425	11.45	7.7	1.48E-05
391.7503@11.00	392.7503	11	10.02	1.58E-05
273.2757@7.46	274.2757	7.46	11.64	1.72E-05
709.3959@11.45	710.3959	11.45	10.71	1.84E-05
584.2306@10.86	585.2306	10.86	10.9	1.96E-05
535.5069@12.73	536.5069	12.73	9.85	2.18E-05
435.3434@11.85	436.3434	11.85	11.42	2.23E-05
686.2005@13.15	687.2005	13.15	10.02	2.40E-05
300.1481@9.43	301.1481	9.43	9.8	2.43E-05
355.2802@9.91	356.2802	9.91	10.57	2.44E-05
657.5092@11.22	658.5092	11.22	10.95	2.44E-05

589.9063@11.15	590.9063	11.15	9.42	2.47E-05
525.3961@10.54	526.3961	10.54	7.55	2.58E-05
611.4174@10.95	612.4174	10.95	7.6	2.58E-05
1117.7355@11.12	1118.7355	11.12	7.59	2.58E-05
645.9616@11.47	646.9616	11.47	7.34	2.58E-05
94.0916@11.64	95.0916	11.64	7.61	2.58E-05
96.1079@11.64	97.1079	11.64	7.94	2.58E-05
997.2943@13.16	998.2943	13.16	7.73	2.58E-05
863.7975@14.93	864.7975	14.93	7.97	2.58E-05
103.0909@0.39	104.0909	0.39	8.48	2.58E-05
713.5812@11.84	714.5812	11.84	7.6	2.58E-05
94.086@11.64	95.086	11.64	7.3	2.58E-05
336.0313@11.45	337.0313	11.45	6.9	2.58E-05
941.3534@12.89	942.3534	12.89	7.53	2.58E-05
439.2165@8.31	440.2165	8.31	6.87	2.59E-05
1127.7791@11.11	1128.7791	11.11	6.65	2.60E-05
963.7128@12.07	964.7128	12.07	6.73	2.60E-05
1105.2102@12.83	1106.2102	12.83	7.31	2.60E-05
831.743@14.21	832.743	14.21	7.49	2.60E-05
847.6925@13.18	848.6925	13.18	7.71	2.60E-05
627.5648@13.46	628.5648	13.46	7.57	2.60E-05
518.1492@12.67	519.1492	12.67	10.04	2.62E-05
904.6787@8.14	905.6787	8.14	6.92	2.67E-05
865.7281@14.01	866.7281	14.01	7.92	2.72E-05
639.5922@12.03	640.5922	12.03	10.7	3.08E-05
488.3186@7.43	489.3186	7.43	8.93	3.15E-05
627.5016@11.51	628.5016	11.51	10.11	3.25E-05
793.7224@14.22	794.7224	14.22	8.92	3.40E-05
775.2329@12.57	776.2329	12.57	9.87	3.41E-05
484.3474@10.60	485.3474	10.6	11.02	3.58E-05
636.3061@11.45	637.3061	11.45	13.12	3.91E-05
446.3486@12.50	447.3486	12.5	11.57	4.05E-05
557.5083@13.11	558.5083	13.11	10.09	4.18E-05
627.2015@11.93	628.2015	11.93	9.59	4.22E-05
620.397@8.15	621.397	8.15	8.24	4.63E-05
108.1012@10.67	109.1012	10.67	10.02	4.79E-05
861.7842@14.66	862.7842	14.66	8.19	4.81E-05
96.1013@11.64	97.1013	11.64	7.99	4.82E-05
294.2578@11.33	295.2578	11.33	7.94	4.91E-05
622.9608@12.13	623.9608	12.13	7.53	5.02E-05
441.802@10.68	442.802	10.68	7.01	5.17E-05
342.7711@7.32	343.7711	7.32	7.57	5.25E-05
399.706@7.32	400.706	7.32	7.8	5.35E-05
124.0983@10.66	125.0983	10.66	8.15	5.46E-05
516.858@10.78	517.858	10.78	7.37	5.48E-05
521.5977@12.18	522.5977	12.18	10.25	5.83E-05
1079.7893@12.41	1080.7893	12.41	6.64	6.14E-05
290.2468@9.85	291.2468	9.85	7.87	6.17E-05
683.5647@12.34	684.5647	12.34	8.17	6.39E-05
543.4687@12.85	544.4687	12.85	9.31	6.41E-05
623.9454@11.47	624.9454	11.47	7.9	6.57E-05
889.6306@11.80	890.6306	11.8	7.56	6.72E-05
340.3458@9.62	341.3458	9.62	8.19	7.37E-05
1275.3471@14.58	1276.3471	14.58	7.66	7.60E-05
56.0792@9.40	57.0792	9.4	9.27	7.89E-05
452.847@8.15	453.847	8.15	7.98	8.09E-05
194.1257@1.57	195.1257	1.57	8.63	8.21E-05
449.3582@11.85	450.3582	11.85	9.81	9.54E-05
553.4754@12.80	554.4754	12.8	9.31	1.04E-04
415.365@12.60	416.365	12.6	9.11	1.10E-04
321.2235@8.06	322.2235	8.06	9.3	1.14E-04
342.2977@8.64	343.2977	8.64	9.17	1.16E-04
333.2263@3.10	334.2263	3.1	6.51	1.21E-04
585.8703@9.37	586.8703	9.37	7	1.21E-04
1161.7626@11.14	1162.7626	11.14	6.14	1.21E-04
464.3361@11.17	465.3361	11.17	7.13	1.21E-04
258.2025@11.89	259.2025	11.89	6.47	1.21E-04
761.5081@12.00	762.5081	12	6.67	1.21E-04
741.6105@12.07	742.6105	12.07	6.68	1.21E-04
785.5939@12.14	786.5939	12.14	6.24	1.21E-04
695.6492@12.42	696.6492	12.42	9.75	1.21E-04
791.0661@12.47	792.0661	12.47	6.2	1.21E-04
917.3594@12.90	918.3594	12.9	6.74	1.21E-04
747.5291@12.97	748.5291	12.97	9.29	1.21E-04
845.4219@12.97	846.4219	12.97	7.46	1.21E-04
835.513@13.06	836.513	13.06	6.52	1.21E-04
428.0964@13.15	429.0964	13.15	5.87	1.21E-04

683.2036@13.15	684.2036	13.15	10.73	1.21E-04
713.5938@13.22	714.5938	13.22	7.09	1.21E-04
592.5593@13.50	593.5593	13.5	6.81	1.21E-04
646.5577@13.58	647.5577	13.58	7.24	1.21E-04
835.7661@14.60	836.7661	14.6	6.87	1.21E-04
458.3537@2.70	459.3537	2.7	5.64	1.21E-04
507.5864@12.07	508.5864	12.07	6.44	1.21E-04
280.0597@12.66	281.0597	12.66	6.72	1.21E-04
581.5404@13.01	582.5404	13.01	7.75	1.21E-04
843.7793@14.16	844.7793	14.16	8.77	1.21E-04
805.762@14.16	806.762	14.16	7.03	1.21E-04
831.7862@14.20	832.7862	14.2	7.01	1.21E-04
393.2106@6.12	394.2106	6.12	6.14	1.21E-04
507.2413@7.24	508.2413	7.24	5.85	1.21E-04
333.2289@8.42	334.2289	8.42	6.18	1.21E-04
963.4303@13.22	964.4303	13.22	6.52	1.21E-04
780.0462@13.41	781.0462	13.41	6.92	1.21E-04
630.8051@1.15	631.8051	1.15	6.66	1.21E-04
679.581@13.52	680.581	13.52	7.33	1.21E-04
867.7753@14.09	868.7753	14.09	7.73	1.21E-04
668.182@8.77	669.182	8.77	6.18	1.23E-04
622.5838@13.47	623.5838	13.47	7.38	1.23E-04
576.5173@13.32	577.5173	13.32	9.79	1.35E-04
665.6075@12.08	666.6075	12.08	8.89	1.47E-04
337.3421@12.14	338.3421	12.14	10.32	1.48E-04
392.3149@8.66	393.3149	8.66	8.46	1.70E-04
889.8147@14.98	890.8147	14.98	7.9	1.82E-04
611.5554@13.32	612.5554	13.32	8.83	1.95E-04
551.4538@7.32	552.4538	7.32	6.48	1.96E-04
837.552@11.07	838.552	11.07	8.39	1.97E-04
637.5741@13.37	638.5741	13.37	8.8	2.17E-04
661.448@10.99	662.448	10.99	9.18	2.18E-04
701.2144@12.29	702.2144	12.29	8.67	2.18E-04
246.243@11.25	247.243	11.25	7.16	2.36E-04
494.8424@10.75	495.8424	10.75	6.95	2.38E-04
303.3001@8.57	304.3001	8.57	10.87	2.47E-04
999.6681@11.22	1000.6681	11.22	6.64	2.50E-04
641.5106@11.76	642.5106	11.76	6.93	2.56E-04
495.4161@11.39	496.4161	11.39	7.95	2.57E-04
773.5449@13.01	774.5449	13.01	9.07	2.61E-04
581.5162@13.01	582.5162	13.01	8.65	2.67E-04
682.9784@12.44	683.9784	12.44	6.75	2.80E-04
875.6617@12.05	876.6617	12.05	6.56	2.83E-04
390.2987@11.85	391.2987	11.85	11.75	2.86E-04
727.5806@12.35	728.5806	12.35	7.23	2.95E-04
761.2088@13.36	762.2088	13.36	7.1	2.95E-04
292.2467@10.76	293.2467	10.76	8.5	2.97E-04
835.5461@14.05	836.5461	14.05	8.31	3.44E-04
793.5257@11.08	794.5257	11.08	8.42	3.63E-04
493.5654@11.96	494.5654	11.96	8.3	3.68E-04
915.2738@7.32	916.2738	7.32	9.24	3.71E-04
406.3302@10.45	407.3302	10.45	7.25	3.74E-04
508.8613@11.22	509.8613	11.22	7.25	3.76E-04
522.3129@10.60	523.3129	10.6	8.29	3.78E-04
634.4018@7.26	635.4018	7.26	6.79	3.93E-04
450.8163@10.68	451.8163	10.68	7.41	4.30E-04
612.1832@12.94	613.1832	12.94	8.88	4.60E-04
418.3248@12.19	419.3248	12.19	10.33	4.62E-04
534.5474@13.97	535.5474	13.97	5.95	4.79E-04
340.2469@7.10	341.2469	7.1	5.9	4.79E-04
250.0474@10.68	251.0474	10.68	7.17	4.79E-04
1043.703@11.24	1044.703	11.24	5.19	4.79E-04
919.5932@11.59	920.5932	11.59	5.43	4.79E-04
973.6411@12.13	974.6411	12.13	5.17	4.79E-04
666.9864@12.14	667.9864	12.14	5.61	4.79E-04
507.4621@12.30	508.4621	12.3	6.14	4.79E-04
639.546@12.33	640.546	12.33	6.31	4.79E-04
562.0763@12.48	563.0763	12.48	5.22	4.79E-04
927.3522@12.99	928.3522	12.99	6.08	4.79E-04
863.2721@13.12	864.2721	13.12	6.08	4.79E-04
482.4455@13.13	483.4455	13.13	5.99	4.79E-04
519.2771@8.31	520.2771	8.31	5.55	4.79E-04
889.4434@13.05	890.4434	13.05	6.21	4.79E-04
845.4776@12.98	846.4776	12.98	6.76	4.79E-04
536.5197@13.17	537.5197	13.17	6.47	4.79E-04
811.6889@14.07	812.6889	14.07	7.15	4.79E-04
711.9953@11.50	712.9953	11.5	5.46	4.79E-04

396.3736@12.38	397.3736	12.38	6.08	4.79E-04
755.0366@12.18	756.0366	12.18	5.18	4.79E-04
597.4192@6.22	598.4192	6.22	5.07	4.85E-04
911.624@11.17	912.624	11.17	7.75	4.88E-04
444.3668@12.36	445.3668	12.36	9.33	4.94E-04
791.741@14.08	792.741	14.08	7.79	5.40E-04
538.1688@12.66	539.1688	12.66	9.04	5.61E-04
893.7968@14.16	894.7968	14.16	7.21	5.71E-04
451.3738@10.38	452.3738	10.38	9.56	6.01E-04
492.3119@10.21	493.3119	10.21	9.37	6.31E-04
823.7688@14.71	824.7688	14.71	7.94	6.39E-04
819.7379@14.27	820.7379	14.27	8.78	6.56E-04
326.0794@9.11	327.0794	9.11	7.45	6.92E-04
791.59@13.47	792.59	13.47	7.44	6.92E-04
457.8268@10.99	458.8268	10.99	6.98	7.34E-04
671.5458@13.01	672.5458	13.01	6.86	7.37E-04
592.5237@13.18	593.5237	13.18	6.82	7.39E-04
569.4608@11.15	570.4608	11.15	7.37	7.49E-04
572.4122@11.12	573.4122	11.12	8.81	7.66E-04
557.9111@11.40	558.9111	11.4	6.08	7.81E-04
807.7377@14.33	808.7377	14.33	6.33	7.92E-04
501.8504@11.05	502.8504	11.05	7.62	8.14E-04
1245.2821@13.27	1246.2821	13.27	5.79	8.29E-04
429.676@7.32	430.676	7.32	6.62	8.36E-04
650.5313@13.07	651.5313	13.07	8.18	8.40E-04
496.4528@13.05	497.4528	13.05	6.73	8.42E-04
644.542@13.49	645.542	13.49	6.98	8.47E-04
673.4881@12.11	674.4881	12.11	6.47	8.57E-04
432.3319@12.33	433.3319	12.33	8.65	8.57E-04
453.3889@10.71	454.3889	10.71	8.54	8.69E-04
578.435@12.11	579.435	12.11	6.39	8.83E-04
601.9355@11.45	602.9355	11.45	6.13	9.15E-04
630.1985@11.92	631.1985	11.92	5.51	9.45E-04
681.7696@11.44	682.7696	11.44	6.16	9.50E-04
1007.7355@12.08	1008.7355	12.08	5.34	1.01E-03
1130.3108@14.12	1131.3108	14.12	6.89	1.01E-03
208.1671@2.70	209.1671	2.7	6.55	1.02E-03
859.667@12.38	860.667	12.38	6.25	1.09E-03
467.791@10.97	468.791	10.97	7.65	1.12E-03
454.2379@7.15	455.2379	7.15	6.14	1.13E-03
804.0596@13.30	805.0596	13.3	6.37	1.15E-03
660.9661@12.45	661.9661	12.45	6.82	1.15E-03
528.5305@10.57	529.5305	10.57	6.99	1.18E-03
807.4979@12.87	808.4979	12.87	7.11	1.19E-03
612.2666@11.55	613.2666	11.55	6.52	1.23E-03
982.0376@11.44	983.0376	11.44	5.46	1.29E-03
749.5016@11.06	750.5016	11.06	8.08	1.31E-03
549.6283@12.38	550.6283	12.38	8.51	1.32E-03
662.455@13.21	663.455	13.21	9.48	1.36E-03
850.3977@8.33	851.3977	8.33	8.06	1.44E-03
616.9398@12.44	617.9398	12.44	7.35	1.46E-03
735.5436@13.20	736.5436	13.2	8.43	1.56E-03
486.8345@11.00	487.8345	11	7.72	1.58E-03
676.4969@6.74	677.4969	6.74	4.28	1.64E-03
301.3058@8.52	302.3058	8.52	7.62	1.64E-03
204.0897@9.45	205.0897	9.45	8.71	1.64E-03
508.8481@11.03	509.8481	11.03	7.58	1.64E-03
771.6155@12.36	772.6155	12.36	5.17	1.64E-03
1102.3348@13.81	1103.3348	13.81	4.57	1.64E-03
753.6927@14.06	754.6927	14.06	4.87	1.64E-03
520.4922@12.94	521.4922	12.94	5.65	1.64E-03
563.5693@12.94	564.5693	12.94	5.7	1.64E-03
565.5887@13.07	566.5887	13.07	6.74	1.64E-03
817.774@14.11	818.774	14.11	6.46	1.64E-03
807.7821@14.33	808.7821	14.33	5.02	1.64E-03
861.8444@14.67	862.8444	14.67	5.23	1.64E-03
454.439@12.90	455.439	12.9	5.52	1.64E-03
534.5101@13.03	535.5101	13.03	5.18	1.64E-03
739.708@13.99	740.708	13.99	5.44	1.64E-03
545.3086@8.31	546.3086	8.31	4.81	1.64E-03
1099.2127@12.80	1100.2127	12.8	4.99	1.64E-03
889.4241@12.91	890.4241	12.91	4.99	1.64E-03
821.6411@13.16	822.6411	13.16	5.48	1.64E-03
342.3042@7.31	343.3042	7.31	5.31	1.64E-03
563.5356@12.94	564.5356	12.94	5.44	1.64E-03
927.8315@14.97	928.8315	14.97	5.27	1.64E-03
411.3483@9.81	412.3483	9.81	5.14	1.65E-03

1019.2664@12.85	1020.2664	12.85	5.01	1.65E-03
811.6523@14.08	812.6523	14.08	8.07	1.68E-03
426.3865@12.58	427.3865	12.58	8.34	1.77E-03
1002.564@8.20	1003.564	8.2	8.66	1.78E-03
514.8471@11.07	515.8471	11.07	7.33	1.99E-03
905.2583@13.64	906.2583	13.64	8.55	2.05E-03
554.3545@7.82	555.3545	7.82	5.56	2.08E-03
431.2807@4.50	432.2807	4.5	0.4	2.11E-03
849.2498@12.80	850.2498	12.8	8.02	2.13E-03
534.2563@8.31	535.2563	8.31	7.23	2.14E-03
631.5707@13.03	632.5707	13.03	6.13	2.16E-03
294.1246@8.33	295.1246	8.33	4.98	2.18E-03
761.5436@12.98	762.5436	12.98	8.5	2.31E-03
671.5827@13.01	672.5827	13.01	6.17	2.33E-03
869.1753@11.44	870.1753	11.44	6.02	2.35E-03
598.3832@8.05	599.3832	8.05	6	2.37E-03
1053.2955@13.93	1054.2955	13.93	8.5	2.38E-03
495.3983@10.40	496.3983	10.4	6.53	2.41E-03
545.8764@11.11	546.8764	11.11	6.08	2.69E-03
523.8668@11.08	524.8668	11.08	6.24	2.70E-03
845.4416@8.33	846.4416	8.33	6.89	2.72E-03
858.5389@10.96	859.5389	10.96	8.04	2.75E-03
1075.2234@12.86	1076.2234	12.86	5.94	2.76E-03
368.3521@12.78	369.3521	12.78	9.18	2.78E-03
727.5847@13.18	728.5847	13.18	6.47	2.85E-03
396.2019@8.33	397.2019	8.33	3.88	2.86E-03
339.7679@7.32	340.7679	7.32	8.19	2.86E-03
1073.7113@11.11	1074.7113	11.11	5.2	2.89E-03
280.1394@8.33	281.1394	8.33	5.22	2.90E-03
444.2917@7.12	445.2917	7.12	5.74	3.05E-03
965.69@11.34	966.69	11.34	4.95	3.06E-03
988.5658@11.45	989.5658	11.45	6.69	3.16E-03
428.3738@12.54	429.3738	12.54	9.38	3.25E-03
474.3285@2.70	475.3285	2.7	5.49	3.28E-03
217.2133@3.99	218.2133	3.99	5.79	3.28E-03
592.4439@12.42	593.4439	12.42	5.65	3.47E-03
632.2298@10.50	633.2298	10.5	7.18	3.48E-03
440.3051@7.15	441.3051	7.15	7.56	3.51E-03
406.2072@7.33	407.2072	7.33	5.03	3.53E-03
99.1127@5.87	100.1127	5.87	6.32	3.62E-03
1020.5296@11.44	1021.5296	11.44	6.44	3.69E-03
611.9166@11.17	612.9166	11.17	7.02	3.78E-03
257.2796@9.09	258.2796	9.09	6.84	3.91E-03
380.2283@7.32	381.2283	7.32	4.87	3.91E-03
690.4627@10.51	691.4627	10.51	7.04	4.06E-03
355.3585@9.59	356.3585	9.59	6.43	4.15E-03
539.4084@10.86	540.4084	10.86	6.47	4.18E-03
735.5195@11.06	736.5195	11.06	6.6	4.35E-03
649.6426@13.57	650.6426	13.57	7.75	4.52E-03
187.1279@10.69	188.1279	10.69	2.47	4.60E-03
655.8099@11.45	656.8099	11.45	7.63	4.60E-03
171.133@10.54	172.133	10.54	7.74	4.65E-03
492.8342@11.05	493.8342	11.05	6.45	4.65E-03
128.057@8.29	129.057	8.29	5.62	4.67E-03
304.2007@8.05	305.2007	8.05	5.83	4.76E-03
384.2222@7.32	385.2222	7.32	4.75	4.88E-03
594.92@12.43	595.92	12.43	6.11	4.88E-03
646.4356@10.45	647.4356	10.45	7.04	4.96E-03
848.6984@14.15	849.6984	14.15	6.04	4.97E-03
481.4076@11.19	482.4076	11.19	4.91	4.99E-03
981.2888@12.98	982.2888	12.98	4.36	4.99E-03
729.2918@13.06	730.2918	13.06	4.4	4.99E-03
572.5256@13.06	573.5256	13.06	4.65	4.99E-03
607.5594@13.06	608.5594	13.06	5.04	4.99E-03
284.2646@13.11	285.2646	13.11	4.35	4.99E-03
633.5616@13.13	634.5616	13.13	5.29	4.99E-03
428.1155@13.15	429.1155	13.15	3.79	4.99E-03
997.3556@13.16	998.3556	13.16	4.24	4.99E-03
699.6145@13.18	700.6145	13.18	4.66	4.99E-03
737.7084@13.87	738.7084	13.87	4.57	4.99E-03
833.7969@14.39	834.7969	14.39	4.33	4.99E-03
181.1541@5.88	182.1541	5.88	4.13	4.99E-03
902.2959@7.32	903.2959	7.32	5.27	5.02E-03
930.4385@13.14	931.4385	13.14	4.04	5.02E-03
421.3358@9.40	422.3358	9.4	6.6	5.02E-03
692.2067@10.46	693.2067	10.46	3.87	5.02E-03
969.3482@12.83	970.3482	12.83	4.02	5.02E-03

479.8374@11.02	480.8374	11.02	4.45	5.08E-03
771.6045@13.51	772.6045	13.51	6.54	5.16E-03
876.7288@14.39	877.7288	14.39	7.12	5.26E-03
941.6347@11.02	942.6347	11.02	6.29	5.53E-03
358.2353@7.32	359.2353	7.32	4.68	6.25E-03
463.3648@12.19	464.3648	12.19	7.75	6.58E-03
982.2767@13.78	983.2767	13.78	7.12	7.05E-03
695.3796@11.45	696.3796	11.45	7.29	7.48E-03
1078.6596@11.11	1079.6596	11.11	5.04	7.50E-03
761.5943@13.05	762.5943	13.05	5.18	8.00E-03
833.5991@13.51	834.5991	13.51	6.35	8.02E-03
434.3324@5.88	435.3324	5.88	2.06	8.09E-03
467.3746@9.80	468.3746	9.8	7.19	8.22E-03
779.5461@11.09	780.5461	11.09	5.85	8.42E-03
903.8324@15.19	904.8324	15.19	6.3	8.56E-03
879.4726@13.28	880.4726	13.28	6.96	8.63E-03
752.4355@7.32	753.4355	7.32	2.8	8.66E-03
475.3578@11.31	476.3578	11.31	4.91	8.73E-03
805.57@13.26	806.57	13.26	9.05	8.73E-03
556.923@12.10	557.923	12.1	4.31	9.19E-03
157.1577@7.06	158.1577	7.06	6.37	9.40E-03
442.8086@10.94	443.8086	10.94	6.39	9.40E-03
169.1173@10.55	170.1173	10.55	7.09	9.49E-03
526.4118@12.41	527.4118	12.41	4.66	9.60E-03
718.5453@13.21	719.5453	13.21	4.33	9.62E-03
841.4932@13.09	842.4932	13.09	4.43	9.90E-03
743.5854@12.01	744.5854	12.01	4.4	1.02E-02
716.6021@13.20	717.6021	13.2	4.46	1.03E-02
112.1335@11.84	113.1335	11.84	6.63	1.03E-02
815.6414@12.37	816.6414	12.37	4.58	1.05E-02
638.9535@12.44	639.9535	12.44	4.41	1.07E-02
824.6915@14.27	825.6915	14.27	6.22	1.09E-02
745.5233@10.79	746.5233	10.79	4.98	1.10E-02
624.9373@12.13	625.9373	12.13	4.04	1.10E-02
609.541@13.18	610.541	13.18	7.57	1.12E-02
532.3409@7.70	533.3409	7.7	4.11	1.16E-02
867.5973@11.15	868.5973	11.15	5.91	1.20E-02
726.4605@10.86	727.4605	10.86	6.92	1.20E-02
631.5251@13.01	632.5251	13.01	6.23	1.27E-02
821.754@14.46	822.754	14.46	6.57	1.33E-02
299.2038@2.94	300.2038	2.94	4.59	1.34E-02
602.5345@13.27	603.5345	13.27	6.63	1.38E-02
682.9773@11.22	683.9773	11.22	3.08	1.39E-02
717.5778@13.60	718.5778	13.6	5.97	1.39E-02
68.0708@3.29	69.0708	3.29	5.55	1.39E-02
607.5231@13.06	608.5231	13.06	6.86	1.47E-02
897.6101@10.99	898.6101	10.99	5.19	1.47E-02
853.5844@10.96	854.5844	10.96	5.4	1.47E-02
140.1729@12.51	141.1729	12.51	5.56	1.50E-02
372.2354@4.97	373.2354	4.97	3.73	1.54E-02
166.0486@11.86	167.0486	11.86	6.91	1.55E-02
1127.3125@14.11	1128.3125	14.11	6.37	1.57E-02
552.8738@11.09	553.8738	11.09	5.18	1.59E-02
823.5722@11.12	824.5722	11.12	4.74	1.62E-02
464.8215@10.98	465.8215	10.98	5.44	1.69E-02
548.5276@13.15	549.5276	13.15	4.62	1.73E-02
684.5174@7.32	685.5174	7.32	1.81	1.76E-02
907.6505@10.98	908.6505	10.98	4.51	1.76E-02
979.2772@13.78	980.2772	13.78	6.79	1.76E-02
171.1326@10.69	172.1326	10.69	3.54	1.80E-02
99.112@2.71	100.112	2.71	1.89	1.83E-02
1171.7281@9.39	1172.7281	9.39	5.36	1.87E-02
487.2994@8.33	488.2994	8.33	1.93	1.91E-02
843.7385@14.16	844.7385	14.16	6.54	1.91E-02
899.8004@14.64	900.8004	14.64	6.68	1.94E-02
530.8624@11.09	531.8624	11.09	5.14	1.96E-02
218.1746@9.83	219.1746	9.83	4.31	2.15E-02
777.5772@13.21	778.5772	13.21	5.51	2.15E-02
866.3357@7.32	867.3357	7.32	4.13	2.15E-02
863.6246@10.95	864.6246	10.95	4.54	2.18E-02
1056.2935@13.93	1057.2935	13.93	5.53	2.18E-02
789.2972@12.93	790.2972	12.93	4.11	2.26E-02
460.3716@12.57	461.3716	12.57	5.61	2.42E-02
115.063@0.42	116.063	0.42	5.65	2.43E-02
809.5586@10.92	810.5586	10.92	4.7	2.63E-02
608.2318@10.59	609.2318	10.59	3.78	2.63E-02
727.0038@12.46	728.0038	12.46	3.52	2.63E-02

414.2126@8.04	415.2126	8.04	1.93	2.64E-02
802.5487@11.85	803.5487	11.85	6.81	2.77E-02
609.185@12.94	610.185	12.94	7	2.80E-02
699.5595@11.99	700.5595	11.99	3.55	2.81E-02
258.2037@2.55	259.2037	2.55	15.93	2.83E-02
811.58@13.04	812.58	13.04	4.52	2.83E-02
443.374@10.01	444.374	10.01	4.15	2.85E-02
445.7872@10.95	446.7872	10.95	5.1	2.86E-02
558.8975@12.10	559.8975	12.1	3.28	2.86E-02
613.8929@11.17	614.8929	11.17	4.23	2.86E-02
110.1157@3.30	111.1157	3.3	5.37	2.89E-02
1034.6408@11.08	1035.6408	11.08	4.03	2.89E-02
572.9083@12.42	573.9083	12.42	4.53	2.89E-02
386.2508@5.96	387.2508	5.96	1.99	2.95E-02
671.4816@10.98	672.4816	10.98	4.55	2.95E-02
797.5461@13.14	798.5461	13.14	4.89	3.16E-02
569.8665@11.13	570.8665	11.13	4.5	3.21E-02
997.6088@8.22	998.6088	8.22	6.1	3.36E-02
914.7018@12.51	915.7018	12.51	5.73	3.39E-02
655.9454@11.22	656.9454	11.22	4.17	3.40E-02
245.2458@6.01	246.2458	6.01	4.2	3.40E-02
452.3431@2.70	453.3431	2.7	5.39	3.41E-02
583.4376@10.90	584.4376	10.9	5.35	3.45E-02
148.0268@9.44	149.0268	9.44	7.02	3.69E-02
528.3732@10.66	529.3732	10.66	3.5	3.71E-02
583.5244@13.14	584.5244	13.14	5.59	3.81E-02
283.3325@9.57	284.3325	9.57	4.45	3.85E-02
902.5645@10.99	903.5645	10.99	4.57	3.94E-02
946.5888@11.02	947.5888	11.02	4.33	4.06E-02
841.7249@14.03	842.7249	14.03	5.34	4.13E-02
428.3731@12.94	429.3731	12.94	6.15	4.33E-02
613.8917@10.96	614.8917	10.96	4.59	4.42E-02
831.6291@12.09	832.6291	12.09	4.66	4.44E-02
640.5131@13.20	641.5131	13.2	5.32	4.47E-02
971.9825@11.44	972.9825	11.44	5.19	4.55E-02
990.6177@11.06	991.6177	11.06	3.73	4.76E-02
926.5345@13.38	927.5345	13.38	4.76	4.86E-02
757.5713@13.38	758.5713	13.38	7.31	4.89E-02
847.7702@14.51	848.7702	14.51	5.82	4.95E-02

Table S3. Heart upregulated unidentified metabolites statistically different from the rest of the studied tissues. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p(Corr)
587.2091@10.30	588.2091	10.3	16.2	9.80E-22
399.1539@0.87	400.1539	0.87	13.86	1.60E-13
358.3426@11.68	359.3426	11.68	17.1	1.60E-13
293.0032@0.50	294.0032	0.5	10.89	2.56E-10
906.1384@0.68	907.1384	0.68	9.34	2.56E-10
414.1563@0.88	415.1563	0.88	10.6	2.56E-10
570.3545@4.12	571.3545	4.12	9.66	2.56E-10
639.6437@12.01	640.6437	12.01	13.88	2.56E-10
590.3574@5.85	591.3574	5.85	9.88	2.63E-10
247.1514@0.57	248.1514	0.57	16.76	1.34E-09
382.0255@0.88	383.0255	0.88	11.55	1.17E-08
204.0858@9.51	205.0858	9.51	15.05	4.42E-08
56.07@9.46	57.07	9.46	10.34	5.73E-08
70.0934@11.90	71.0934	11.9	9.33	5.73E-08
665.6561@12.07	666.6561	12.07	10.03	5.73E-08
430.3873@12.74	431.3873	12.74	10.1	5.73E-08
891.613@13.46	892.613	13.46	9.67	5.73E-08
811.7167@14.15	812.7167	14.15	10.61	5.73E-08
693.6911@12.26	694.6911	12.26	9.71	5.73E-08
440.8072@10.98	441.8072	10.98	10.29	5.74E-08
627.2645@11.97	628.2645	11.97	10.81	6.61E-08
782.6772@11.94	783.6772	11.94	11.69	8.23E-08
496.1985@8.37	497.1985	8.37	10.18	9.90E-08
890.3321@8.37	891.3321	8.37	9.55	1.45E-07
337.3701@12.18	338.3701	12.18	14.94	1.97E-07
580.3677@10.38	581.3677	10.38	13.33	7.54E-07
913.2768@7.33	914.2768	7.33	13.63	3.07E-06
549.6754@12.35	550.6754	12.35	11.6	3.07E-06
418.2775@10.50	419.2775	10.5	12.34	3.19E-06

695.1226@0.65	696.1226	0.65	7.21	3.80E-06
387.3056@8.41	388.3056	8.41	8.55	3.80E-06
440.3347@12.24	441.3347	12.24	11.59	3.80E-06
446.3918@12.56	447.3918	12.56	9.54	3.80E-06
1020.5965@11.49	1021.5965	11.49	8.19	3.80E-06
758.2971@11.49	759.2971	11.49	8.93	3.80E-06
292.2729@12.01	293.2729	12.01	7.74	3.80E-06
667.6777@12.22	668.6777	12.22	12.88	6.40E-06
318.2863@12.12	319.2863	12.12	11.65	9.91E-06
244.1509@0.52	245.1509	0.52	12.2	1.25E-05
616.1374@0.67	617.1374	0.67	8.92	1.43E-05
418.3486@12.23	419.3486	12.23	13.68	1.43E-05
273.2606@7.47	274.2606	7.47	14	2.13E-05
914.7843@12.56	915.7843	12.56	10.86	2.47E-05
432.363@12.38	433.363	12.38	11.27	2.87E-05
275.183@1.35	276.183	1.35	9.24	2.95E-05
468.3788@12.56	469.3788	12.56	12.52	3.95E-05
538.2058@12.72	539.2058	12.72	8.94	7.32E-05
622.5479@13.06	623.5479	13.06	9.48	1.04E-04
626.0637@0.89	627.0637	0.89	6.34	1.04E-04
554.2386@5.89	555.2386	5.89	9.96	1.05E-04
502.3031@5.25	503.3031	5.25	6.86	1.11E-04
387.3082@8.29	388.3082	8.29	7.87	1.16E-04
918.2729@7.33	919.2729	7.33	8.28	1.27E-04
974.525@11.49	975.525	11.49	7.74	1.33E-04
362.2765@11.48	363.2765	11.48	9.39	1.39E-04
484.8427@11.04	485.8427	11.04	8.53	1.54E-04
205.1705@9.39	206.1705	9.39	10.67	2.13E-04
641.2674@10.37	642.2674	10.37	9.61	2.57E-04
794.3328@7.43	795.3328	7.43	7.67	2.73E-04
578.2745@5.89	579.2745	5.89	9.16	4.21E-04
399.1592@0.67	400.1592	0.67	10.84	5.10E-04
390.3413@11.91	391.3413	11.91	11.91	5.59E-04
635.4142@7.10	636.4142	7.1	7.65	6.22E-04
440.1427@5.99	441.1427	5.99	8.75	7.29E-04
518.1856@12.72	519.1856	12.72	7.97	7.99E-04
535.2073@12.74	536.2073	12.74	8.91	8.34E-04
220.1527@8.72	221.1527	8.72	10.44	8.95E-04
423.125@9.49	424.125	9.49	6.78	1.02E-03
616.9866@12.47	617.9866	12.47	6.77	1.16E-03
701.2746@12.33	702.2746	12.33	7.36	1.21E-03
360.1597@9.50	361.1597	9.5	7.06	1.29E-03
568.2357@10.26	569.2357	10.26	6.62	1.30E-03
502.1465@12.72	503.1465	12.72	6.7	1.30E-03
738.2699@6.01	739.2699	6.01	7.19	1.38E-03
416.1989@10.49	417.1989	10.49	6.7	1.41E-03
451.8734@8.66	452.8734	8.66	9.29	1.73E-03
454.352@12.39	455.352	12.39	7.82	1.77E-03
472.0892@5.99	473.0892	5.99	10.25	1.84E-03
479.3964@10.90	480.3964	10.9	7.78	1.84E-03
480.0855@5.99	481.0855	5.99	10.51	2.10E-03
512.1721@8.37	513.1721	8.37	9.45	2.46E-03
612.2844@9.49	613.2844	9.49	8.36	3.24E-03
635.4184@6.97	636.4184	6.97	9.17	3.66E-03
921.0096@9.88	922.0096	9.88	9.03	3.89E-03
428.408@12.58	429.408	12.58	8.24	4.09E-03
841.0881@13.47	842.0881	13.47	6.7	4.26E-03
378.2505@6.57	379.2505	6.57	6.44	4.53E-03
484.3964@12.40	485.3964	12.4	8.4	4.80E-03
444.4009@12.41	445.4009	12.41	8.35	4.83E-03
679.4489@7.16	680.4489	7.16	6.83	4.89E-03
574.2784@5.89	575.2784	5.89	8.76	4.96E-03
775.3039@12.61	776.3039	12.61	6.8	5.95E-03
672.5691@12.78	673.5691	12.78	6.99	5.95E-03
421.7958@13.21	422.7958	13.21	6.7	6.02E-03
715.2862@12.73	716.2862	12.73	7.84	6.40E-03
536.3391@10.31	537.3391	10.31	7.78	6.41E-03
591.2038@10.29	592.2038	10.29	8.47	6.63E-03
506.3298@10.63	507.3298	10.63	11.24	7.27E-03
606.55@12.82	607.55	12.82	8.45	7.34E-03
528.1518@8.35	529.1518	8.35	9.17	8.78E-03
253.1355@5.88	254.1355	5.88	9.35	9.07E-03
1064.4952@10.28	1065.4952	10.28	7.17	1.00E-02
566.2835@5.89	567.2835	5.89	7.46	1.07E-02
539.237@10.29	540.237	10.29	7.21	1.09E-02
118.0834@8.37	119.0834	8.37	8.27	1.22E-02
496.2045@10.26	497.2045	10.26	6.67	1.22E-02

333.1928@5.64	334.1928	5.64	7.06	1.32E-02
445.2444@8.37	446.2444	8.37	6.28	1.39E-02
695.7031@12.39	696.7031	12.39	6.74	1.45E-02
270.1183@2.17	271.1183	2.17	7.78	1.58E-02
1047.1419@7.32	1048.1419	7.32	7.67	1.58E-02
311.3513@12.19	312.3513	12.19	6.67	1.59E-02
624.3929@10.43	625.3929	10.43	8.83	1.62E-02
834.3705@7.33	835.3705	7.33	7.36	1.84E-02
536.1471@8.34	537.1471	8.34	8.23	1.92E-02
705.4731@7.32	706.4731	7.32	6.48	1.97E-02
508.1054@7.42	509.1054	7.42	7.87	1.98E-02
270.2865@12.01	271.2865	12.01	6.05	1.98E-02
467.3746@9.80	468.3746	9.8	8.46	2.04E-02
715.5665@12.94	716.5665	12.94	8.97	2.34E-02
148.0398@11.91	149.0398	11.91	8.1	2.43E-02
257.1337@5.89	258.1337	5.89	7.46	2.46E-02
432.1919@11.15	433.1919	11.15	5.86	2.53E-02
376.1314@9.47	377.1314	9.47	7.79	2.85E-02
668.4188@10.48	669.4188	10.48	8.52	2.85E-02
423.7782@13.49	424.7782	13.49	7.12	2.85E-02
638.4069@10.80	639.4069	10.8	7.47	2.99E-02
591.3894@6.73	592.3894	6.73	7.16	3.00E-02
456.1114@6.00	457.1114	6	6.38	3.21E-02
424.1281@7.43	425.1281	7.43	5.93	3.68E-02
614.2303@10.27	615.2303	10.27	6.46	3.91E-02
550.2891@5.88	551.2891	5.88	6.14	3.95E-02
492.3119@10.21	493.3119	10.21	7.79	4.13E-02
623.1842@10.26	624.1842	10.26	5.97	4.17E-02
486.3084@6.21	487.3084	6.21	5.76	4.28E-02
563.2125@10.24	564.2125	10.24	7.58	4.34E-02
392.1018@9.47	393.1018	9.47	7.42	4.66E-02
550.356@10.67	551.356	10.67	8.6	4.82E-02
712.4448@10.53	713.4448	10.53	7.24	4.93E-02

Table S4. Liver upregulated unidentified metabolites statistically different from the rest of the studied tissues. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p (Corr)
443.2452@10.33	444.2522	10.33	19.29	4.89E-29
598.4966@12.89	599.5036	12.89	18.59	3.67E-27
700.5515@12.91	701.5585	12.91	17.63	1.99E-25
540.4541@13	541.4611	13	17.52	2.45E-25
540.4554@13.15	541.4624	13.15	18.77	2.62E-23
482.3743@12.97	483.3813	12.97	16.51	3.27E-23
329.1342@1.06	330.1412	1.06	16.24	3.68E-23
285.2221@10.97	286.2291	10.97	16.88	3.93E-22
709.3981@12.8	710.4051	12.8	16.97	2.62E-21
898.7051@14.15	899.7121	14.15	16.16	2.62E-21
886.4731@7.31	887.4801	7.31	15.42	4.29E-21
585.2289@10.85	586.2359	10.85	15.01	4.29E-21
484.3482@12.34	485.3552	12.34	15.46	4.29E-21
759.4927@12.73	760.4997	12.73	15.99	4.29E-21
689.5016@12.84	690.5086	12.84	15.08	4.29E-21
765.5318@12.95	766.5388	12.95	20.31	4.29E-21
394.7593@13.1	395.7663	13.1	14.10	4.29E-21
753.533@13.11	754.54	13.11	17.91	4.29E-21
729.5324@13.17	730.5394	13.17	16.19	4.29E-21
389.7679@13.35	390.7749	13.35	14.09	4.29E-21
823.608@13.64	824.615	13.64	16.78	4.29E-21
267.2115@11.73	268.2185	11.73	17.09	4.29E-21
262.1598@0.43	263.1668	0.43	15.03	5.52E-21
532.3223@9.45	533.3293	9.45	14.79	6.12E-21
856.7518@14.56	857.7588	14.56	15.08	6.12E-21
268.2194@13.53	269.2264	13.53	17.23	8.76E-21
1127.7559@13.26	1128.7629	13.26	12.42	6.01E-15
376.2689@11.6	377.2759	11.6	15.88	1.28E-14
980.041@11.44	981.048	11.44	13.58	1.28E-14
192.0617@0.93	193.0687	0.93	13.36	1.51E-14
575.1915@8.47	576.1985	8.47	12.58	1.51E-14
553.1789@10.54	554.1859	10.54	12.63	1.51E-14
997.3287@10.91	998.3357	10.91	12.45	1.51E-14
729.5304@13.01	730.5374	13.01	13.38	1.51E-14
402.7484@13.09	403.7554	13.09	13.00	1.51E-14

1594.5773@13.26	1595.5843	13.26	11.60	1.51E-14
891.5733@13.51	892.5803	13.51	13.20	1.51E-14
626.5166@14.08	627.5236	14.08	13.14	1.51E-14
422.1721@7.31	423.1791	7.31	12.07	1.61E-14
421.7582@13.21	422.7652	13.21	14.39	1.84E-14
719.5815@13.7	720.5885	13.7	14.02	5.39E-13
713.5001@12.79	714.5071	12.79	15.76	1.21E-12
624.5011@12.95	625.5081	12.95	15.01	4.38E-12
748.5415@13.76	749.5485	13.76	16.31	1.19E-11
512.4067@12.3	513.4137	12.3	14.07	2.43E-11
777.0358@13.36	778.0428	13.36	11.78	5.51E-11
397.756@13.37	398.763	13.37	12.18	5.51E-11
706.1675@12.28	707.1745	12.28	11.87	6.35E-11
670.5628@14.95	671.5698	14.95	12.45	7.17E-11
1041.9026@11.44	1042.9096	11.44	10.90	7.73E-11
581.4527@12.8	582.4597	12.8	12.13	7.73E-11
1170.2931@13.1	1171.3001	13.1	9.78	7.73E-11
817.5572@13.13	818.5642	13.13	11.96	7.73E-11
1582.5928@13.28	1583.5998	13.28	10.03	7.73E-11
1045.7083@13.34	1046.7153	13.34	9.75	7.73E-11
410.7623@13.4	411.7693	13.4	9.99	7.73E-11
846.6154@13.9	847.6224	13.9	13.28	7.73E-11
854.7359@14.37	855.7429	14.37	13.61	7.73E-11
828.7119@14.7	829.7189	14.7	12.12	7.73E-11
672.5773@15.24	673.5843	15.24	10.81	7.73E-11
880.5082@16.32	881.5152	16.32	11.59	7.73E-11
688.1625@13.15	689.1695	13.15	10.67	7.73E-11
401.7436@12.96	402.7506	12.96	10.87	7.80E-11
479.2739@9.44	480.2809	9.44	11.38	8.01E-11
777.5346@13.2	778.5416	13.2	12.97	8.07E-11
622.2176@9.44	623.2246	9.44	10.29	8.11E-11
616.4925@12.77	617.4995	12.77	13.02	8.11E-11
540.4547@12.81	541.4617	12.81	12.64	8.34E-11
801.5308@13.18	802.5378	13.18	13.02	9.96E-11
527.224@8.88	528.231	8.88	10.97	1.07E-10
788.5286@11.84	789.5356	11.84	11.67	1.24E-10
977.4159@11.45	978.4229	11.45	13.85	1.97E-10
737.5014@12.74	738.5084	12.74	15.80	2.26E-10
978.5527@13.51	979.5597	13.51	13.52	2.92E-10
534.3168@10.86	535.3238	10.86	14.38	7.69E-10
597.2231@10.84	598.2301	10.84	13.85	8.55E-10
792.6071@13.9	793.6141	13.9	15.02	9.68E-10
852.718@14.51	853.725	14.51	13.38	4.03E-09
795.5773@13.42	796.5843	13.42	14.89	4.09E-09
734.2597@11.46	735.2667	11.46	15.39	7.59E-09
612.4743@13.05	613.4813	13.05	15.35	8.08E-09
606.4793@12.77	607.4863	12.77	12.55	9.55E-09
552.2269@5.88	553.2339	5.88	12.77	1.71E-08
152.0601@1.39	153.0671	1.39	11.04	2.39E-08
717.0266@0.87	718.0336	0.87	9.47	2.63E-08
789.0448@10.85	790.0518	10.85	9.22	2.63E-08
754.4505@11.05	755.4575	11.05	9.20	2.63E-08
548.4435@12.85	549.4505	12.85	12.96	2.63E-08
578.4355@12.79	579.4425	12.79	10.08	2.63E-08
1152.743@12.87	1153.75	12.87	8.41	2.63E-08
388.7314@12.89	389.7384	12.89	9.52	2.63E-08
522.4451@12.96	523.4521	12.96	11.26	2.63E-08
1236.8671@13.5	1237.8741	13.5	10.60	2.63E-08
268.2188@13.68	269.2258	13.68	9.61	2.63E-08
811.5424@14.09	812.5494	14.09	11.66	2.63E-08
654.1409@0.52	655.1479	0.52	8.88	2.63E-08
299.2378@11.65	300.2448	11.65	10.56	2.63E-08
1128.7463@12.9	1129.7533	12.9	8.54	2.63E-08
769.0469@13.35	770.0539	13.35	8.96	2.63E-08
731.551@13.28	732.558	13.28	13.13	2.68E-08
736.2042@11.45	737.2112	11.45	11.05	2.72E-08
685.7721@11.46	686.7791	11.46	11.68	5.06E-08
312.2585@13.18	313.2655	13.18	10.72	5.12E-08
715.5171@12.92	716.5241	12.92	17.66	1.01E-07
821.0816@13.48	822.0886	13.48	11.62	1.05E-07
830.5636@12.2	831.5706	12.2	12.45	1.31E-07
415.7821@13.48	416.7891	13.48	11.64	1.67E-07
1041.3595@10.96	1042.3665	10.96	11.12	1.89E-07
622.4946@12.87	623.5016	12.87	14.59	1.95E-07
991.9521@11.44	992.9591	11.44	10.15	2.53E-07
641.23@10.57	642.237	10.57	11.93	3.51E-07
234.1538@0.43	235.1608	0.43	12.41	5.03E-07

247.1428@5.02	248.1498	5.02	13.79	5.14E-07
1292.5988@11.45	1293.6058	11.45	13.64	5.91E-07
629.6096@13.44	630.6166	13.44	11.65	5.91E-07
983.0213@11.44	984.0283	11.44	9.94	6.77E-07
690.4152@11.86	691.4222	11.86	13.33	8.22E-07
1069.7155@13.25	1070.7225	13.25	9.10	8.75E-07
152.034@1	153.041	1	12.94	9.74E-07
626.4549@10.73	627.4619	10.73	11.58	1.31E-06
344.0251@6.89	345.0321	6.89	10.58	1.50E-06
753.5313@13	754.5383	13	10.58	1.55E-06
758.2352@11.46	759.2422	11.46	12.74	1.56E-06
336.0308@6.89	337.0378	6.89	10.55	1.57E-06
812.6667@13.77	813.6737	13.77	12.28	1.66E-06
383.109@1.78	384.116	1.78	10.59	1.66E-06
954.5537@13.61	955.5607	13.61	8.95	1.94E-06
349.2108@5.74	350.2178	5.74	8.25	2.04E-06
479.2758@8.41	480.2828	8.41	7.66	2.04E-06
429.2887@8.88	430.2957	8.88	9.05	2.04E-06
471.3511@10.11	472.3581	10.11	7.91	2.04E-06
433.2538@10.63	434.2608	10.63	7.68	2.04E-06
777.0514@10.86	778.0584	10.86	7.51	2.04E-06
494.4137@12.86	495.4207	12.86	7.67	2.04E-06
380.7418@12.9	381.7488	12.9	7.75	2.04E-06
746.9934@12.91	748.0004	12.91	7.35	2.04E-06
368.743@12.92	369.75	12.92	7.14	2.04E-06
614.1499@12.94	615.1569	12.94	7.50	2.04E-06
617.5381@13.15	618.5451	13.15	8.17	2.04E-06
1594.0822@13.25	1595.0892	13.25	7.23	2.04E-06
1583.086@13.28	1584.093	13.28	7.22	2.04E-06
1233.8616@13.48	1234.8686	13.48	10.97	2.04E-06
1211.877@13.51	1212.884	13.51	8.83	2.04E-06
862.6089@13.85	863.6159	13.85	7.98	2.04E-06
548.4782@14.48	549.4852	14.48	7.93	2.04E-06
576.5091@14.76	577.5161	14.76	8.69	2.04E-06
490.1472@0.45	491.1542	0.45	7.47	2.04E-06
407.3091@11.39	408.3161	11.39	8.89	2.04E-06
997.6083@12.91	998.6153	12.91	7.84	2.04E-06
1170.7913@13.09	1171.7983	13.09	7.33	2.04E-06
837.6263@13.78	838.6333	13.78	8.42	2.04E-06
600.5079@14.57	601.5149	14.57	8.59	2.04E-06
833.5246@14.06	834.5316	14.06	10.56	2.04E-06
695.3779@12.81	696.3849	12.81	8.86	2.04E-06
400.7332@12.85	401.7402	12.85	7.97	2.04E-06
630.2094@9.45	631.2164	9.45	7.29	2.09E-06
729.3719@11.29	730.3789	11.29	8.00	2.09E-06
592.4523@13.01	593.4593	13.01	8.09	2.09E-06
789.0397@13.34	790.0467	13.34	9.32	2.09E-06
575.1432@0.68	576.1502	0.68	7.12	2.09E-06
463.2949@8.05	464.3019	8.05	8.86	2.09E-06
908.78@15.17	909.787	15.17	12.84	2.10E-06
670.487@10.77	671.494	10.77	8.25	2.25E-06
656.4855@12.77	657.4925	12.77	9.37	2.25E-06
726.1581@10.56	727.1651	10.56	12.67	2.42E-06
514.0959@8.33	515.1029	8.33	11.45	2.66E-06
401.7668@13.26	402.7738	13.26	8.94	3.11E-06
484.1351@7.39	485.1421	7.39	10.97	3.44E-06
717.5321@13.04	718.5391	13.04	14.31	4.62E-06
793.5674@13.17	794.5744	13.17	14.96	4.88E-06
900.7202@14.26	901.7272	14.26	12.86	5.27E-06
954.4345@11.44	955.4415	11.44	9.71	5.35E-06
1159.3259@13.35	1160.3329	13.35	7.90	5.80E-06
874.7044@14.21	875.7114	14.21	13.03	7.58E-06
614.4496@11.14	615.4566	11.14	11.97	8.94E-06
653.5896@12.12	654.5966	12.12	10.67	8.94E-06
373.0564@7.66	374.0634	7.66	10.14	1.07E-05
850.7035@14.32	851.7105	14.32	13.69	1.10E-05
733.0809@10.85	734.0879	10.85	11.76	1.12E-05
741.5302@12.95	742.5372	12.95	14.87	1.23E-05
1167.8077@13.36	1168.8147	13.36	10.69	1.36E-05
586.4581@13	587.4651	13	10.49	1.36E-05
445.2779@10.95	446.2849	10.95	12.27	1.37E-05
409.7569@13.26	410.7639	13.26	12.09	1.49E-05
414.1515@0.68	415.1585	0.68	11.74	1.51E-05
103.0912@0.41	104.0982	0.41	13.01	1.56E-05
440.7937@10.96	441.8007	10.96	11.64	1.62E-05
702.5694@13.09	703.5764	13.09	16.37	1.65E-05
881.5939@10.96	882.6009	10.96	9.41	1.75E-05

990.6603@10.84	991.6673	10.84	8.51	1.92E-05
845.1724@11.44	846.1794	11.44	12.75	2.05E-05
893.7476@14.15	894.7546	14.15	12.47	2.43E-05
880.7498@14.8	881.7568	14.8	13.89	2.91E-05
638.4862@13.14	639.4932	13.14	12.70	3.16E-05
1081.3096@13.92	1082.3166	13.92	8.59	3.24E-05
930.4638@11.44	931.4708	11.44	9.90	3.50E-05
854.7201@14.74	855.7271	14.74	12.34	3.80E-05
275.1749@5.03	276.1819	5.03	12.42	4.12E-05
549.2612@8.31	550.2682	8.31	8.29	4.19E-05
829.5598@13.22	830.5668	13.22	14.24	4.22E-05
866.7335@14.65	867.7405	14.65	8.16	4.30E-05
267.1481@6.89	268.1551	6.89	9.20	4.50E-05
1170.8248@13.3	1171.8318	13.3	11.04	5.07E-05
318.2546@12.08	319.2616	12.08	11.32	5.28E-05
694.1252@0.61	695.1322	0.61	7.66	5.45E-05
657.5309@13.07	658.5379	13.07	9.50	5.72E-05
319.0888@0.56	320.0958	0.56	7.27	5.72E-05
743.5484@13.12	744.5554	13.12	14.94	5.84E-05
1182.3188@13.3	1183.3258	13.3	7.53	6.37E-05
828.4438@12.87	829.4508	12.87	8.23	6.50E-05
798.4783@11.09	799.4853	11.09	7.24	6.71E-05
839.6983@14.04	840.7053	14.04	11.87	6.79E-05
837.4235@12.87	838.4305	12.87	7.85	6.83E-05
974.5211@13.23	975.5281	13.23	10.07	6.91E-05
779.5489@13.22	780.5559	13.22	14.53	7.08E-05
904.7511@14.64	905.7581	14.64	12.00	7.51E-05
761.4983@12.87	762.5053	12.87	14.25	7.97E-05
773.5834@13.67	774.5904	13.67	7.70	8.05E-05
666.4002@10.98	667.4072	10.98	7.28	8.08E-05
311.2836@11.77	312.2906	11.77	7.90	8.58E-05
1132.2844@14.11	1133.2914	14.11	7.04	8.69E-05
1245.8557@13.46	1246.8627	13.46	9.08	8.71E-05
783.5782@13.43	784.5852	13.43	15.50	8.82E-05
1078.1075@7.31	1079.1145	7.31	7.06	9.15E-05
1320.5587@11.44	1321.5657	11.44	7.03	9.15E-05
697.7644@11.45	698.7714	11.45	6.82	9.84E-05
871.7633@14.38	872.7703	14.38	13.95	1.02E-04
270.2647@11.96	271.2717	11.96	11.95	1.11E-04
331.3298@9.36	332.3368	9.36	12.34	1.11E-04
462.8008@10.99	463.8078	10.99	11.39	1.13E-04
869.7465@14.21	870.7535	14.21	12.96	1.13E-04
855.5745@13.46	856.5815	13.46	11.69	1.22E-04
632.1446@11.94	633.1516	11.94	9.11	1.24E-04
341.2669@2.71	342.2739	2.71	10.51	1.28E-04
873.7787@14.57	874.7857	14.57	13.73	1.62E-04
897.7773@14.43	898.7843	14.43	12.78	2.02E-04
751.5515@13.17	752.5585	13.17	11.21	2.11E-04
807.5791@13.36	808.5861	13.36	15.27	2.14E-04
861.4112@12.86	862.4182	12.86	11.06	2.42E-04
1201.3257@14.32	1202.3327	14.32	10.62	2.50E-04
753.1026@10.56	754.1096	10.56	8.01	2.52E-04
1204.312@13.29	1205.319	13.29	9.43	2.54E-04
780.1867@12.58	781.1937	12.58	8.20	2.57E-04
727.0922@10.85	728.0992	10.85	9.06	2.80E-04
570.3756@11.13	571.3826	11.13	10.97	3.02E-04
477.3805@12.22	478.3875	12.22	9.06	3.05E-04
794.6234@14.06	795.6304	14.06	13.50	3.09E-04
798.6697@14.22	799.6767	14.22	10.18	3.20E-04
1203.8094@13.28	1204.8164	13.28	9.11	3.28E-04
510.8289@11.23	511.8359	11.23	8.15	3.37E-04
598.8105@11.5	599.8175	11.5	8.44	3.47E-04
1191.315@13.29	1192.322	13.29	9.18	3.47E-04
696.4409@11.04	697.4479	11.04	11.26	3.87E-04
845.7479@14.31	846.7549	14.31	12.46	3.95E-04
723.5207@12.99	724.5277	12.99	12.50	4.07E-04
755.5475@13.25	756.5545	13.25	12.89	4.10E-04
349.9807@7.66	350.9877	7.66	7.77	4.16E-04
318.2662@11.76	319.2732	11.76	10.57	4.59E-04
562.459@13.08	563.466	13.08	8.93	4.70E-04
1204.3289@14.32	1205.3359	14.32	7.63	4.97E-04
537.5236@12.87	538.5306	12.87	11.68	5.08E-04
767.5476@13.1	768.5546	13.1	14.56	5.48E-04
398.3489@10.57	399.3559	10.57	10.25	5.89E-04
785.5958@13.6	786.6028	13.6	14.16	6.17E-04
894.7619@14.97	895.7689	14.97	6.82	7.29E-04
240.1689@7.87	241.1759	7.87	10.43	7.35E-04

608.3848@10.95	609.3918	10.95	7.51	7.89E-04
758.5353@10.86	759.5423	10.86	7.76	7.90E-04
166.0283@11.84	167.0353	11.84	12.65	8.07E-04
737.4984@12.9	738.5054	12.9	12.15	8.35E-04
321.1807@5.85	322.1877	5.85	7.29	8.94E-04
985.9878@11.45	986.9948	11.45	7.63	9.15E-04
678.1546@10.83	679.1616	10.83	10.77	9.51E-04
849.7786@14.75	850.7856	14.75	11.60	9.58E-04
617.2416@10.47	618.2486	10.47	6.63	9.93E-04
533.3321@11.07	534.3391	11.07	9.74	1.07E-03
835.6096@13.63	836.6166	13.63	10.60	1.08E-03
749.5353@13.03	750.5423	13.03	12.32	1.10E-03
726.1605@10.43	727.1675	10.43	7.69	1.17E-03
826.702@14.46	827.709	14.46	9.83	1.24E-03
847.7632@14.51	848.7702	14.51	11.76	1.24E-03
895.7631@14.27	896.7701	14.27	11.19	1.27E-03
276.1407@7.94	277.1477	7.94	9.46	1.28E-03
270.252@11.4	271.259	11.4	7.56	1.32E-03
609.178@12.94	610.185	12.94	12.62	1.33E-03
453.2863@10.57	454.2933	10.57	11.40	1.37E-03
484.8061@11.02	485.8131	11.02	10.37	1.38E-03
699.5699@12.64	700.5769	12.64	7.95	1.40E-03
396.216@7.32	397.223	7.32	8.44	1.41E-03
607.5161@13.06	608.5231	13.06	11.18	1.42E-03
446.2695@10.78	447.2765	10.78	8.25	1.42E-03
70.0796@11.84	71.0866	11.84	9.56	1.46E-03
401.6869@7.32	402.6939	7.32	9.61	1.55E-03
746.4919@12.52	747.4989	12.52	8.26	1.56E-03
468.3367@12.51	469.3437	12.51	11.70	1.63E-03
408.3472@12.79	409.3542	12.79	7.18	1.76E-03
599.1795@10.23	600.1865	10.23	9.85	1.95E-03
916.5693@11.18	917.5763	11.18	9.18	2.07E-03
902.7277@14.44	903.7347	14.44	10.03	2.13E-03
463.3595@11.86	464.3665	11.86	10.15	2.37E-03
609.534@13.18	610.541	13.18	11.40	2.54E-03
757.5643@13.38	758.5713	13.38	14.03	2.57E-03
536.1579@0.88	537.1649	0.88	9.55	2.63E-03
906.7654@14.88	907.7724	14.88	9.76	2.79E-03
366.1393@0.74	367.1463	0.74	6.39	2.89E-03
875.7942@14.8	876.8012	14.8	11.41	2.98E-03
791.5471@13.07	792.5541	13.07	11.90	3.00E-03
782.5673@11.88	783.5743	11.88	10.13	3.05E-03
542.2328@5.88	543.2398	5.88	8.39	3.05E-03
550.349@10.67	551.356	10.67	12.08	3.06E-03
303.2931@8.57	304.3001	8.57	11.63	3.28E-03
323.2135@9.46	324.2205	9.46	11.34	3.28E-03
1167.3174@13.36	1168.3244	13.36	7.13	3.59E-03
428.3661@12.94	429.3731	12.94	11.21	3.74E-03
882.765@15.11	883.772	15.11	7.52	3.92E-03
877.8104@15.11	878.8174	15.11	10.34	4.00E-03
641.2359@10.41	642.2429	10.41	8.80	4.11E-03
1012.9112@11.45	1013.9182	11.45	6.09	4.19E-03
787.4542@10.88	788.4612	10.88	6.51	4.20E-03
974.4539@11.45	975.4609	11.45	9.15	4.22E-03
1215.8105@13.27	1216.8175	13.27	7.17	4.28E-03
550.2821@5.88	551.2891	5.88	8.13	4.28E-03
398.7736@10.88	399.7806	10.88	8.83	4.77E-03
841.7179@14.03	842.7249	14.03	9.44	4.77E-03
256.1574@7.13	257.1644	7.13	8.29	4.86E-03
936.4236@11.46	937.4306	11.46	6.36	4.87E-03
276.1229@5.89	277.1299	5.89	9.59	4.93E-03
791.8876@11.44	792.8946	11.44	5.76	5.36E-03
438.2832@10.96	439.2902	10.96	9.95	5.64E-03
878.7339@14.57	879.7409	14.57	10.25	5.77E-03
245.1429@5.88	246.1499	5.88	9.20	6.39E-03
582.4342@10.69	583.4412	10.69	8.76	6.54E-03
1016.5885@11.63	1017.5955	11.63	8.52	6.57E-03
781.5634@13.28	782.5704	13.28	13.30	7.44E-03
939.5612@7.75	940.5682	7.75	9.25	7.65E-03
376.2635@10.92	377.2705	10.92	9.15	7.66E-03
489.3056@11.02	490.3126	11.02	8.51	7.66E-03
423.7712@13.49	424.7782	13.49	8.45	7.71E-03
979.2702@13.78	980.2772	13.78	9.88	8.31E-03
56.0661@9.4	57.0731	9.4	9.37	8.78E-03
313.1398@0.69	314.1468	0.69	6.13	8.82E-03
793.0508@13.33	794.0578	13.33	6.82	8.97E-03
442.274@5.88	443.281	5.88	6.97	9.54E-03

548.4797@13.1	549.4867	13.1	9.13	9.74E-03
602.5275@13.27	603.5345	13.27	9.20	9.74E-03
872.5435@11.15	873.5505	11.15	8.24	9.94E-03
431.2246@7.41	432.2316	7.41	10.08	1.02E-02
1233.3538@13.4	1234.3608	13.4	6.34	1.02E-02
311.3191@12.14	312.3261	12.14	9.30	1.03E-02
500.1057@7.41	501.1127	7.41	8.38	1.08E-02
888.5406@10.7	889.5476	10.7	8.30	1.08E-02
222.0962@6.91	223.1032	6.91	9.33	1.11E-02
370.3092@11.89	371.3162	11.89	10.24	1.11E-02
470.325@10.2	471.332	10.2	8.82	1.12E-02
960.5888@11.19	961.5958	11.19	5.79	1.13E-02
614.4893@13.18	615.4963	13.18	9.52	1.15E-02
459.2568@7.4	460.2638	7.4	8.21	1.17E-02
583.5174@13.14	584.5244	13.14	8.96	1.18E-02
745.5107@12.98	746.5177	12.98	8.51	1.20E-02
740.4675@11.06	741.4745	11.06	8.78	1.24E-02
418.7839@10.93	419.7909	10.93	7.80	1.26E-02
789.5318@12.93	790.5388	12.93	9.11	1.26E-02
982.2697@13.78	983.2767	13.78	8.79	1.27E-02
914.6948@12.51	915.7018	12.51	8.78	1.37E-02
773.5393@13.14	774.5463	13.14	9.32	1.37E-02
828.5118@11.14	829.5188	11.14	8.47	1.46E-02
1158.825@13.36	1159.832	13.36	5.74	1.48E-02
701.4882@10.74	702.4952	10.74	7.19	1.50E-02
583.4306@10.9	584.4376	10.9	8.18	1.55E-02
572.4901@13.08	573.4971	13.08	8.14	1.57E-02
594.3753@10.73	595.3823	10.73	10.52	1.57E-02
448.2806@10.14	449.2876	10.14	9.07	1.57E-02
901.81@14.87	902.817	14.87	8.93	1.60E-02
428.3668@12.54	429.3738	12.54	10.39	1.68E-02
501.2571@7.4	502.2641	7.4	6.93	1.68E-02
1053.2885@13.93	1054.2955	13.93	9.03	1.83E-02
789.5814@11.23	790.5884	11.23	6.23	1.87E-02
403.2002@6	404.2072	6	9.48	1.90E-02
347.0641@0.65	348.0711	0.65	9.17	1.96E-02
246.1267@11.41	247.1337	11.41	7.08	2.07E-02
783.5154@12.89	784.5224	12.89	7.22	2.07E-02
822.674@14.1	823.681	14.1	7.63	2.13E-02
472.0822@5.99	473.0892	5.99	8.02	2.14E-02
370.3203@9.72	371.3273	9.72	8.99	2.16E-02
460.295@11.01	461.302	11.01	8.77	2.27E-02
508.0984@7.42	509.1054	7.42	7.82	2.32E-02
702.1652@10.58	703.1722	10.58	6.55	2.43E-02
809.5944@13.51	810.6014	13.51	9.71	2.48E-02
297.09@3.01	298.097	3.01	7.05	2.55E-02
462.2954@10.56	463.3024	10.56	9.56	2.56E-02
274.2502@10.62	275.2572	10.62	7.55	2.59E-02
357.2005@9.45	358.2075	9.45	5.95	2.70E-02
71.0678@0.44	72.0748	0.44	6.19	2.71E-02
849.2428@12.8	850.2498	12.8	8.02	2.72E-02
459.2641@8.05	460.2711	8.05	7.09	2.73E-02
480.0785@5.99	481.0855	5.99	8.01	2.75E-02
787.6197@13.85	788.6267	13.85	6.97	2.77E-02
442.8016@10.94	443.8086	10.94	7.40	2.82E-02
712.4378@10.53	713.4448	10.53	8.19	2.82E-02
271.2271@2.71	272.2341	2.71	7.30	2.86E-02
1182.8217@13.34	1183.8287	13.34	6.82	2.91E-02
289.1275@0.55	290.1345	0.55	7.31	2.91E-02
558.1259@11.49	559.1329	11.49	5.40	2.96E-02
218.1673@5.88	219.1743	5.88	7.93	3.01E-02
658.7752@11.45	659.7822	11.45	7.32	3.03E-02
444.3598@12.36	445.3668	12.36	8.22	3.13E-02
926.5275@13.38	927.5345	13.38	7.01	3.28E-02
899.7934@14.64	900.8004	14.64	8.35	3.31E-02
374.2444@10.4	375.2514	10.4	8.32	3.31E-02
759.5794@13.53	760.5864	13.53	9.47	3.31E-02
843.7315@14.16	844.7385	14.16	8.10	3.39E-02
517.8281@11.07	518.8351	11.07	5.46	3.44E-02
296.2779@12.06	297.2849	12.06	7.12	3.47E-02
640.5061@13.2	641.5131	13.2	7.58	3.58E-02
454.2502@11.27	455.2572	11.27	6.10	3.61E-02
299.2859@9.19	300.2929	9.19	7.26	3.81E-02
525.4254@5.87	526.4324	5.87	5.65	3.89E-02
1020.5226@11.44	1021.5296	11.44	6.39	3.93E-02
1179.8083@13.35	1180.8153	13.35	6.50	4.07E-02
263.2255@5.89	264.2325	5.89	7.22	4.13E-02

567.3361@10.46	568.3431	10.46	7.57	4.32E-02
368.3451@12.78	369.3521	12.78	8.75	4.32E-02
247.2517@10.83	248.2587	10.83	6.68	4.32E-02
836.5497@10.95	837.5567	10.95	6.49	4.32E-02
649.6356@13.57	650.6426	13.57	7.68	4.32E-02
776.4168@7.32	777.4238	7.32	6.25	4.32E-02
497.3949@5.88	498.4019	5.88	3.53	4.40E-02
911.2738@7.32	912.2808	7.32	7.41	4.40E-02
403.1919@7.41	404.1989	7.41	8.07	4.40E-02
1191.8124@13.28	1192.8194	13.28	5.59	4.41E-02
657.9095@11.22	658.9165	11.22	5.92	4.43E-02
555.8442@11.1	556.8512	11.1	5.55	4.53E-02
821.747@14.46	822.754	14.46	7.26	4.87E-02
273.2687@7.46	274.2757	7.46	8.00	4.87E-02
294.2554@11.78	295.2624	11.78	6.65	4.92E-02

Table S5. Kidney upregulated unidentified metabolites statistically different from the rest of the studied tissues. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p (Corr)
358.1682@11.23	359.1752	11.23	14.65	9.12E-20
806.496@8.37	807.503	8.37	13.68	4.62E-16
621.2669@10.84	622.2739	10.84	15.91	7.86E-16
812.732@13.7	813.739	13.7	18.36	1.60E-15
366.1633@11.23	367.1703	11.23	14.4	2.17E-14
380.7439@10.82	381.7509	10.82	13.1	2.72E-14
388.7562@12.93	389.7632	12.93	15.01	5.08E-14
871.5801@13.01	872.5871	13.01	13.26	5.08E-14
1114.8284@13.01	1115.8354	13.01	11.75	5.08E-14
745.6456@13.68	746.6526	13.68	13.58	5.08E-14
626.5745@14.06	627.5815	14.06	13.53	5.08E-14
362.7934@13.01	363.8004	13.01	11.95	5.08E-14
203.9726@0.51	204.9796	0.51	14.36	7.73E-11
689.3995@11.31	690.4065	11.31	11.7	2.08E-10
605.3754@11.58	606.3824	11.58	11.81	2.08E-10
340.2524@11.8	341.2594	11.8	12.35	2.08E-10
598.5376@12.93	599.5446	12.93	12.62	2.08E-10
630.144@13	631.151	13	9.63	2.08E-10
1115.3538@13.01	1116.3608	13.01	10.18	2.08E-10
1083.8707@13.02	1084.8777	13.02	9.97	2.08E-10
814.7396@13.86	815.7466	13.86	14.53	2.08E-10
909.5038@14.07	910.5108	14.07	11.81	2.08E-10
894.8444@15.22	895.8514	15.22	10.74	2.08E-10
401.7665@12.97	402.7735	12.97	11.9	2.41E-10
245.1633@1.81	246.1703	1.81	13.4	8.97E-10
301.2825@8.57	302.2895	8.57	15.24	1.21E-08
394.7787@13.14	395.7857	13.14	12.81	1.32E-08
582.5325@13.02	583.5395	13.02	12.29	2.58E-08
811.6063@14.08	812.6133	14.08	13.71	3.47E-08
924.8027@14.39	925.8097	14.39	10.45	4.85E-08
369.7644@12.83	370.7714	12.83	9.2	6.83E-08
636.3469@12.83	637.3539	12.83	11.25	6.83E-08
385.7738@13.46	386.7808	13.46	9.27	6.83E-08
827.7032@13.82	828.7102	13.82	10.55	6.83E-08
426.3517@13.88	427.3587	13.88	10.53	6.83E-08
261.1558@0.79	262.1628	0.79	9.4	6.83E-08
370.7815@13.02	371.7885	13.02	10.05	6.83E-08
719.5795@13.37	720.5865	13.37	10.13	6.84E-08
326.2211@11.22	327.2281	11.22	11.63	9.47E-08
670.4428@9.5	671.4498	9.5	13.71	1.50E-07
537.5494@12.9	538.5564	12.9	12.49	1.54E-07
719.6284@13.67	720.6354	13.67	10.87	1.56E-07
614.1857@13	615.1927	13	11.17	5.79E-07
316.2477@11.83	317.2547	11.83	11.98	7.15E-07
317.2947@9	318.3017	9	11.52	1.13E-06
694.6259@14.92	695.6329	14.92	11.24	1.35E-06
402.7646@13.13	403.7716	13.13	10.66	1.50E-06
370.1042@0.59	371.1112	0.59	11.63	1.80E-06
845.798@14.42	846.805	14.42	14.04	2.57E-06
852.7884@14.67	853.7954	14.67	11.64	2.57E-06
908.8559@15.48	909.8629	15.48	11.02	2.80E-06
335.2908@11.76	336.2978	11.76	13.66	2.88E-06
882.8312@15.39	883.8382	15.39	11.41	3.20E-06

646.5907@13.63	647.5977	13.63	10.88	3.37E-06
950.5492@13.25	951.5562	13.25	9.3	4.32E-06
501.4028@0.55	502.4098	0.55	7.49	4.68E-06
290.983@0.59	291.99	0.59	7.51	4.68E-06
750.4318@6.03	751.4388	6.03	7.03	4.68E-06
976.5723@10.8	977.5793	10.8	6.57	4.68E-06
722.0831@13.01	723.0901	13.01	7.88	4.68E-06
717.5816@13.07	718.5886	13.07	14.27	4.68E-06
410.2816@13.27	411.2886	13.27	7.91	4.68E-06
377.7827@13.46	378.7897	13.46	7.09	4.68E-06
1173.8777@13.47	1174.8847	13.47	7.06	4.68E-06
398.7838@13.49	399.7908	13.49	8.28	4.68E-06
826.7638@14.58	827.7708	14.58	12.51	4.68E-06
648.1455@10.26	649.1525	10.26	7.19	4.68E-06
576.5475@15	577.5545	15	8.6	4.68E-06
535.5348@12.77	536.5418	12.77	8.47	4.68E-06
1222.4199@10.83	1223.4269	10.83	8.5	5.37E-06
214.1214@5	215.1284	5	13.04	5.92E-06
874.783@14.31	875.79	14.31	12.75	6.21E-06
862.7589@14.59	863.7659	14.59	12.49	6.47E-06
765.5759@12.99	766.5829	12.99	13.78	1.35E-05
390.7915@13.48	391.7985	13.48	8.57	3.21E-05
1201.417@14.42	1202.424	14.42	9.34	3.64E-05
552.4954@12.88	553.5024	12.88	9.99	3.84E-05
302.1208@0.81	303.1278	0.81	10.17	3.88E-05
854.8015@14.91	855.8085	14.91	10.84	4.35E-05
248.1403@0.43	249.1473	0.43	10.98	4.51E-05
839.7269@14.14	840.7339	14.14	11.73	4.67E-05
849.5797@13.14	850.5867	13.14	9.39	4.93E-05
828.5118@11.14	829.5188	11.14	12.57	6.39E-05
850.7502@14.4	851.7572	14.4	11.86	6.82E-05
586.5059@13.06	587.5129	13.06	11.08	8.03E-05
588.3411@9.4	589.3481	9.4	8.08	1.08E-04
321.2689@11.21	322.2759	11.21	12.23	1.13E-04
400.766@12.87	401.773	12.87	8.32	1.29E-04
702.6095@13.05	703.6165	13.05	15.09	1.29E-04
928.829@14.78	929.836	14.78	7.28	1.33E-04
649.4105@11.02	650.4175	11.02	10.47	1.51E-04
606.5944@13.62	607.6014	13.62	7.57	1.53E-04
837.4774@12.92	838.4844	12.92	7.65	1.53E-04
715.5595@12.94	716.5665	12.94	13.84	1.58E-04
361.2302@7.32	362.2372	7.32	11.12	1.66E-04
878.8022@14.7	879.8092	14.7	11.07	1.86E-04
611.5864@13.37	612.5934	13.37	7.56	1.98E-04
318.2662@11.76	319.2732	11.76	11.44	2.02E-04
905.2976@13.68	906.3046	13.68	11.46	2.05E-04
512.1651@8.37	513.1721	8.37	11.1	2.29E-04
590.487@13.33	591.494	13.33	10.49	2.29E-04
496.8062@10.81	497.8132	10.81	10.96	2.44E-04
614.2233@10.27	615.2303	10.27	10.62	2.60E-04
452.2179@11.14	453.2249	11.14	12.8	2.80E-04
475.3669@10.29	476.3739	10.29	11.84	3.01E-04
370.1053@0.8	371.1123	0.8	8.42	3.10E-04
789.599@14.33	790.606	14.33	9.23	3.33E-04
897.8311@14.54	898.8381	14.54	11.85	3.67E-04
899.8472@14.77	900.8542	14.77	11.66	4.00E-04
731.5861@13.28	732.5931	13.28	10.29	4.25E-04
757.5959@13.35	758.6029	13.35	11.86	4.36E-04
871.8373@14.48	872.8443	14.48	12.56	5.65E-04
289.1275@0.55	290.1345	0.55	10.7	6.06E-04
797.5844@13.07	798.5914	13.07	9.38	6.19E-04
794.6813@14.14	795.6883	14.14	14.1	6.20E-04
879.5351@13.29	880.5421	13.29	9.06	6.51E-04
760.45@11.14	761.457	11.14	10.23	6.61E-04
1064.4882@10.28	1065.4952	10.28	9.03	7.87E-04
550.2853@5.9	551.2923	5.9	8.15	8.08E-04
643.2297@10.45	644.2367	10.45	9.71	8.11E-04
381.7096@7.33	382.7166	7.33	9.92	9.90E-04
482.3112@11.03	483.3182	11.03	12.21	9.93E-04
923.3179@13.02	924.3249	13.02	10	1.04E-03
749.5898@13.06	750.5968	13.06	13.19	1.08E-03
832.6794@13.82	833.6864	13.82	8.95	1.13E-03
906.8132@15.05	907.8202	15.05	9.74	1.16E-03
739.5772@12.93	740.5842	12.93	11.13	1.21E-03
1074.11@7.32	1075.117	7.32	7.01	1.34E-03
974.5731@13.19	975.5801	13.19	6.68	1.52E-03
1257.5342@11.49	1258.5412	11.49	6.37	1.56E-03

1025.3895@13.73	1026.3965	13.73	7.12	1.64E-03
449.3552@10.04	450.3622	10.04	10.01	1.81E-03
790.6768@13.81	791.6838	13.81	6.99	1.87E-03
971.6362@10.78	972.6432	10.78	9.11	1.90E-03
693.0969@5.88	694.1039	5.88	7.52	1.97E-03
767.5803@13.12	768.5873	13.12	13.51	2.02E-03
450.3098@10.71	451.3168	10.71	7.02	2.05E-03
932.5641@10.75	933.5711	10.75	9.06	2.09E-03
327.2565@10.3	328.2635	10.3	9.65	2.10E-03
787.6714@13.76	788.6784	13.76	9.41	2.10E-03
873.8271@14.7	874.8341	14.7	10.8	2.17E-03
148.0328@11.91	149.0398	11.91	10.76	2.48E-03
1039.7206@11.08	1040.7276	11.08	9.4	2.63E-03
875.8459@14.95	876.8529	14.95	11.25	2.65E-03
278.0923@7.91	279.0993	7.91	10.33	2.83E-03
895.8098@14.36	896.8168	14.36	10.66	2.91E-03
380.762@13	381.769	13	7.72	3.09E-03
368.3682@12.83	369.3752	12.83	10.28	3.10E-03
428.2551@11.14	429.2621	11.14	10.34	3.30E-03
880.8282@14.94	881.8352	14.94	10.75	3.30E-03
635.4114@6.97	636.4184	6.97	9.42	3.41E-03
847.8362@14.62	848.8432	14.62	10.77	3.53E-03
612.2774@9.49	613.2844	9.49	8.46	3.66E-03
916.5693@11.18	917.5763	11.18	9.17	3.70E-03
824.7364@14.34	825.7434	14.34	10.13	4.10E-03
748.5973@13.83	749.6043	13.83	7.89	4.37E-03
257.1267@5.89	258.1337	5.89	9.46	4.69E-03
979.3156@13.82	980.3226	13.82	9.96	5.62E-03
1293.0837@11.47	1294.0907	11.47	7.32	5.81E-03
723.57@13.01	724.577	13.01	11.77	6.03E-03
777.0932@10.53	778.1002	10.53	6.38	6.09E-03
503.3284@6.19	504.3354	6.19	9.05	6.51E-03
563.2055@10.24	564.2125	10.24	10.28	6.57E-03
276.1229@5.89	277.1299	5.89	9.77	6.64E-03
533.8404@11.08	534.8474	11.08	7.6	6.64E-03
471.826@11.34	472.833	11.34	6.64	6.64E-03
1132.3765@14.18	1133.3835	14.18	6.29	6.64E-03
424.3467@12.29	425.3537	12.29	8.41	6.89E-03
908.2879@13.67	909.2949	13.67	7.66	6.92E-03
599.1795@10.23	600.1865	10.23	9.31	6.92E-03
543.4911@12.9	544.4981	12.9	7.53	7.08E-03
384.1262@0.89	385.1332	0.89	6.17	7.75E-03
846.6871@14	847.6941	14	8.55	7.85E-03
566.2765@5.89	567.2835	5.89	7.95	7.99E-03
726.1581@10.56	727.1651	10.56	8.74	7.99E-03
605.2496@10.44	606.2566	10.44	8.56	8.12E-03
338.3005@13.36	339.3075	13.36	6.5	8.29E-03
616.5434@13.31	617.5504	13.31	7.42	8.41E-03
360.2668@10.24	361.2738	10.24	9.55	8.46E-03
904.8216@14.77	905.8286	14.77	8.9	8.88E-03
398.2466@10.01	399.2536	10.01	9.56	9.51E-03
888.5406@10.7	889.5476	10.7	8.74	9.51E-03
759.5502@12.87	760.5572	12.87	6.89	1.04E-02
384.2853@10.4	385.2923	10.4	9.82	1.12E-02
787.0354@13.21	788.0424	13.21	6.28	1.14E-02
753.5683@13.03	754.5753	13.03	7.2	1.17E-02
901.8735@15.05	902.8805	15.05	8.42	1.17E-02
609.2104@12.98	610.2174	12.98	10.58	1.35E-02
798.7368@14.3	799.7438	14.3	8.33	1.38E-02
528.1448@8.35	529.1518	8.35	8.97	1.44E-02
493.8339@11.35	494.8409	11.35	6.99	1.47E-02
460.295@11.01	461.302	11.01	9.59	1.49E-02
751.5833@13.19	752.5903	13.19	9.95	1.57E-02
262.9841@0.51	263.9911	0.51	7.31	1.62E-02
351.239@10.7	352.246	10.7	9.47	1.62E-02
876.7811@14.46	877.7881	14.46	8.15	1.62E-02
333.1858@5.64	334.1928	5.64	7.14	1.62E-02
574.3544@6.74	575.3614	6.74	5.82	1.62E-02
453.2863@10.57	454.2933	10.57	9.49	1.62E-02
402.234@10.75	403.241	10.75	6.6	1.62E-02
496.1975@10.26	497.2045	10.26	6.63	1.69E-02
213.0832@6.22	214.0902	6.22	9.39	1.97E-02
70.0913@11.88	71.0983	11.88	7.67	2.04E-02
612.2208@12.97	613.2278	12.97	7.96	2.12E-02
1127.3804@14.17	1128.3874	14.17	7.31	2.19E-02
821.7952@14.57	822.8022	14.57	7.63	2.21E-02
401.6869@7.32	402.6939	7.32	7.69	2.28E-02

864.7008@13.85	865.7078	13.85	6.9	2.30E-02
306.0749@0.46	307.0819	0.46	8.68	2.36E-02
1122.6729@11.14	1123.6799	11.14	5.26	2.52E-02
594.3753@10.73	595.3823	10.73	10.15	2.54E-02
273.2536@7.47	274.2606	7.47	8.78	2.54E-02
318.2742@10.72	319.2812	10.72	6.37	2.66E-02
591.3824@6.73	592.3894	6.73	7.63	2.78E-02
374.2444@10.4	375.2514	10.4	8.76	2.85E-02
452.7829@10.7	453.7899	10.7	7.09	2.87E-02
218.1673@5.88	219.1743	5.88	8.14	2.89E-02
263.2255@5.89	264.2325	5.89	7.75	2.98E-02
723.5613@7.32	724.5683	7.32	7.22	3.01E-02
702.1652@10.58	703.1722	10.58	6.45	3.06E-02
785.639@13.6	786.646	13.6	7.9	3.09E-02
554.2316@5.89	555.2386	5.89	6.43	3.12E-02
761.6437@13.77	762.6507	13.77	7.52	3.13E-02
869.7999@14.28	870.8069	14.28	8.26	3.17E-02
462.2954@10.56	463.3024	10.56	9.43	3.17E-02
789.5794@11.31	790.5864	11.31	7.89	3.22E-02
638.3999@10.8	639.4069	10.8	7.72	3.23E-02
822.7145@14.19	823.7215	14.19	7.01	3.50E-02
563.2033@10.35	564.2103	10.35	6.36	3.52E-02
584.2236@10.86	585.2306	10.86	8.16	3.52E-02
562.4969@13.16	563.5039	13.16	7.38	3.63E-02
536.1401@8.34	537.1471	8.34	7.76	3.63E-02
506.3228@10.63	507.3298	10.63	9.29	3.63E-02
526.34@11.09	527.347	11.09	8.3	3.63E-02
275.1749@5.03	276.1819	5.03	7.59	3.68E-02
256.1574@7.13	257.1644	7.13	6.61	3.84E-02
376.1244@9.47	377.1314	9.47	7.69	3.93E-02
902.7899@14.53	903.7969	14.53	7.06	3.95E-02
606.543@12.82	607.55	12.82	6.86	3.97E-02
357.2005@9.45	358.2075	9.45	5.67	4.00E-02
330.2217@10.3	331.2287	10.3	6.85	4.00E-02
226.1693@5.88	227.1763	5.88	7.76	4.11E-02
574.2714@5.89	575.2784	5.89	6.77	4.19E-02
548.3469@11.1	549.3539	11.1	7.05	4.19E-02
408.7575@10.62	409.7645	10.62	5.91	4.24E-02
205.1635@9.39	206.1705	9.39	6.72	4.27E-02
657.9095@11.22	658.9165	11.22	6.06	4.38E-02
376.289@11.62	377.296	11.62	6.48	4.44E-02
424.1211@7.43	425.1281	7.43	5.93	4.57E-02
220.1457@8.72	221.1527	8.72	7.04	4.59E-02
599.1788@10.31	600.1858	10.31	7.22	4.68E-02
995.6952@11.05	996.7022	11.05	7.01	4.74E-02
271.2271@2.71	272.2341	2.71	6.76	4.84E-02

8.3 Annex 3

This section contains all the information of the concentrations obtained for each lipid specie at the targeted lipidomic analysis. Furthermore, after each table of lipid concentration, results from the statistic test one-way ANOVA with a Tuckey post hoc are represented.

8.3.1. Fatty acyls

Table S6. Fatty acylcarnitine concentration detected by targeted lipidomic analysis in all the studied tissues.

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Acyl carnitines							
AcylCarnitine(12:0)	0.11 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	1.07 ± 0.27	1.04 ± 0.18	0.12 ± 0.01	0.18 ± 0.01
AcylCarnitine(13:0)	0.08 ± 0.01	0.08 ± 0.01	0.08 ± 0.004	0.11 ± 0.01	0.11 ± 0.01	0.06 ± 0.004	0.08 ± 0.01
AcylCarnitine(14:0)	0.10 ± 0.01	0.15 ± 0.02	0.21 ± 0.01	4.08 ± 1.21	4.26 ± 0.87	0.21 ± 0.03	0.36 ± 0.05
AcylCarnitine(14:1)	0.09 ± 0.01	0.09 ± 0.01	0.08 ± 0.01	1.36 ± 0.40	1.37 ± 0.25	0.11 ± 0.01	0.18 ± 0.02
AcylCarnitine(14:2)	0.03 ± 0.004	0.04 ± 0.005	0.03 ± 0.003	0.35 ± 0.11	0.36 ± 0.06	0.03 ± 0.004	0.06 ± 0.01
AcylCarnitine(15:0) (a)	0.02 ± 0.003	0.03 ± 0.004	0.02 ± 0.003	0.08 ± 0.02	0.08 ± 0.02	0.02 ± 0.001	0.03 ± 0.002
AcylCarnitine(15:0) (b)	0.02 ± 0.003	0.02 ± 0.003	0.03 ± 0.003	0.31 ± 0.09	0.26 ± 0.06	0.02 ± 0.003	0.04 ± 0.01
AcylCarnitine(16:0)	0.32 ± 0.04	0.62 ± 0.10	2.52 ± 0.28	49.94 ± 16.40	37.25 ± 9.44	0.66 ± 0.13	2.02 ± 0.38
AcylCarnitine(16:1)	0.09 ± 0.01	0.12 ± 0.02	0.11 ± 0.00	6.41 ± 2.12	5.36 ± 1.26	0.14 ± 0.03	0.34 ± 0.07
AcylCarnitine(17:0) (a)	0.13 ± 0.03	0.18 ± 0.06	0.17 ± 0.01	0.55 ± 0.14	0.47 ± 0.10	0.13 ± 0.02	0.15 ± 0.01
AcylCarnitine(17:0) (b)	0.05 ± 0.01	0.06 ± 0.01	0.11 ± 0.01	0.57 ± 0.16	0.48 ± 0.10	0.04 ± 0.003	0.06 ± 0.01
AcylCarnitine(18:0)	0.29 ± 0.04	1.43 ± 0.24	8.27 ± 0.71	24.16 ± 5.19	23.20 ± 5.20	0.23 ± 0.03	0.63 ± 0.09
AcylCarnitine(18:1)	0.28 ± 0.04	0.88 ± 0.17	0.74 ± 0.05	48.18 ± 15.45	34.98 ± 9.44	0.47 ± 0.08	1.46 ± 0.30
AcylCarnitine(18:2)	0.68 ± 0.03	0.86 ± 0.08	0.73 ± 0.03	14.59 ± 5.07	10.13 ± 2.64	0.65 ± 0.05	1.04 ± 0.12

Values are represented as mean and standard error in nmol/g tissue.

Table S7. Statistic multiple comparison post hoc Tuckey of the fatty acylcarnitines between all the studied tissues.

		p value													
		AcylCarnitines													
		(12:0)	(13:0)	(14:0)	(14:1)	(14:2)	(15:0) (a)	(15:0) (b)	(16:0)	(16:1)	(17:0) (a)	(17:0) (b)	(18:0)	(18:1)	(18:2)
Liver	Heart	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000
	Kidney	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.998	.466	1.000	1.000
	Gluteus	**.000**	.128	**.000**	**.000**	**.001**	**.010**	**.000**	**.001**	**.001**	**.005**	**.000**	**.000**	**.001**	**.002**
	Soleus	**.000**	.367	**.000**	**.001**	**.001**	**.026**	**.007**	**.031**	**.013**	.051	**.006**	**.000**	**.036**	.105
	VAT	1.000	.480	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	SAT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Heart	Liver	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000
	Kidney	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.998	.644	1.000	1.000
	Gluteus	**.000**	.095	**.001**	**.000**	**.001**	**.023**	**.000**	**.001**	**.001**	**.019**	**.000**	**.000**	**.001**	**.002**
	Soleus	**.000**	.298	**.001**	**.001**	**.002**	.055	**.008**	**.033**	**.014**	.144	**.007**	**.000**	**.041**	.118
	VAT	1.000	.571	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000
	SAT	1.000	.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
Kidney	Liver	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.998	.466	1.000	1.000
	Heart	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.998	.644	1.000	1.000
	Gluteus	**.000**	.078	**.001**	**.001**	**.002**	**.019**	**.001**	**.003**	**.002**	**.028**	**.003**	**.012**	**.001**	**.004**
	Soleus	**.001**	.241	**.001**	**.001**	**.003**	**.043**	**.018**	.075	**.023**	.171	**.043**	**.030**	.060	.148
	VAT	1.000	.793	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.994	.489	1.000	1.000
	SAT	1.000	.994	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.631	1.000	1.000
Gluteus	Liver	**.000**	.128	**.000**	**.000**	**.001**	**.010**	**.000**	**.001**	**.001**	**.005**	**.000**	**.000**	**.001**	**.002**
	Heart	**.000**	.095	**.001**	**.000**	**.001**	**.023**	**.000**	**.001**	**.001**	**.019**	**.000**	**.000**	**.001**	**.002**
	Kidney	**.000**	.078	**.001**	**.001**	**.002**	**.019**	**.001**	**.003**	**.002**	**.028**	**.003**	**.012**	**.001**	**.004**
	Soleus	1.000	.999	1.000	1.000	1.000	1.000	.991	.935	.993	.995	.987	1.000	.905	.875
	VAT	**.000**	**.001**	**.001**	**.001**	**.001**	**.011**	**.001**	**.001**	**.001**	**.007**	**.000**	**.000**	**.001**	**.003**
	SAT	**.001**	.361	**.004**	**.004**	**.007**	.058	**.004**	**.004**	**.005**	**.025**	**.002**	**.000**	**.003**	**.008**
Soleus	Liver	**.000**	.367	**.000**	**.001**	**.001**	**.026**	**.007**	**.031**	**.013**	.051	**.006**	**.000**	**.036**	.105
	Heart	**.000**	.298	**.001**	**.001**	**.002**	.055	**.008**	**.033**	**.014**	.144	**.007**	**.000**	**.041**	.118
	Kidney	**.001**	.241	**.001**	**.001**	**.003**	**.043**	**.018**	.075	**.023**	.171	**.043**	**.030**	.060	.148
	Gluteus	1.000	.999	1.000	1.000	1.000	1.000	.991	.935	.993	.995	.987	1.000	.905	.875
	VAT	**.001**	**.008**	**.001**	**.001**	**.002**	**.027**	**.011**	**.041**	**.018**	.060	**.006**	**.000**	**.045**	.120
	SAT	**.003**	.668	**.004**	**.006**	**.010**	.111	**.040**	.087	**.046**	.145	**.021**	**.000**	.089	.211
VAT	Liver	1.000	.480	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Heart	1.000	.571	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000
	Kidney	1.000	.793	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.994	.489	1.000	1.000
	Gluteus	**.000**	**.001**	**.001**	**.001**	**.001**	**.011**	**.001**	**.001**	**.001**	**.007**	**.000**	**.000**	**.001**	**.003**
	Soleus	**.001**	**.008**	**.001**	**.001**	**.002**	**.027**	**.011**	**.041**	**.018**	.060	**.006**	**.000**	**.045**	.120
	SAT	1.000	.403	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
SAT	Liver	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Heart	1.000	.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Kidney	1.000	.994	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.631	1.000	1.000
	Gluteus	**.001**	.361	**.004**	**.004**	**.007**	.058	**.004**	**.004**	**.005**	**.025**	**.002**	**.000**	**.003**	**.008**
	Soleus	**.003**	.668	**.004**	**.006**	**.010**	.111	**.040**	.087	**.046**	.145	**.021**	**.000**	.089	.211
	VAT	1.000	.403	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

p values < 0.05 are represented in bold numbers.

8.3.2. Glycerolipids

Table S8. Glycerolipid concentration detected by targeted lipidomic analysis in all the studied tissues. Lipid species detected were 20 DAGs, 44 TAGs and 3 TAG(O-).

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Diacylglycerols							
DAG(14:0/16:0)	6.82 ± 0.70	5.38 ± 0.43	12.00 ± 1.04	4.16 ± 0.18	5.73 ± 0.63	16.57 ± 2.49	39.57 ± 4.93
DAG(16:0/16:0)	334.6 ± 29.40	334.6 ± 32.94	1,086 ± 78.37	169.1 ± 5.18	237.8 ± 21.45	1,063 ± 177.0	2,160 ± 254.8
DAG(16:0/16:1)	121.7 ± 21.30	24.03 ± 2.44	55.32 ± 5.41	22.04 ± 1.69	35.32 ± 5.56	214.9 ± 43.22	860.1 ± 82.56
DAG(14:0/18:2)	92.21 ± 9.22	19.01 ± 1.95	10.09 ± 0.93	7.61 ± 0.70	26.01 ± 6.11	215.5 ± 35.41	672.9 ± 88.57
DAG(16:0/18:1)	2,010 ± 169.5	649.6 ± 69.00	738.1 ± 74.65	261.6 ± 14.12	444.6 ± 59.20	2,621 ± 420.6	7,080 ± 776.9
DAG(16:1/18:1)	228.3 ± 38.40	22.77 ± 2.49	17.08 ± 1.90	20.93 ± 2.03	40.08 ± 8.23	298.32 ± 60.03	1,429 ± 125.6
DAG(16:0/18:2)	2,007 ± 113.5	312.3 ± 35.66	338.5 ± 35.40	83.42 ± 5.82	227.5 ± 36.92	3,530.37 ± 620.54	10,161 ± 1,567
DAG(18:0/18:1)	176.2 ± 14.57	83.12 ± 9.17	77.62 ± 5.48	41.08 ± 3.04	67.37 ± 8.25	274.1 ± 41.25	725.2 ± 62.93
DAG(18:1/18:1)	1,883 ± 198.6	342.6 ± 37.91	181.7 ± 14.14	153.1 ± 11.83	315.9 ± 51.25	2,203 ± 344.6	7,063 ± 678.5
DAG(18:0/18:2)	308.07 ± 13.48	250.7 ± 29.48	224.2 ± 18.08	42.58 ± 2.82	112.1 ± 16.11	573.1 ± 91.33	1,149 ± 143.3
DAG(18:1/18:2)	3,112 ± 277.0	399.4 ± 53.87	164.0 ± 14.57	102.6 ± 8.67	331.8 ± 66.83	5,082.08 ± 924.22	16,931 ± 2,439
DAG(18:2/18:2)	1,192 ± 111.2	114.6 ± 16.53	38.27 ± 3.99	20.69 ± 2.50	89.03 ± 17.96	1,548 ± 254.0	4,497 ± 708.6
DAG(18:1/18:3)	247.6 ± 21.78	17.75 ± 2.39	7.76 ± 0.58	4.69 ± 0.39	15.25 ± 2.80	246.0 ± 43.86	670.5 ± 93.28
DAG(16:0/20:4)	250.6 ± 31.42	74.36 ± 7.49	251.7 ± 16.62	27.18 ± 1.11	32.09 ± 3.41	59.22 ± 12.99	172.0 ± 20.62
DAG(18:1/20:3)	59.22 ± 5.43	21.70 ± 1.61	17.38 ± 1.78	16.34 ± 2.44	22.15 ± 3.70	56.54 ± 10.47	146.6 ± 13.72
DAG(18:0/20:4)	977.1 ± 106.44	877.1 ± 136.36	1,459 ± 122.5	408.7 ± 44.29	408.2 ± 122.64	100.2 ± 19.61	374.8 ± 38.54
DAG(18:1/20:4)	305.4 ± 21.73	70.23 ± 7.14	83.92 ± 5.94	13.74 ± 0.58	24.01 ± 3.47	77.34 ± 17.08	269.8 ± 32.92
DAG(16:0/22:5)	51.72 ± 6.39	50.78 ± 5.05	53.80 ± 5.46	22.73 ± 1.69	30.98 ± 5.03	75.29 ± 17.57	172.7 ± 20.03
DAG(18:2/20:4)	596.4 ± 62.93	72.47 ± 6.56	33.92 ± 2.05	10.21 ± 0.58	24.21 ± 3.80	112.7 ± 23.76	327.3 ± 43.43
DAG(16:0/22:6)	68.01 ± 9.78	39.34 ± 4.01	60.04 ± 5.74	24.47 ± 1.48	29.50 ± 4.97	48.09 ± 12.39	107.4 ± 14.25
Triacylglycerols							
TAG(14:0/16:0/18:2)	82.97 ± 14.99	14.45 ± 1.90	14.31 ± 1.16	59.09 ± 9.26	71.38 ± 8.11	424.6 ± 16.37	1,191 ± 50.95
TAG(14:0/16:1/18:1)	26.74 ± 5.65	4.55 ± 0.39	3.36 ± 0.30	18.97 ± 2.73	20.47 ± 3.30	95.14 ± 7.78	367.6 ± 24.98
TAG(14:0/16:1/18:2)	31.61 ± 5.65	3.27 ± 0.46	2.03 ± 0.19	10.12 ± 2.03	18.41 ± 2.86	341.6 ± 29.94	1,160 ± 61.00
TAG(14:0/18:0/18:1)	1.14 ± 0.11	0.96 ± 0.07	0.79 ± 0.04	1.71 ± 0.14	3.06 ± 0.33	8.54 ± 0.29	20.63 ± 1.11
TAG(14:0/18:2/18:2)	49.84 ± 6.26	3.60 ± 0.83	2.37 ± 0.19	4.69 ± 0.94	15.72 ± 2.42	304.0 ± 23.37	623.3 ± 37.37
TAG(14:1/16:0/18:1)	6.17 ± 1.14	1.81 ± 0.16	0.80 ± 0.07	4.64 ± 0.70	4.33 ± 0.56	16.20 ± 1.26	54.83 ± 3.63
TAG(14:1/16:1/18:0)	96.79 ± 22.47	10.34 ± 0.83	10.71 ± 1.13	88.56 ± 15.19	64.00 ± 9.69	266.4 ± 30.85	1,231 ± 95.35
TAG(14:1/18:0/18:2)	1.43 ± 0.17	0.87 ± 0.10	0.35 ± 0.03	1.85 ± 0.31	2.02 ± 0.25	7.00 ± 0.36	25.81 ± 1.25
TAG(14:1/18:1/18:1)	41.56 ± 5.72	6.63 ± 1.05	4.96 ± 0.34	22.84 ± 3.97	30.60 ± 3.82	154.5 ± 6.48	510.9 ± 16.93
TAG(15:0/16:0/18:1)	4.83 ± 0.42	2.77 ± 0.16	3.53 ± 0.39	3.62 ± 0.36	5.46 ± 0.58	21.20 ± 0.83	54.90 ± 1.20
TAG(15:0/18:1/18:1)	10.27 ± 1.21	1.42 ± 0.16	1.12 ± 0.10	1.88 ± 0.30	4.23 ± 0.69	35.23 ± 1.70	96.48 ± 1.97
TAG(16:0/16:0/16:0)	34.01 ± 4.28	30.00 ± 2.46	49.95 ± 6.24	32.50 ± 3.48	56.69 ± 5.24	263.7 ± 23.80	517.2 ± 48.41
TAG(16:0/16:0/18:0)	18.56 ± 1.95	14.59 ± 1.47	35.15 ± 6.87	12.84 ± 1.33	30.19 ± 5.20	251.8 ± 24.62	389.6 ± 30.10
TAG(16:0/16:0/18:1)	218.9 ± 18.60	103.2 ± 10.30	162.5 ± 19.54	115.7 ± 13.98	195.9 ± 19.28	1,080 ± 30.13	2,334 ± 47.65
TAG(16:0/16:0/18:2)	121.5 ± 6.83	74.29 ± 7.85	147.9 ± 24.45	61.35 ± 6.60	147.6 ± 17.16	664.2 ± 28.14	1,163 ± 30.27
TAG(16:0/16:1/18:1)	234.3 ± 33.08	30.15 ± 3.58	26.19 ± 1.75	118.1 ± 16.87	118.1 ± 12.92	467.6 ± 24.58	1,591 ± 58.76
TAG(16:0/18:0/18:1)	62.59 ± 7.33	25.02 ± 3.03	24.23 ± 3.30	30.18 ± 4.45	70.34 ± 13.27	874.4 ± 56.90	1,771 ± 92.50

TAG(16:0/18:1/18:1)	689.5 ± 45.23	104.6 ± 12.50	73.11 ± 3.69	147.2 ± 21.99	236.1 ± 28.57	1,283 ± 28.88	3,101 ± 32.47
TAG(16:0/18:1/18:2)	818.3 ± 35.27	147.3 ± 20.41	101.3 ± 4.96	141.0 ± 19.68	289.3 ± 28.72	1,258 ± 24.60	2,864 ± 49.13
TAG(16:0/18:2/18:2)	672.2 ± 33.10	76.06 ± 11.74	61.70 ± 4.47	62.06 ± 10.71	177.3 ± 24.81	980.7 ± 22.89	1,840 ± 48.92
TAG(16:1/16:1/16:1)	12.31 ± 2.89	1.16 ± 0.11	1.09 ± 0.11	9.82 ± 2.03	9.06 ± 1.66	109.8 ± 11.64	589.0 ± 43.57
TAG(16:1/16:1/18:0)	1.48 ± 0.12	1.66 ± 0.16	1.15 ± 0.05	3.33 ± 0.33	5.89 ± 0.65	11.38 ± 0.50	26.63 ± 1.28
TAG(16:1/16:1/18:1)	123.29 ± 14.34	15.14 ± 2.26	13.85 ± 1.02	60.89 ± 11.09	77.15 ± 8.94	401.1 ± 19.48	1,258 ± 49.14
TAG(16:1/18:1/18:1)	55.16 ± 5.69	13.30 ± 1.60	10.91 ± 0.98	45.06 ± 7.55	48.56 ± 5.75	144.3 ± 10.10	580.7 ± 30.72
TAG(16:1/18:1/18:2)	174.6 ± 13.26	29.63 ± 4.73	23.64 ± 2.02	63.41 ± 12.61	104.9 ± 11.59	502.1 ± 22.22	1,608 ± 51.28
TAG(16:0/16:1/17:0)	11.03 ± 1.09	5.92 ± 0.39	7.19 ± 0.80	8.25 ± 0.86	11.60 ± 1.02	40.75 ± 1.44	101.5 ± 3.21
TAG(16:0/17:0/18:0)	1.11 ± 0.11	1.07 ± 0.08	1.26 ± 0.19	0.87 ± 0.10	1.81 ± 0.28	26.61 ± 2.60	45.91 ± 4.39
TAG(14:0/17:0/18:1)	6.03 ± 0.55	4.13 ± 0.24	5.55 ± 0.62	4.98 ± 0.48	7.18 ± 0.79	26.54 ± 1.39	64.55 ± 1.62
TAG(16:0/17:0/18:1)	9.61 ± 1.11	3.72 ± 0.30	4.58 ± 0.68	3.99 ± 0.46	8.51 ± 1.36	107.3 ± 9.16	222.7 ± 8.73
TAG(16:1/17:0/18:1)	38.86 ± 5.26	5.25 ± 0.48	4.37 ± 0.36	8.18 ± 1.19	14.86 ± 1.71	105.8 ± 4.98	324.1 ± 10.71
TAG(17:0/18:1/18:1)	11.60 ± 1.29	2.04 ± 0.30	1.44 ± 0.12	2.29 ± 0.41	6.56 ± 1.43	162.8 ± 15.10	373.5 ± 17.85
TAG(16:0/17:0/18:2)	23.96 ± 3.26	4.02 ± 0.48	3.79 ± 0.42	4.96 ± 0.73	13.45 ± 2.38	120.8 ± 7.25	261.4 ± 6.15
TAG(18:0/18:0/18:0)	0.94 ± 0.06	0.59 ± 0.03	0.70 ± 0.05	0.58 ± 0.01	0.72 ± 0.05	5.92 ± 0.73	6.29 ± 0.69
TAG(18:0/18:0/18:1)	5.66 ± 0.45	3.06 ± 0.28	2.65 ± 0.27	2.57 ± 0.30	6.16 ± 1.30	193.5 ± 19.48	300.8 ± 30.07
TAG(18:0/18:1/18:1)	46.73 ± 3.13	18.79 ± 2.50	11.39 ± 0.71	20.89 ± 3.82	57.20 ± 12.03	914.1 ± 64.25	1,863 ± 107.6
TAG(18:0/18:2/18:2)	34.30 ± 2.40	15.61 ± 1.98	8.64 ± 0.66	7.20 ± 1.01	30.07 ± 5.56	207.7 ± 8.56	326.9 ± 14.47
TAG(14:0/16:0/18:1)	31.00 ± 3.98	10.88 ± 1.01	12.30 ± 0.94	24.41 ± 2.52	36.92 ± 4.22	156.1 ± 7.73	404.1 ± 22.91
TAG(18:1/18:1/18:1)	124.2 ± 6.03	46.70 ± 5.99	33.29 ± 1.70	60.31 ± 9.69	101.0 ± 11.64	747.0 ± 26.14	2,136 ± 61.17
TAG(18:1/18:1/18:2)	91.88 ± 3.86	36.11 ± 5.65	23.05 ± 1.33	30.75 ± 4.72	71.62 ± 8.93	465.3 ± 17.10	1,177 ± 24.07
TAG(18:1/18:1/20:4)	23.67 ± 2.09	12.84 ± 1.12	5.83 ± 0.65	3.47 ± 0.42	10.83 ± 1.43	23.95 ± 1.68	59.11 ± 3.11
TAG(18:1/18:1/22:6)	3.71 ± 0.31	2.44 ± 0.32	0.57 ± 0.09	0.56 ± 0.06	1.14 ± 0.17	5.63 ± 1.03	11.38 ± 1.30
TAG(18:1/18:2/18:2)	300.6 ± 15.63	90.50 ± 15.19	58.46 ± 3.69	68.98 ± 12.10	184.4 ± 26.39	1,312 ± 38.60	3,061 ± 71.95
TAG(18:2/18:2/18:2)	151.0 ± 12.82	24.66 ± 4.94	14.57 ± 1.23	14.97 ± 3.09	55.36 ± 11.46	983.9 ± 47.65	2,167 ± 96.22
TAG(18:2/18:2/20:4)	79.54 ± 8.15	6.36 ± 0.80	3.71 ± 0.29	2.01 ± 0.36	9.58 ± 1.65	85.05 ± 8.36	162.6 ± 7.77
Alkyl triacylglycerols							
TAG(O-50:1)	1.30 ± 0.11	1.67 ± 0.22	0.85 ± 0.13	0.65 ± 0.05	1.64 ± 0.29	32.85 ± 6.04	90.46 ± 9.51
TAG(O-52:0)	0.40 ± 0.02	0.15 ± 0.01	0.17 ± 0.02	0.10 ± 0.005	0.14 ± 0.02	1.19 ± 0.21	2.11 ± 0.25
TAG(O-52:2)	0.72 ± 0.06	1.26 ± 0.17	0.46 ± 0.07	0.45 ± 0.04	0.87 ± 0.15	12.80 ± 2.10	41.36 ± 5.28

Values are represented as mean and standard error in nmol/g tissue.

Table S9. Statistic multiple comparison post hoc Tuckey of the diacylglycerol species between all the studied tissues.

		p value									
		Diacylglycerols									
		DAG(14:0/16:0)	DAG(16:0/16:0)	DAG(16:0/16:1)	DAG(14:0/18:2)	DAG(16:0/18:1)	DAG(16:1/18:1)	DAG(16:0/18:2)	DAG(18:0/18:1)	DAG(18:1/18:1)	DAG(18:0/18:2)
Liver	Heart	.999	1.000	.465	.749	.085	.119	.452	.290	**.009**	.996
	Kidney	.663	**.003**	.877	.706	.183	.148	.550	.301	**.006**	.978
	Gluteus	.980	.971	.521	.677	**.020**	.163	.380	.054	**.005**	.125
	Soleus	1.000	.999	.722	.889	.070	.305	.527	.242	**.023**	.492
	VAT	**.039**	**.003**	.556	.209	.872	.971	.612	.269	.988	.101
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	.999	1.000	.465	.749	.085	.119	.452	.290	**.009**	.996
	Kidney	.379	**.003**	.997	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Gluteus	1.000	.971	1.000	1.000	.987	1.000	1.000	.962	.999	.366
	Soleus	1.000	.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.828
	VAT	**.011**	**.003**	**.010**	**.006**	**.004**	**.016**	**.012**	**.001**	**.001**	**.023**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	.663	**.003**	.877	.706	.183	.148	.550	.301	**.006**	.978
	Heart	.379	**.003**	.997	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Gluteus	.254	**.000**	.997	1.000	.973	1.000	1.000	.986	1.000	.598
	Soleus	.562	**.002**	1.000	1.000	.998	1.000	1.000	1.000	1.000	.945
	VAT	.798	1.000	.080	**.007**	**.013**	**.023**	**.024**	**.002**	**.001**	**.020**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	.980	.971	.521	.677	**.020**	.163	.380	.054	**.005**	.125
	Heart	1.000	.971	1.000	1.000	.987	1.000	1.000	.962	.999	.366
	Kidney	.254	**.000**	.997	1.000	.973	1.000	1.000	.986	1.000	.598
	Soleus	.999	1.000	1.000	1.000	1.000	1.000	1.000	.998	1.000	.995
	VAT	**.007**	**.000**	**.017**	**.006**	**.001**	**.027**	**.012**	**.000**	**.001**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Soleus	Liver	1.000	.999	.722	.889	.070	.305	.527	.242	**.023**	.492
	Heart	1.000	.999	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.828
	Kidney	.562	**.002**	1.000	1.000	.998	1.000	1.000	1.000	1.000	.945
	Gluteus	.999	1.000	1.000	1.000	1.000	1.000	1.000	.998	1.000	.995
	VAT	**.039**	**.002**	**.046**	**.024**	**.004**	.065	**.026**	**.001**	**.004**	**.001**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
VAT	Liver	**.039**	**.003**	.556	.209	.872	.971	.612	.269	.988	.101
	Heart	**.011**	**.003**	**.010**	**.006**	**.004**	**.016**	**.012**	**.001**	**.001**	**.023**
	Kidney	.798	1.000	.080	**.007**	**.013**	**.023**	**.024**	**.002**	**.001**	**.020**
	Gluteus	**.007**	**.000**	**.017**	**.006**	**.001**	**.027**	**.012**	**.000**	**.001**	**.000**
	Soleus	**.039**	**.002**	**.046**	**.024**	**.004**	.065	**.026**	**.001**	**.004**	**.001**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**

		DAG(18:1/18:2)	DAG(18:2/18:2)	DAG(18:1/18:3)	DAG(16:0/20:4)	DAG(18:1/20:3)	DAG(18:0/20:4)	DAG(18:1/20:4)	DAG(16:0/22:5)	DAG(18:2/20:4)	DAG(16:0/22:6)
Liver	Heart	.415	.105	**.002**	**.000**	**.010**	.993	**.000**	1.000	**.000**	.296
	Kidney	.395	.103	**.003**	1.000	**.006**	**.048**	**.000**	1.000	**.000**	.997
	Gluteus	.370	.094	**.003**	**.000**	**.005**	**.011**	**.000**	.605	**.000**	**.039**
	Soleus	.520	.171	**.008**	**.000**	**.032**	**.017**	**.000**	.899	**.000**	.124
	VAT	.785	.973	1.000	**.000**	1.000	**.000**	**.000**	.771	**.000**	.737
	SAT	**.000**	**.000**	**.000**	.113	**.000**	**.009**	.844	**.000**	**.000**	.109
Heart	Liver	.415	.105	**.002**	**.000**	**.010**	.993	**.000**	1.000	**.000**	.296
	Kidney	1.000	1.000	1.000	**.000**	1.000	**.008**	.998	1.000	.988	.736
	Gluteus	1.000	1.000	1.000	.609	.999	.059	.327	.641	.879	.929
	Soleus	1.000	1.000	1.000	.760	1.000	.080	.617	.917	.969	.993
	VAT	**.023**	**.014**	**.004**	.997	**.027**	**.000**	1.000	.738	.981	.994
	SAT	**.000**	**.000**	**.000**	**.022**	**.000**	**.049**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	.395	.103	**.003**	1.000	**.006**	**.048**	**.000**	1.000	**.000**	.997
	Heart	1.000	1.000	1.000	**.000**	1.000	**.008**	.998	1.000	.988	.736
	Gluteus	1.000	1.000	1.000	**.000**	1.000	**.000**	.166	.594	.999	.202
	Soleus	1.000	1.000	1.000	**.000**	1.000	**.000**	.375	.879	1.000	.416
	VAT	**.026**	**.015**	**.005**	**.000**	**.016**	**.000**	1.000	.873	.735	.978
	SAT	**.000**	**.000**	**.000**	.142	**.000**	**.000**	**.000**	**.000**	**.000**	**.044**
Gluteus	Liver	.370	.094	**.003**	**.000**	**.005**	**.011**	**.000**	.605	**.000**	**.039**
	Heart	1.000	1.000	1.000	.609	.999	.059	.327	.641	.879	.929
	Kidney	1.000	1.000	1.000	**.000**	1.000	**.000**	.166	.594	.999	.202
	Soleus	1.000	1.000	1.000	1.000	.999	1.000	1.000	.999	1.000	1.000
	VAT	**.023**	**.014**	**.004**	.914	**.013**	.468	.228	.056	.448	.632
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**
Soleus	Liver	.520	.171	**.008**	**.000**	**.032**	**.017**	**.000**	.899	**.000**	.124
	Heart	1.000	1.000	1.000	.760	1.000	.080	.617	.917	.969	.993
	Kidney	1.000	1.000	1.000	**.000**	1.000	**.000**	.375	.879	1.000	.416
	Gluteus	1.000	1.000	1.000	1.000	.999	1.000	1.000	.999	1.000	1.000
	VAT	**.049**	**.031**	**.010**	.967	.068	.521	.479	.200	.665	.863
	SAT	**.000**	**.000**	**.000**	**.001**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**
VAT	Liver	.785	.973	1.000	**.000**	1.000	**.000**	**.000**	.771	**.000**	.737
	Heart	**.023**	**.014**	**.004**	.997	**.027**	**.000**	1.000	.738	.981	.994
	Kidney	**.026**	**.015**	**.005**	**.000**	**.016**	**.000**	1.000	.873	.735	.978
	Gluteus	**.023**	**.014**	**.004**	.914	**.013**	.468	.228	.056	.448	.632
	Soleus	**.049**	**.031**	**.010**	.967	.068	.521	.479	.200	.665	.863
	SAT	**.000**	**.000**	**.000**	**.007**	**.000**	.650	**.000**	**.000**	**.005**	**.004**
SAT	Liver	**.000**	**.000**	**.000**	.113	**.000**	**.009**	.844	**.000**	**.000**	.109
	Heart	**.000**	**.000**	**.000**	**.022**	**.000**	**.049**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	.142	**.000**	**.000**	**.000**	**.000**	**.000**	**.044**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.001**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.007**	**.000**	.650	**.000**	**.000**	**.005**	**.004**

p values < 0.05 are represented in bold numbers

Table S10. Statistic multiple comparison post hoc Tuckey of the triacylglycerol species between all the studied tissues.

		p value										
		Triacylglycerols										
		TAG(14:0/16:0/18:2)	TAG(14:0/16:1/18:1)	TAG(14:0/16:1/18:2)	TAG(14:0/18:0/18:1)	TAG(14:0/18:2/18:2)	TAG(14:1/16:0/18:1)	TAG(14:1/16:1/18:0)	TAG(14:1/18:0/18:2)	TAG(14:1/18:1/18:1)	TAG(15:0/16:0/18:1)	TAG(15:0/18:1/18:1)
Liver	Heart	.253	.684	.983	1.000	.447	.404	.674	.985	**.024**	.290	**.000**
	Kidney	.325	.698	.985	.998	.496	.242	.741	.775	**.028**	.837	**.000**
	Gluteus	.988	.998	.997	.975	.556	.994	1.000	.998	.624	.874	**.000**
	Soleus	1.000	1.000	1.000	.092	.848	.987	.998	.987	.962	.996	**.029**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	.051	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	.253	.684	.983	1.000	.447	.404	.674	.985	**.024**	.290	**.000**
	Kidney	1.000	1.000	1.000	1.000	1.000	.999	1.000	.992	1.000	.986	1.000
	Gluteus	.789	.958	1.000	.912	1.000	.875	.816	.847	.763	.976	1.000
	Soleus	.600	.945	1.000	**.050**	.999	.937	.971	.758	.386	.144	.726
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	.325	.698	.985	.998	.496	.242	.741	.775	**.028**	.837	**.000**
	Heart	1.000	1.000	1.000	1.000	1.000	.999	1.000	.992	1.000	.986	1.000
	Gluteus	.828	.953	1.000	.834	1.000	.692	.856	.496	.729	1.000	1.000
	Soleus	.656	.940	1.000	**.041**	.999	.798	.979	.409	.370	.570	.679
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	.988	.998	.997	.975	.556	.994	1.000	.998	.624	.874	**.000**
	Heart	.789	.958	1.000	.912	1.000	.875	.816	.847	.763	.976	1.000
	Kidney	.828	.953	1.000	.834	1.000	.692	.856	.496	.729	1.000	1.000
	Soleus	1.000	1.000	1.000	.497	1.000	1.000	1.000	1.000	.995	.619	.886
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.058	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Soleus	Liver	1.000	1.000	1.000	.092	.848	.987	.998	.987	.962	.996	**.029**
	Heart	.600	.945	1.000	**.050**	.999	.937	.971	.758	.386	.144	.726
	Kidney	.656	.940	1.000	**.041**	.999	.798	.979	.409	.370	.570	.679
	Gluteus	1.000	1.000	1.000	.497	1.000	1.000	1.000	1.000	.995	.619	.886
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.029**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	.051	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.058	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.029**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**

		TAG(16:0/16:0/16:0)	TAG(16:0/16:0/18:0)	TAG(16:0/16:0/18:1)	TAG(16:0/16:0/18:2)	TAG(16:0/16:1/18:1)	TAG(16:0/18:0/18:1)	TAG(16:0/18:1/18:1)	TAG(16:0/18:1/18:2)	TAG(16:0/18:2/18:2)	TAG(16:1/16:1/16:1)	TAG(16:1/16:1/18:0)
Liver	Heart	1.000	1.000	**.039**	.644	**.000**	.994	**.000**	**.000**	**.000**	.999	1.000
	Kidney	.998	.990	.769	.975	**.000**	.996	**.000**	**.000**	**.000**	.999	1.000
	Gluteus	1.000	1.000	.132	.440	.123	.998	**.000**	**.000**	**.000**	1.000	.336
	Soleus	.991	.999	.997	.981	.157	1.000	**.000**	**.000**	**.000**	1.000	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	1.000	1.000	**.039**	.644	**.000**	.994	**.000**	**.000**	**.000**	.999	1.000
	Kidney	.994	.971	.727	.212	1.000	1.000	.992	.947	1.000	1.000	.997
	Gluteus	1.000	1.000	1.000	.999	.405	1.000	.962	1.000	1.000	1.000	.459
	Soleus	.979	.994	.273	.262	.459	.992	.098	.061	.232	1.000	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	.998	.990	.769	.975	**.000**	.996	**.000**	**.000**	**.000**	.999	1.000
	Heart	.994	.971	.727	.212	1.000	1.000	.992	.947	1.000	1.000	.997
	Gluteus	.998	.967	.913	.124	.423	1.000	.711	.981	1.000	1.000	.221
	Soleus	1.000	1.000	.986	1.000	.471	.993	**.030**	**.008**	.159	1.000	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	1.000	1.000	.132	.440	.123	.998	**.000**	**.000**	**.000**	1.000	.336
	Heart	1.000	1.000	1.000	.999	.405	1.000	.962	1.000	1.000	1.000	.459
	Kidney	.998	.967	.913	.124	.423	1.000	.711	.981	1.000	1.000	.221
	Soleus	.990	.993	.507	.158	1.000	.997	.560	.066	.162	1.000	.124
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Soleus	Liver	.991	.999	.997	.981	.157	1.000	**.000**	**.000**	**.000**	1.000	**.000**
	Heart	.979	.994	.273	.262	.459	.992	.098	.061	.232	1.000	**.000**
	Kidney	1.000	1.000	.986	1.000	.471	.993	**.030**	**.008**	.159	1.000	**.000**
	Gluteus	.990	.993	.507	.158	1.000	.997	.560	.066	.162	1.000	.124
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.006**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.006**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**

		TAG(16:1/16:1/18:1)	TAG(16:1/18:1/18:1)	TAG(16:1/18:1/18:2)	TAG(16:0/16:1/17:0)	TAG(16:0/17:0/18:0)	TAG(14:0/17:0/18:1)	TAG(16:0/17:0/18:1)	TAG(16:1/17:0/18:1)	TAG(17:0/18:1/18:1)	TAG(16:0/17:0/18:2)	TAG(18:0/18:0/18:0)
Liver	Heart	**.011**	.228	**.001**	.212	1.000	.788	.979	**.000**	.988	**.020**	.995
	Kidney	**.018**	.239	**.001**	.616	1.000	1.000	.993	**.001**	.988	**.032**	1.000
	Gluteus	.440	.998	**.027**	.876	1.000	.990	.988	**.003**	.992	.051	.996
	Soleus	.798	1.000	.434	1.000	1.000	.987	1.000	.053	1.000	.667	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.011**	.228	**.001**	.212	1.000	.788	.979	**.000**	.988	**.020**	.995
	Kidney	1.000	1.000	1.000	.998	1.000	.953	1.000	1.000	1.000	1.000	1.000
	Gluteus	.770	.623	.949	.944	1.000	.997	1.000	1.000	1.000	1.000	1.000
	Soleus	.501	.556	.343	.219	1.000	.409	.996	.880	1.000	.766	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	**.018**	.239	**.001**	.616	1.000	1.000	.993	**.001**	.988	**.032**	1.000
	Heart	1.000	1.000	1.000	.998	1.000	.953	1.000	1.000	1.000	1.000	1.000
	Gluteus	.794	.608	.918	.999	1.000	1.000	1.000	.999	1.000	1.000	1.000
	Soleus	.541	.542	.317	.573	1.000	.945	.999	.862	1.000	.791	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	.440	.998	**.027**	.876	1.000	.990	.988	**.003**	.992	.051	.996
	Heart	.770	.623	.949	.944	1.000	.997	1.000	1.000	1.000	1.000	1.000
	Kidney	.794	.608	.918	.999	1.000	1.000	1.000	.999	1.000	1.000	1.000
	Soleus	.999	1.000	.918	.826	1.000	.808	.998	.983	1.000	.872	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Soleus	Liver	.798	1.000	.434	1.000	1.000	.987	1.000	.053	1.000	.667	1.000
	Heart	.501	.556	.343	.219	1.000	.409	.996	.880	1.000	.766	1.000
	Kidney	.541	.542	.317	.573	1.000	.945	.999	.862	1.000	.791	1.000
	Gluteus	.999	1.000	.918	.826	1.000	.808	.998	.983	1.000	.872	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.997
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.997

		TAG(18:0/18:0/18:1)	TAG(18:0/18:1/18:1)	TAG(18:0/18:2/18:2)	TAG(14:0/16:0/18:1)	TAG(18:1/18:1/18:1)	TAG(18:1/18:1/18:2)	TAG(18:1/18:1/20:4)	TAG(18:1/18:1/22:6)	TAG(18:1/18:2/18:2)	TAG(18:2/18:2/18:2)	TAG(18:2/18:2/20:4)
Liver	Heart	1.000	1.000	.439	.699	.320	**.031**	**.002**	.821	**.001**	.295	**.000**
	Kidney	1.000	.999	.168	.815	.220	**.008**	**.000**	**.043**	**.000**	.284	**.000**
	Gluteus	1.000	1.000	.125	.999	.626	**.025**	**.000**	**.042**	**.001**	.287	**.000**
	Soleus	1.000	1.000	1.000	1.000	.997	.935	**.001**	.200	.308	.733	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.429	**.000**	**.000**	.994
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	1.000	1.000	.439	.699	.320	**.031**	**.002**	.821	**.001**	.295	**.000**
	Kidney	1.000	1.000	.992	1.000	1.000	.991	.144	.508	.995	1.000	1.000
	Gluteus	1.000	1.000	.980	.954	1.000	1.000	**.017**	.497	.999	1.000	.999
	Soleus	1.000	.998	.813	.541	.813	.512	.991	.873	.561	.999	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	**.028**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	1.000	.999	.168	.815	.220	**.008**	**.000**	**.043**	**.000**	.284	**.000**
	Heart	1.000	1.000	.992	1.000	1.000	.991	.144	.508	.995	1.000	1.000
	Gluteus	1.000	1.000	1.000	.980	.993	1.000	.980	1.000	1.000	1.000	1.000
	Soleus	1.000	.997	.474	.663	.669	.215	.625	.998	.279	.996	.996
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	1.000	1.000	.125	.999	.626	**.025**	**.000**	**.042**	**.001**	.287	**.000**
	Heart	1.000	1.000	.980	.954	1.000	1.000	**.017**	.497	.999	1.000	.999
	Kidney	1.000	1.000	1.000	.980	.993	1.000	.980	1.000	1.000	1.000	1.000
	Soleus	1.000	.999	.396	.981	.957	.407	.187	.998	.379	.996	.985
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Soleus	Liver	1.000	1.000	1.000	1.000	.997	.935	**.001**	.200	.308	.733	**.000**
	Heart	1.000	.998	.813	.541	.813	.512	.991	.873	.561	.999	1.000
	Kidney	1.000	.997	.474	.663	.669	.215	.625	.998	.279	.996	.996
	Gluteus	1.000	.999	.396	.981	.957	.407	.187	.998	.379	.996	.985
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.002**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.429	**.000**	**.000**	.994
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	**.028**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.002**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**

p values < 0.05 are represented in bold numbers

Table S11. Statistic multiple comparison post hoc Tuckey of the alkyl triacylglycerol species between all the studied tissues.

		p value		
		Alkyl triacylglycerols		
		TAG(O-50:1)	TAG(O-52:0)	TAG(O-52:2)
Liver	Heart	1.000	.803	1.000
	Kidney	1.000	.895	1.000
	Gluteus	1.000	.705	1.000
	Soleus	1.000	.853	1.000
	VAT	**.000**	**.001**	**.004**
	SAT	**.000**	**.000**	**.000**
Heart	Liver	1.000	.803	1.000
	Kidney	1.000	1.000	1.000
	Gluteus	1.000	1.000	1.000
	Soleus	1.000	1.000	1.000
	VAT	**.000**	**.000**	**.006**
	SAT	**.000**	**.000**	**.000**
Kidney	Liver	1.000	.895	1.000
	Heart	1.000	1.000	1.000
	Gluteus	1.000	1.000	1.000
	Soleus	1.000	1.000	1.000
	VAT	**.000**	**.000**	**.006**
	SAT	**.000**	**.000**	**.000**
Gluteus	Liver	1.000	.705	1.000
	Heart	1.000	1.000	1.000
	Kidney	1.000	1.000	1.000
	Soleus	1.000	1.000	1.000
	VAT	**.000**	**.000**	**.006**
	SAT	**.000**	**.000**	**.000**
Soleus	Liver	1.000	.853	1.000
	Heart	1.000	1.000	1.000
	Kidney	1.000	1.000	1.000
	Gluteus	1.000	1.000	1.000
	VAT	**.001**	**.000**	**.013**
	SAT	**.000**	**.000**	**.000**
VAT	Liver	**.000**	**.001**	**.004**
	Heart	**.000**	**.000**	**.006**
	Kidney	**.000**	**.000**	**.006**
	Gluteus	**.000**	**.000**	**.006**
	Soleus	**.001**	**.000**	**.013**
	SAT	**.000**	**.001**	**.000**
SAT	Liver	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**
	VAT	**.000**	**.001**	**.000**

p values < 0.05 are represented in bold numbers

8.3.3. Glycerophospholipids

Table S12. Lysoglycerophospholipid concentration detected by targeted lipidomic analysis in all the studied tissues. Lipid species detected were 61 LPC, 14 LPE, 8 LPI and 4 LPS.

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Lysophosphatidylcholine							
LPC(14:0) [sn2]	0.08 ± 0.01	0.07 ± 0.01	0.05 ± 0.01	0.04 ± 0.003	0.05 ± 0.01	0.01 ± 0.001	0.04 ± 0.004
LPC(14:0) [sn1]	0.60 ± 0.07	0.25 ± 0.03	0.20 ± 0.02	0.07 ± 0.01	0.11 ± 0.01	0.03 ± 0.003	0.12 ± 0.01
LPC(15:0) [sn2]	0.10 ± 0.01	0.07 ± 0.01	0.07 ± 0.01	0.03 ± 0.002	0.03 ± 0.004	0.01 ± 0.002	0.04 ± 0.004
LPC(15:0) [sn1]	0.38 ± 0.05	0.16 ± 0.02	0.26 ± 0.03	0.06 ± 0.004	0.10 ± 0.01	0.04 ± 0.004	0.12 ± 0.01
LPC(16:0) [sn2]	9.04 ± 0.98	9.65 ± 1.23	13.04 ± 1.55	2.04 ± 0.11	4.07 ± 0.51	1.08 ± 0.16	4.21 ± 0.40
LPC(16:0) [sn1]	68.46 ± 7.84	33.22 ± 3.85	62.94 ± 5.56	11.60 ± 0.85	28.28 ± 4.00	4.57 ± 0.68	18.54 ± 1.87
LPC(16:1) [sn2]	1.81 ± 0.30	0.39 ± 0.06	0.32 ± 0.08	0.10 ± 0.005	0.17 ± 0.03	0.05 ± 0.01	0.28 ± 0.02
LPC(16:1) [sn1]	1.88 ± 0.24	0.70 ± 0.07	0.59 ± 0.08	0.19 ± 0.01	0.41 ± 0.07	0.08 ± 0.01	0.41 ± 0.03
LPC(15-MHDA) [sn2]	0.09 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.02 ± 0.001	0.02 ± 0.002	0.01 ± 0.002	0.03 ± 0.003
LPC(15-MHDA) [sn1] / LPC(17:0) [sn2]	0.36 ± 0.04	0.18 ± 0.02	0.25 ± 0.03	0.05 ± 0.004	0.10 ± 0.01	0.05 ± 0.01	0.15 ± 0.01
LPC(15-MHDA) [sn1] [104_sn1]	0.28 ± 0.03	0.10 ± 0.01	0.17 ± 0.01	0.03 ± 0.004	0.06 ± 0.01	0.02 ± 0.004	0.09 ± 0.01
LPC(17:0) [sn1]	1.09 ± 0.11	0.60 ± 0.06	0.70 ± 0.07	0.13 ± 0.01	0.27 ± 0.02	0.12 ± 0.01	0.33 ± 0.04
LPC(17:1) [sn2] (a)	0.07 ± 0.01	0.02 ± 0.004	0.02 ± 0.004	0.01 ± 0.001	0.01 ± 0.002	0.00 ± 0.001	0.01 ± 0.003
LPC(17:1) [sn1] (a) / LPC(17:1) [sn2] (b)	0.07 ± 0.01	0.04 ± 0.01	0.03 ± 0.003	0.02 ± 0.002	0.04 ± 0.01	0.01 ± 0.001	0.02 ± 0.002
LPC(17:1) (a) [sn1] [104_sn1]	0.06 ± 0.01	0.04 ± 0.005	0.02 ± 0.004	0.01 ± 0.001	0.03 ± 0.005	0.01 ± 0.001	0.02 ± 0.000
LPC(17:1) [sn1] (b)	0.01 ± 0.002	0.01 ± 0.002	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.005 ± 0.001	0.01 ± 0.001
LPC(18:0) [sn2]	6.09 ± 0.74	5.46 ± 0.71	8.26 ± 0.82	0.44 ± 0.04	1.40 ± 0.12	0.81 ± 0.13	3.06 ± 0.36
LPC(18:0) [sn1]	58.40 ± 7.15	54.31 ± 6.10	54.28 ± 4.67	2.99 ± 0.19	8.88 ± 0.97	3.76 ± 0.56	15.18 ± 1.88
LPC(18:1) [sn2]	17.03 ± 2.96	15.54 ± 3.26	5.14 ± 1.14	0.64 ± 0.03	1.26 ± 0.15	0.41 ± 0.06	1.84 ± 0.19
LPC(18:1) [sn1]	11.85 ± 1.33	5.93 ± 0.65	5.78 ± 0.57	1.19 ± 0.09	2.71 ± 0.32	0.65 ± 0.10	2.73 ± 0.27
LPC(18:2) [sn2]	76.81 ± 15.48	22.56 ± 4.76	4.75 ± 1.26	1.48 ± 0.07	3.65 ± 0.51	1.51 ± 0.23	5.15 ± 0.50
LPC(18:2) [sn1]	11.37 ± 1.86	7.93 ± 0.90	2.83 ± 0.33	1.06 ± 0.14	2.02 ± 0.22	0.71 ± 0.07	2.55 ± 0.21
LPC(18:3) [sn2] (a)	0.10 ± 0.02	0.02 ± 0.003	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.002	0.01 ± 0.001	0.01 ± 0.001
LPC(18:3) [sn1] (a)/LPC(18:3) [sn2] (b)	1.79 ± 0.36	0.17 ± 0.03	0.06 ± 0.01	0.02 ± 0.002	0.03 ± 0.004	0.01 ± 0.001	0.03 ± 0.005
LPC(18:3) (a) [sn1] [104_sn1]	0.06 ± 0.01	0.03 ± 0.003	0.03 ± 0.002	0.01 ± 0.002	0.02 ± 0.002	0.01 ± 0.001	0.02 ± 0.002
LPC(18:3) [sn1] (b)	0.28 ± 0.05	0.05 ± 0.01	0.04 ± 0.01	0.02 ± 0.001	0.02 ± 0.003	0.01 ± 0.001	0.03 ± 0.004
LPC(19:0) [sn2] (a)	0.09 ± 0.01	0.06 ± 0.01	0.11 ± 0.01	0.01 ± 0.001	0.02 ± 0.003	0.01 ± 0.002	0.05 ± 0.01
LPC(19:0) [sn1] (a) / LPC(19:0) [sn2] (b)	0.78 ± 0.08	0.34 ± 0.05	0.48 ± 0.04	0.03 ± 0.004	0.10 ± 0.01	0.05 ± 0.01	0.21 ± 0.03
LPC(19:0) (a) [sn1] [104_sn1]	0.66 ± 0.07	0.30 ± 0.04	0.40 ± 0.03	0.03 ± 0.004	0.08 ± 0.01	0.05 ± 0.01	0.19 ± 0.03
LPC(19:0) [sn1] (b)	0.48 ± 0.06	0.26 ± 0.03	0.33 ± 0.03	0.03 ± 0.003	0.07 ± 0.01	0.04 ± 0.01	0.15 ± 0.02

LPC(19:1) (a)	0.03 ± 0.002	0.03 ± 0.003	0.01 ± 0.001	0.01 ± 0.0002	0.01 ± 0.001	0.002 ± 0.001	0.01 ± 0.001
LPC(19:1) (b)	0.08 ± 0.01	0.02 ± 0.004	0.02 ± 0.003	0.01 ± 0.001	0.02 ± 0.002	0.01 ± 0.001	0.01 ± 0.001
LPC(19:1) (c)	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.003 ± 0.0004	0.005 ± 0.001
LPC(20:0) [sn2]	0.15 ± 0.02	0.11 ± 0.01	0.21 ± 0.01	0.02 ± 0.002	0.04 ± 0.004	0.02 ± 0.002	0.07 ± 0.01
LPC(20:0) [sn1]	0.44 ± 0.04	0.30 ± 0.04	0.69 ± 0.04	0.05 ± 0.004	0.12 ± 0.02	0.06 ± 0.01	0.21 ± 0.03
LPC(20:1) [sn2]	0.22 ± 0.03	0.13 ± 0.02	0.09 ± 0.01	0.01 ± 0.002	0.03 ± 0.003	0.01 ± 0.002	0.04 ± 0.004
LPC(20:1) [sn1]	0.83 ± 0.11	0.25 ± 0.04	0.41 ± 0.05	0.04 ± 0.003	0.10 ± 0.01	0.03 ± 0.01	0.11 ± 0.01
LPC(20:2) [sn2]	0.32 ± 0.04	0.27 ± 0.05	0.08 ± 0.01	0.01 ± 0.001	0.02 ± 0.003	0.00 ± 0.001	0.02 ± 0.003
LPC(20:2) [sn1]	0.45 ± 0.04	0.13 ± 0.02	0.17 ± 0.01	0.02 ± 0.002	0.05 ± 0.01	0.01 ± 0.003	0.06 ± 0.01
LPC(20:3) [sn2]	2.92 ± 0.59	0.84 ± 0.16	0.39 ± 0.10	0.08 ± 0.005	0.12 ± 0.01	0.03 ± 0.004	0.10 ± 0.01
LPC(20:3) [sn1]	0.60 ± 0.10	0.23 ± 0.03	0.16 ± 0.02	0.06 ± 0.005	0.08 ± 0.004	0.03 ± 0.004	0.09 ± 0.01
LPC(20:4) [sn2]	138.92 ± 27.60	65.78 ± 17.04	11.25 ± 2.49	2.13 ± 0.14	3.37 ± 0.63	0.94 ± 0.16	2.52 ± 0.27
LPC(20:4) [sn1]	20.26 ± 4.04	9.40 ± 2.55	2.19 ± 0.48	0.38 ± 0.02	0.66 ± 0.08	0.30 ± 0.03	1.07 ± 0.10
LPC(20:5) [sn2]	0.25 ± 0.04	0.08 ± 0.02	0.02 ± 0.004	0.02 ± 0.002	0.02 ± 0.003	0.00 ± 0.001	0.01 ± 0.002
LPC(20:5) [sn1]	0.17 ± 0.03	0.05 ± 0.01	0.02 ± 0.002	0.02 ± 0.003	0.02 ± 0.001	0.01 ± 0.001	0.02 ± 0.005
LPC(22:0) [sn2]	0.04 ± 0.00	0.04 ± 0.00	0.07 ± 0.005	0.01 ± 0.001	0.02 ± 0.002	0.01 ± 0.001	0.02 ± 0.002
LPC(22:0) [sn1]	0.11 ± 0.01	0.09 ± 0.01	0.23 ± 0.010	0.02 ± 0.003	0.06 ± 0.008	0.02 ± 0.002	0.06 ± 0.010
LPC(22:1) [sn2]	0.01 ± 0.001	0.01 ± 0.002	0.02 ± 0.001	0.002 ± 0.001	0.005 ± 0.001	0.002 ± 0.0002	0.01 ± 0.002
LPC(22:1) [sn1]	0.04 ± 0.005	0.03 ± 0.003	0.09 ± 0.008	0.01 ± 0.001	0.02 ± 0.002	0.01 ± 0.001	0.02 ± 0.004
LPC(22:4) [sn2]	1.33 ± 0.33	1.47 ± 0.35	0.17 ± 0.03	0.06 ± 0.006	0.16 ± 0.02	0.03 ± 0.004	0.08 ± 0.011
LPC(22:4) [sn1]	0.23 ± 0.05	0.25 ± 0.05	0.08 ± 0.007	0.03 ± 0.002	0.05 ± 0.006	0.02 ± 0.002	0.03 ± 0.003
LPC(22:5) [sn2] (n3)	2.62 ± 0.63	2.56 ± 0.61	0.13 ± 0.04	0.35 ± 0.03	0.64 ± 0.11	0.02 ± 0.002	0.04 ± 0.007
LPC(22:5) [sn1] (n3)/LPC(22:5) [sn2] (n6)	3.09 ± 0.68	1.35 ± 0.32	0.10 ± 0.02	0.11 ± 0.01	0.22 ± 0.03	0.01 ± 0.002	0.05 ± 0.003
LPC(22:5) (n3) [sn1] [104_sn1]	0.20 ± 0.04	0.17 ± 0.04	0.02 ± 0.004	0.02 ± 0.001	0.04 ± 0.005	0.00 ± 0.001	0.02 ± 0.002
LPC(22:5) [sn1] (n6)	0.41 ± 0.08	0.17 ± 0.04	0.03 ± 0.003	0.02 ± 0.002	0.03 ± 0.004	0.00 ± 0.001	0.01 ± 0.002
LPC(22:6) [sn2]	21.06 ± 3.82	5.20 ± 1.37	0.85 ± 0.23	1.02 ± 0.07	2.08 ± 0.33	0.03 ± 0.006	0.10 ± 0.009
LPC(22:6) [sn1]	3.99 ± 0.71	1.05 ± 0.26	0.22 ± 0.06	0.19 ± 0.01	0.44 ± 0.07	0.01 ± 0.002	0.06 ± 0.006
LPC(24:0) [sn2]	0.07 ± 0.003	0.06 ± 0.01	0.27 ± 0.012	0.02 ± 0.002	0.04 ± 0.003	0.02 ± 0.002	0.04 ± 0.004
LPC(24:0) [sn1]	0.24 ± 0.02	0.17 ± 0.02	0.91 ± 0.045	0.06 ± 0.003	0.10 ± 0.01	0.04 ± 0.004	0.10 ± 0.009
LPC(26:0) [sn2]	0.01 ± 0.002	0.01 ± 0.001	0.23 ± 0.03	0.01 ± 0.001	0.01 ± 0.001	0.00 ± 0.001	0.01 ± 0.002
LPC(26:0) [sn1]	0.03 ± 0.003	0.02 ± 0.003	0.84 ± 0.08	0.01 ± 0.001	0.02 ± 0.001	0.01 ± 0.002	0.02 ± 0.002
Lysophosphatidylethanolamine							
LPE(16:0) [sn2]	3.44 ± 0.28	2.19 ± 0.25	3.32 ± 0.25	1.09 ± 0.09	2.07 ± 0.32	0.15 ± 0.04	0.53 ± 0.04
LPE(16:0) [sn1]	33.18 ± 4.09	7.29 ± 0.93	21.48 ± 1.89	1.02 ± 0.08	2.42 ± 0.36	0.63 ± 0.09	1.83 ± 0.09
LPE(17:0) [sn2]	0.54 ± 0.04	0.30 ± 0.02	0.36 ± 0.06	0.23 ± 0.01	0.22 ± 0.02	0.26 ± 0.01	0.22 ± 0.02
LPE(17:0) [sn1]	1.02 ± 0.10	0.51 ± 0.05	0.77 ± 0.07	0.19 ± 0.01	0.25 ± 0.02	0.23 ± 0.03	0.27 ± 0.03
LPE(18:0) [sn2]	4.48 ± 0.35	2.23 ± 0.26	4.89 ± 0.46	0.31 ± 0.03	0.74 ± 0.12	0.15 ± 0.02	0.50 ± 0.04
LPE(18:0) [sn1]	37.12 ± 3.45	22.07 ± 2.47	48.25 ± 3.95	2.93 ± 0.27	6.59 ± 1.05	0.66 ± 0.10	2.52 ± 0.32

LPE(18:1) [sn2]	8.01 ± 0.66	3.85 ± 0.46	5.15 ± 0.39	0.45 ± 0.03	3.18 ± 0.38	0.81 ± 0.11	2.32 ± 0.35
LPE(18:1) [sn1]	9.49 ± 0.85	3.65 ± 0.38	11.59 ± 1.15	0.21 ± 0.03	1.66 ± 0.26	0.51 ± 0.07	1.65 ± 0.21
LPE(18:2) [sn2]	81.12 ± 7.84	12.16 ± 1.64	4.26 ± 0.49	0.94 ± 0.05	2.44 ± 0.38	1.17 ± 0.20	2.55 ± 0.27
LPE(18:2) [sn1]	14.90 ± 1.45	3.63 ± 0.38	1.65 ± 0.19	0.32 ± 0.03	1.14 ± 0.20	0.42 ± 0.05	0.75 ± 0.09
LPE(20:4) [sn2]	162.9 ± 18.53	35.77 ± 4.23	31.04 ± 2.49	1.57 ± 0.11	3.86 ± 0.57	5.15 ± 0.93	8.87 ± 1.05
LPE(20:4) [sn1]	30.37 ± 3.08	6.01 ± 0.68	5.63 ± 0.58	0.48 ± 0.02	0.95 ± 0.10	1.50 ± 0.21	2.33 ± 0.27
LPE(22:6) [sn2]	105.2 ± 12.49	36.02 ± 5.14	2.12 ± 0.20	9.78 ± 0.78	17.74 ± 2.34	0.39 ± 0.08	0.76 ± 0.08
LPE(22:6) [sn1]	21.45 ± 2.12	6.73 ± 0.99	0.49 ± 0.07	1.77 ± 0.15	3.71 ± 0.58	0.08 ± 0.02	0.27 ± 0.03
Lysophosphatidyloinositol							
LPI(18:0) [sn2]	0.17 ± 0.01	0.05 ± 0.01	0.14 ± 0.02	0.06 ± 0.007	0.05 ± 0.01	0.06 ± 0.01	0.05 ± 0.008
LPI(18:0) [sn1]	2.47 ± 0.24	0.38 ± 0.04	1.61 ± 0.11	0.16 ± 0.01	0.20 ± 0.02	0.06 ± 0.01	0.10 ± 0.01
LPI(18:1) [sn2]	0.07 ± 0.01	0.04 ± 0.01	0.05 ± 0.01	0.03 ± 0.009	0.01 ± 0.005	0.02 ± 0.008	0.03 ± 0.007
LPI(18:1) [sn1]	0.24 ± 0.03	0.08 ± 0.01	0.09 ± 0.01	0.03 ± 0.005	0.07 ± 0.01	0.05 ± 0.008	0.05 ± 0.01
LPI(18:2) [sn2]	1.12 ± 0.10	0.16 ± 0.02	0.05 ± 0.01	0.02 ± 0.002	0.02 ± 0.003	0.02 ± 0.004	0.05 ± 0.004
LPI(18:2) [sn1]	0.24 ± 0.03	0.07 ± 0.01	0.06 ± 0.01	0.03 ± 0.005	0.04 ± 0.01	0.03 ± 0.01	0.05 ± 0.01
LPI(20:4) [sn2]	11.53 ± 0.98	0.99 ± 0.12	1.40 ± 0.14	0.13 ± 0.02	0.22 ± 0.02	0.05 ± 0.01	0.19 ± 0.02
LPI(20:4) [sn1]	2.05 ± 0.15	0.14 ± 0.02	0.32 ± 0.03	0.04 ± 0.01	0.05 ± 0.01	0.02 ± 0.004	0.06 ± 0.01
Lysophosphatidylserine							
LPS(16:0)	0.18 ± 0.02	0.11 ± 0.02	0.14 ± 0.01	0.08 ± 0.01	0.09 ± 0.01	0.04 ± 0.01	0.11 ± 0.004
LPS(18:0)	0.10 ± 0.02	0.12 ± 0.005	0.13 ± 0.01	0.05 ± 0.01	0.06 ± 0.01	0.04 ± 0.01	0.06 ± 0.01
LPS(18:1)	0.05 ± 0.01	0.04 ± 0.004	0.02 ± 0.004	0.03 ± 0.01	0.04 ± 0.005	0.02 ± 0.005	0.04 ± 0.01
LPS(18:2)	0.05 ± 0.01	0.04 ± 0.01	0.04 ± 0.005	0.03 ± 0.01	0.03 ± 0.004	0.02 ± 0.004	0.05 ± 0.01

Table S13. Statistic multiple comparison post hoc Tuckey of the lysophosphatidylcholine species between all the studied tissues.

		p value												
		Lysophosphatidylcholine												
		LPC(14:0) [sn2]	LPC(14:0) [sn1]	LPC(15:0) [sn2]	LPC(15:0) [sn1]	LPC(16:0) [sn2]	LPC(16:0) [sn1]	LPC(16:1) [sn2]	LPC(16:1) [sn1]	LPC(15-MHDA) [sn2]	LPC(15-MHDA) [sn1] / LPC(17:0) [sn2]	LPC(15-MHDA) [sn1] [104_sn1]	LPC(17:0) [sn1]	LPC(17:1) [sn2] (a)
Liver	Heart	.688	**.000**	.184	**.000**	.999	**.000**	**.000**	**.000**	.094	**.000**	**.000**	**.000**	**.000**
	Kidney	**.015**	**.000**	.278	**.045**	.101	.986	**.000**	**.000**	.384	**.037**	**.000**	**.004**	**.000**
	Gluteus	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.029**	**.000**	**.000**	**.000**	**.028**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.002**	**.000**	**.000**	**.000**	**.035**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	.688	**.000**	.184	**.000**	.999	**.000**	**.000**	**.000**	.094	**.000**	**.000**	**.000**	**.000**
	Kidney	.402	.928	1.000	.104	.238	**.002**	1.000	.996	.998	.377	.100	.940	1.000
	Gluteus	.120	**.018**	**.006**	.140	**.000**	.057	.831	.085	**.016**	**.005**	.055	**.000**	.652
	Soleus	.505	.134	**.037**	.757	**.009**	.994	.960	.710	.077	.191	.714	**.030**	.932
	VAT	**.000**	**.001**	**.000**	**.033**	**.000**	**.002**	.664	**.012**	**.001**	**.002**	**.012**	**.000**	.306
	SAT	.088	.229	.095	.947	**.012**	.449	.999	.692	.156	.969	.996	.115	.849
Kidney	Liver	**.015**	**.000**	.278	**.045**	.101	.986	**.000**	**.000**	.384	**.037**	**.000**	**.004**	**.000**
	Heart	.402	.928	1.000	.104	.238	**.002**	1.000	.996	.998	.377	.100	.940	1.000
	Gluteus	.996	.292	**.010**	**.000**	**.000**	**.000**	.959	.359	**.007**	**.000**	**.000**	**.000**	.859
	Soleus	1.000	.727	**.049**	**.005**	**.000**	**.001**	.996	.968	**.032**	**.002**	**.004**	**.003**	.988
	VAT	**.027**	.056	**.000**	**.000**	**.000**	**.000**	.880	.098	**.001**	**.000**	**.000**	**.000**	.558
	SAT	.978	.860	.116	**.018**	**.000**	**.000**	1.000	.963	.069	.109	**.048**	**.016**	.960
Gluteus	Liver	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.120	**.018**	**.006**	.140	**.000**	.057	.831	.085	**.016**	**.005**	.055	**.000**	.652
	Kidney	.996	.292	**.010**	**.000**	**.000**	**.000**	.959	.359	**.007**	**.000**	**.000**	**.000**	.859
	Soleus	.993	.995	.999	.954	.854	.360	1.000	.919	.999	.886	.853	.836	.999
	VAT	.124	.991	.866	.999	.995	.960	1.000	.996	.995	1.000	.999	1.000	.999
	SAT	1.000	.973	.980	.787	.813	.974	.989	.927	.989	.121	.326	.517	1.000
Soleus	Liver	**.029**	**.000**	**.000**	**.000**	**.028**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.505	.134	**.037**	.757	**.009**	.994	.960	.710	.077	.191	.714	**.030**	.932
	Kidney	1.000	.727	**.049**	**.005**	**.000**	**.001**	.996	.968	**.032**	**.002**	**.004**	**.003**	.988
	Gluteus	.993	.995	.999	.954	.854	.360	1.000	.919	.999	.886	.853	.836	.999
	VAT	**.031**	.830	.632	.754	.460	**.048**	.998	.595	.936	.810	.594	.756	.962
	SAT	.973	1.000	1.000	1.000	1.000	.893	1.000	1.000	1.000	.780	.977	.999	1.000
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.001**	**.000**	**.033**	**.000**	**.002**	.664	**.012**	**.001**	**.002**	**.012**	**.000**	.306
	Kidney	**.027**	.056	**.000**	**.000**	**.000**	**.000**	.880	.098	**.001**	**.000**	**.000**	**.000**	.558
	Gluteus	.124	.991	.866	.999	.995	.960	1.000	.996	.995	1.000	.999	1.000	.999
	Soleus	**.031**	.830	.632	.754	.460	**.048**	.998	.595	.936	.810	.594	.756	.962
	SAT	.256	.683	.389	.473	.406	.538	.956	.613	.811	.076	.133	.414	.990
SAT	Liver	**.002**	**.000**	**.000**	**.000**	**.035**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.088	.229	.095	.947	**.012**	.449	.999	.692	.156	.969	.996	.115	.849
	Kidney	.978	.860	.116	**.018**	**.000**	**.000**	1.000	.963	.069	.109	**.048**	**.016**	.960
	Gluteus	1.000	.973	.980	.787	.813	.974	.989	.927	.989	.121	.326	.517	1.000
	Soleus	.973	1.000	1.000	1.000	1.000	.893	1.000	1.000	1.000	.780	.977	.999	1.000
	VAT	.256	.683	.389	.473	.406	.538	.956	.613	.811	.076	.133	.414	.990

		p value												
		Lysophosphatidylcholine												
		LPC(17:1) [sn1] (a) / LPC(17:1) [sn2] (b)	LPC(17:1) (a) [sn1] [104_sn1]	LPC(17:1) [sn1] (b)	LPC(18:0) [sn2]	LPC(18:0) [sn1]	LPC(18:1) [sn2]	LPC(18:1) [sn1]	LPC(18:2) [sn2]	LPC(18:2) [sn1]	LPC(18:3) [sn2] (a)	LPC(18:3) [sn1] (a)/LPC(18:3) [sn2] (b)	LPC(18:3) (a) [sn1] [104_sn1]	LPC(18:3) [sn1] (b)
Liver	Heart	**.004**	**.006**	.148	.986	.996	.998	**.000**	**.000**	.150	**.000**	**.000**	**.000**	**.000**
	Kidney	**.001**	**.000**	1.000	.183	.997	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	.361	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.012**	**.004**	.788	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.009**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	.236	**.026**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.004**	**.006**	.148	.986	.996	.998	**.000**	**.000**	.150	**.000**	**.000**	**.000**	**.000**
	Kidney	.986	.687	.404	**.035**	1.000	**.021**	1.000	.663	**.013**	.930	.999	.993	1.000
	Gluteus	.256	**.031**	1.000	**.000**	**.000**	**.000**	**.001**	.471	**.000**	.958	.997	.201	.955
	Soleus	1.000	.998	.969	**.001**	**.000**	**.001**	.085	.647	**.004**	.975	.998	.365	.977
	VAT	**.006**	**.001**	.884	**.000**	**.000**	**.000**	**.000**	.429	**.000**	.835	.994	**.027**	.853
	SAT	.347	.079	1.000	.137	**.000**	**.002**	.089	.728	**.012**	.960	.998	.586	.993
Kidney	Liver	**.001**	**.000**	1.000	.183	.997	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.986	.687	.404	**.035**	1.000	**.021**	1.000	.663	**.013**	.930	.999	.993	1.000
	Gluteus	.768	.689	.670	**.000**	**.000**	.801	**.004**	1.000	.897	1.000	1.000	.636	.995
	Soleus	.996	.964	.954	**.000**	**.000**	.907	.155	1.000	.998	1.000	1.000	.807	.998
	VAT	.082	.103	**.045**	**.000**	**.000**	.734	**.001**	1.000	.768	1.000	1.000	.195	.969
	SAT	.837	.850	.502	**.000**	**.000**	.955	.161	1.000	1.000	1.000	1.000	.940	1.000
Gluteus	Liver	**.000**	**.000**	.361	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.256	**.031**	1.000	**.000**	**.000**	**.000**	**.001**	.471	**.000**	.958	.997	.201	.955
	Kidney	.768	.689	.670	**.000**	**.000**	.801	**.004**	1.000	.897	1.000	1.000	.636	.995
	Soleus	.415	.195	.997	.952	.987	1.000	.860	1.000	.996	1.000	1.000	1.000	1.000
	VAT	.813	.914	.769	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000	.989	1.000
	SAT	1.000	1.000	1.000	.112	.693	1.000	.852	1.000	.960	1.000	1.000	.998	1.000
Soleus	Liver	**.012**	**.004**	.788	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	1.000	.998	.969	**.001**	**.000**	**.001**	.085	.647	**.004**	.975	.998	.365	.977
	Kidney	.996	.964	.954	**.000**	**.000**	.907	.155	1.000	.998	1.000	1.000	.807	.998
	Gluteus	.415	.195	.997	.952	.987	1.000	.860	1.000	.996	1.000	1.000	1.000	1.000
	VAT	**.022**	**.012**	.439	.995	.993	1.000	.571	1.000	.976	1.000	1.000	.964	1.000
	SAT	.506	.339	.976	.635	.985	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
VAT	Liver	**.000**	**.000**	**.009**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.006**	**.001**	.884	**.000**	**.000**	**.000**	**.000**	.429	**.000**	.835	.994	**.027**	.853
	Kidney	.082	.103	**.045**	**.000**	**.000**	.734	**.001**	1.000	.768	1.000	1.000	.195	.969
	Gluteus	.813	.914	.769	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000	.989	1.000
	Soleus	**.022**	**.012**	.439	.995	.993	1.000	.571	1.000	.976	1.000	1.000	.964	1.000
	SAT	.802	.837	.936	.213	.726	.999	.559	1.000	.885	1.000	1.000	.853	.999
SAT	Liver	**.000**	**.000**	.236	**.026**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.347	.079	1.000	.137	**.000**	**.002**	.089	.728	**.012**	.960	.998	.586	.993
	Kidney	.837	.850	.502	**.000**	**.000**	.955	.161	1.000	1.000	1.000	1.000	.940	1.000
	Gluteus	1.000	1.000	1.000	.112	.693	1.000	.852	1.000	.960	1.000	1.000	.998	1.000
	Soleus	.506	.339	.976	.635	.985	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	.802	.837	.936	.213	.726	.999	.559	1.000	.885	1.000	1.000	.853	.999

		p value												
		Lysophosphatidylcholine												
		LPC(19:0) [sn2] (a)	LPC(19:0) [sn1] (a) / LPC(19:0) [sn2] (b)	LPC(19:0) (a) [sn1] [104_sn1]	LPC(19:0) [sn1] (b)	LPC(19:1) (a)	LPC(19:1) (b)	LPC(19:1) (c)	LPC(20:0) [sn2]	LPC(20:0) [sn1]	LPC(20:1) [sn2]	LPC(20:1) [sn1]	LPC(20:2) [sn2]	LPC(20:2) [sn1]
Liver	Heart	.108	**.000**	**.000**	**.000**	.999	**.000**	.972	.099	**.018**	**.008**	**.000**	.868	**.000**
	Kidney	.744	**.002**	**.001**	.052	**.001**	**.000**	1.000	**.010**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.999	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.047**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.073	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	.885	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	.108	**.000**	**.000**	**.000**	.999	**.000**	.972	.099	**.018**	**.008**	**.000**	.868	**.000**
	Kidney	**.003**	.403	.633	.804	**.000**	1.000	.931	**.000**	**.000**	.805	.416	**.002**	.779
	Gluteus	**.000**	**.001**	**.001**	**.000**	**.000**	.427	.843	**.000**	**.000**	**.001**	.187	**.000**	**.011**
	Soleus	**.034**	**.021**	**.014**	**.009**	**.000**	.957	**.005**	**.005**	**.013**	**.008**	.617	**.000**	.172
	VAT	**.001**	**.001**	**.001**	**.000**	**.000**	.198	.394	**.000**	**.000**	**.001**	.116	**.000**	**.003**
	SAT	.825	.546	.500	.323	**.000**	.887	1.000	.275	.576	**.022**	.705	**.000**	.296
Kidney	Liver	.744	**.002**	**.001**	.052	**.001**	**.000**	1.000	**.010**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.003**	.403	.633	.804	**.000**	1.000	.931	**.000**	**.000**	.805	.416	**.002**	.779
	Gluteus	**.000**	**.000**	**.000**	**.000**	.433	.563	1.000	**.000**	**.000**	.072	**.002**	.850	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	.685	.981	.115	**.000**	**.000**	.255	**.020**	.938	**.010**
	VAT	**.000**	**.000**	**.000**	**.000**	**.037**	.312	.064	**.000**	**.000**	.059	**.001**	.713	**.000**
	SAT	**.000**	**.014**	**.028**	**.027**	.840	.939	.814	**.000**	**.000**	.444	**.028**	.939	**.021**
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.999	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.001**	**.001**	**.000**	**.000**	.427	.843	**.000**	**.000**	**.001**	.187	**.000**	**.011**
	Kidney	**.000**	**.000**	**.000**	**.000**	.433	.563	1.000	**.000**	**.000**	.072	**.002**	.850	**.000**
	Soleus	.874	.984	.979	.989	1.000	.972	.178	.902	.834	.999	.995	1.000	.970
	VAT	1.000	1.000	1.000	1.000	.912	1.000	**.037**	1.000	1.000	1.000	1.000	1.000	1.000
	SAT	.057	.258	.204	.326	.997	.994	.695	.120	.053	.979	.986	1.000	.898
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.047**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.034**	**.021**	**.014**	**.009**	**.000**	.957	**.005**	**.005**	**.013**	**.008**	.617	**.000**	.172
	Kidney	**.000**	**.000**	**.000**	**.000**	.685	.981	.115	**.000**	**.000**	.255	**.020**	.938	**.010**
	Gluteus	.874	.984	.979	.989	1.000	.972	.178	.902	.834	.999	.995	1.000	.970
	VAT	.963	.996	.998	.995	.787	.863	**.000**	.886	.856	.999	.985	1.000	.882
	SAT	.605	.764	.717	.803	1.000	1.000	**.005**	.755	.641	1.000	1.000	1.000	1.000
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.073	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.001**	**.001**	**.001**	**.000**	**.000**	.198	.394	**.000**	**.000**	**.001**	.116	**.000**	**.003**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.037**	.312	.064	**.000**	**.000**	.059	**.001**	.713	**.000**
	Gluteus	1.000	1.000	1.000	1.000	.912	1.000	**.037**	1.000	1.000	1.000	1.000	1.000	1.000
	Soleus	.963	.996	.998	.995	.787	.863	**.000**	.886	.856	.999	.985	1.000	.882
	SAT	.101	.334	.310	.354	.614	.943	.773	.099	.053	.977	.967	1.000	.738
SAT	Liver	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	.885	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.825	.546	.500	.323	**.000**	.887	1.000	.275	.576	**.022**	.705	**.000**	.296
	Kidney	**.000**	**.014**	**.028**	**.027**	.840	.939	.814	**.000**	**.000**	.444	**.028**	.939	**.021**
	Gluteus	.057	.258	.204	.326	.997	.994	.695	.120	.053	.979	.986	1.000	.898
	Soleus	.605	.764	.717	.803	1.000	1.000	**.005**	.755	.641	1.000	1.000	1.000	1.000
	VAT	.101	.334	.310	.354	.614	.943	.773	.099	.053	.977	.967	1.000	.738

		p value												
		Lysophosphatidylcholine												
		LPC(20:3) [sn2]	LPC(20:3) [sn1]	LPC(20:4) [sn2]	LPC(20:4) [sn1]	LPC(20:5) [sn2]	LPC(20:5) [sn1]	LPC(22:0) [sn2]	LPC(22:0) [sn1]	LPC(22:1) [sn2]	LPC(22:1) [sn1]	LPC(22:4) [sn2]	LPC(22:4) [sn1]	LPC(22:5) [sn2] (n3)
Liver	Heart	**.000**	**.000**	**.014**	**.013**	**.000**	**.000**	.827	.376	.677	.548	.999	.999	1.000
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.027**	**.000**	**.012**	**.032**	**.002**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.005**	**.002**	**.007**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	**.002**	**.016**	**.027**	**.018**	**.013**	**.038**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	**.001**	**.001**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	**.008**	.287	.172	**.009**	**.005**	**.003**
Heart	Liver	**.000**	**.000**	**.014**	**.013**	**.000**	**.000**	.827	.376	.677	.548	.999	.999	1.000
	Kidney	.926	.977	.185	.296	.486	.634	**.000**	**.000**	**.000**	**.000**	**.003**	**.010**	**.003**
	Gluteus	.522	.278	.076	.098	.431	.686	**.000**	**.000**	**.029**	**.041**	**.001**	**.000**	**.009**
	Soleus	.643	.473	.114	.153	.557	.582	**.047**	.259	.373	.618	**.005**	**.004**	**.050**
	VAT	.413	.118	.051	.073	.153	.175	**.000**	**.000**	**.007**	**.006**	**.000**	**.000**	**.001**
	SAT	.611	.550	.105	.194	.356	.670	.106	.480	.982	.968	**.002**	**.001**	**.004**
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.027**	**.000**	**.012**	**.032**	**.002**
	Heart	.926	.977	.185	.296	.486	.634	**.000**	**.000**	**.000**	**.000**	**.003**	**.010**	**.003**
	Gluteus	.991	.830	1.000	.998	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.957	1.000
	Soleus	.997	.939	1.000	.999	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.999	.986
	VAT	.980	.611	.999	.997	.997	.989	**.000**	**.000**	**.000**	**.000**	.999	.886	1.000
	SAT	.996	.964	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.984	1.000
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.005**	**.002**	**.007**
	Heart	.522	.278	.076	.098	.431	.686	**.000**	**.000**	**.029**	**.041**	**.001**	**.000**	**.009**
	Kidney	.991	.830	1.000	.998	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.957	1.000
	Soleus	1.000	1.000	1.000	1.000	1.000	1.000	.373	.201	.950	.867	1.000	.999	.999
	VAT	1.000	1.000	1.000	1.000	.999	.982	.999	1.000	1.000	.997	1.000	1.000	.998
	SAT	1.000	1.000	1.000	1.000	1.000	1.000	.213	.091	.309	.426	1.000	1.000	.999
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	**.002**	**.016**	**.027**	**.018**	**.013**	**.038**
	Heart	.643	.473	.114	.153	.557	.582	**.047**	.259	.373	.618	**.005**	**.004**	**.050**
	Kidney	.997	.939	1.000	.999	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.999	.986
	Gluteus	1.000	1.000	1.000	1.000	1.000	1.000	.373	.201	.950	.867	1.000	.999	.999
	VAT	1.000	.998	1.000	1.000	.997	.998	.158	.081	.801	.531	1.000	.992	.956
	SAT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.904	.991	1.000	1.000	.974
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	**.001**	**.001**
	Heart	.413	.118	.051	.073	.153	.175	**.000**	**.000**	**.007**	**.006**	**.000**	**.000**	**.001**
	Kidney	.980	.611	.999	.997	.997	.989	**.000**	**.000**	**.000**	**.000**	.999	.886	1.000
	Gluteus	1.000	1.000	1.000	1.000	.999	.982	.999	1.000	1.000	.997	1.000	1.000	.998
	Soleus	1.000	.998	1.000	1.000	.997	.998	.158	.081	.801	.531	1.000	.992	.956
	SAT	1.000	.993	1.000	1.000	1.000	.993	.076	**.031**	.138	.148	1.000	1.000	1.000
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	**.008**	.287	.172	**.009**	**.005**	**.003**
	Heart	.611	.550	.105	.194	.356	.670	.106	.480	.982	.968	**.002**	**.001**	**.004**
	Kidney	.996	.964	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.984	1.000
	Gluteus	1.000	1.000	1.000	1.000	1.000	1.000	.213	.091	.309	.426	1.000	1.000	.999
	Soleus	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.904	.991	1.000	1.000	.974
	VAT	1.000	.993	1.000	1.000	1.000	.993	.076	**.031**	.138	.148	1.000	1.000	1.000

		p value										
		Lysophosphatidylcholine										
		LPC(22:5) [sn1] (n3)/LPC(22:5) [sn2] (n6)	LPC(22:5) (n3) [sn1] [104_sn1]	LPC(22:5) [sn1] (n6)	LPC(22:6) [sn2]	LPC(22:6) [sn1]	LPC(24:0) [sn2]	LPC(24:0) [sn1]	LPC(26:0) [sn2]	LPC(26:0) [sn1]	LPC(22:5) [sn1] (n3)/LPC(22:5) [sn2] (n6)	LPC(22:5) (n3) [sn1] [104_sn1]
Liver	Heart	**.010**	.943	**.003**	**.000**	**.000**	.791	.288	1.000	1.000	**.010**	.943
	Kidney	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	1.000	**.000**	**.000**
	Soleus	**.000**	**.005**	**.000**	**.000**	**.000**	**.032**	**.005**	1.000	1.000	**.000**	**.005**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.997	.999	**.000**	**.000**
	SAT	**.000**	**.001**	**.000**	**.000**	**.000**	.076	**.005**	1.000	1.000	**.000**	**.001**
Heart	Liver	**.010**	.943	**.003**	**.000**	**.000**	.791	.288	1.000	1.000	**.010**	.943
	Kidney	.184	**.010**	.257	.690	.662	**.000**	**.000**	**.000**	**.000**	.184	**.010**
	Gluteus	.196	**.009**	.202	.728	.621	**.009**	**.015**	1.000	1.000	.196	**.009**
	Soleus	.343	.062	.345	.928	.907	.431	.464	1.000	1.000	.343	.062
	VAT	.105	**.002**	.107	.455	.360	**.000**	**.002**	1.000	1.000	.105	**.002**
	SAT	.189	**.013**	.222	.568	.512	.656	.466	1.000	1.000	.189	**.013**
Kidney	Liver	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	Heart	.184	**.010**	.257	.690	.662	**.000**	**.000**	**.000**	**.000**	.184	**.010**
	Gluteus	1.000	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	1.000
	Soleus	1.000	.999	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.999
	VAT	1.000	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	1.000
	SAT	1.000	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	1.000
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	1.000	**.000**	**.000**
	Heart	.196	**.009**	.202	.728	.621	**.009**	**.015**	1.000	1.000	.196	**.009**
	Kidney	1.000	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	1.000
	Soleus	1.000	.998	1.000	1.000	.999	.746	.815	1.000	1.000	1.000	.998
	VAT	1.000	1.000	1.000	1.000	1.000	.983	.998	1.000	1.000	1.000	1.000
	SAT	1.000	1.000	1.000	1.000	1.000	.536	.814	1.000	1.000	1.000	1.000
Soleus	Liver	**.000**	**.005**	**.000**	**.000**	**.000**	**.032**	**.005**	1.000	1.000	**.000**	**.005**
	Heart	.343	.062	.345	.928	.907	.431	.464	1.000	1.000	.343	.062
	Kidney	1.000	.999	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	.999
	Gluteus	1.000	.998	1.000	1.000	.999	.746	.815	1.000	1.000	1.000	.998
	VAT	1.000	.969	1.000	.992	.986	.260	.482	1.000	1.000	1.000	.969
	SAT	1.000	.998	1.000	.995	.995	1.000	1.000	1.000	1.000	1.000	.998
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.997	.999	**.000**	**.000**
	Heart	.105	**.002**	.107	.455	.360	**.000**	**.002**	1.000	1.000	.105	**.002**
	Kidney	1.000	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	1.000
	Gluteus	1.000	1.000	1.000	1.000	1.000	.983	.998	1.000	1.000	1.000	1.000
	Soleus	1.000	.969	1.000	.992	.986	.260	.482	1.000	1.000	1.000	.969
	SAT	1.000	1.000	1.000	1.000	1.000	.133	.481	1.000	1.000	1.000	1.000
SAT	Liver	**.000**	**.001**	**.000**	**.000**	**.000**	.076	**.005**	1.000	1.000	**.000**	**.001**
	Heart	.189	**.013**	.222	.568	.512	.656	.466	1.000	1.000	.189	**.013**
	Kidney	1.000	1.000	1.000	1.000	1.000	**.000**	**.000**	**.000**	**.000**	1.000	1.000
	Gluteus	1.000	1.000	1.000	1.000	1.000	.536	.814	1.000	1.000	1.000	1.000
	Soleus	1.000	.998	1.000	.995	.995	1.000	1.000	1.000	1.000	1.000	.998
	VAT	1.000	1.000	1.000	1.000	1.000	.133	.481	1.000	1.000	1.000	1.000

		p value													
		Lysophosphatidylethanolamine													
		LPE(16:0) [sn2]	LPE(16:0) [sn1]	LPE(17:0) [sn2]	LPE(17:0) [sn1]	LPE(18:0) [sn2]	LPE(18:0) [sn1]	LPE(18:1) [sn2]	LPE(18:1) [sn1]	LPE(18:2) [sn2]	LPE(18:2) [sn1]	LPE(20:4) [sn2]	LPE(20:4) [sn1]	LPE(22:6) [sn2]	LPE(22:6) [sn1]
Liver	Heart	**.005**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	1.000	**.006**	**.017**	.090	.945	.062	**.001**	.299	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.005**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.030**	**.001**	.870	.088	**.000**	**.000**	.432	**.000**	.763	.469	1.000	1.000	**.010**	**.006**
	Gluteus	**.038**	.389	.801	**.016**	**.000**	**.000**	**.000**	**.011**	.381	**.034**	.134	.160	.085	**.049**
	Soleus	1.000	.724	.769	.110	**.015**	**.004**	.953	.414	.605	.251	.236	.293	.488	.555
	VAT	**.000**	.278	.988	**.033**	**.000**	**.000**	**.000**	**.019**	.363	**.032**	.197	.332	**.004**	**.002**
	SAT	**.001**	.607	.763	.161	**.003**	**.000**	.291	.406	.617	.123	.431	.663	**.010**	**.006**
Kidney	Liver	1.000	**.006**	**.017**	.090	.945	.062	**.001**	.299	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.030**	**.001**	.870	.088	**.000**	**.000**	.432	**.000**	.763	.469	1.000	1.000	**.010**	**.006**
	Gluteus	**.000**	**.000**	.186	**.000**	**.000**	**.000**	**.000**	**.000**	.997	.880	.339	.287	.985	.988
	Soleus	**.031**	**.000**	.180	**.000**	**.000**	**.000**	.110	**.000**	1.000	.999	.484	.448	.718	.540
	VAT	**.000**	**.000**	.477	**.000**	**.000**	**.000**	**.000**	**.000**	.998	.898	.455	.512	1.000	1.000
	SAT	**.000**	**.000**	.176	**.000**	**.000**	**.000**	**.005**	**.000**	1.000	.984	.708	.806	1.000	1.000
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.038**	.389	.801	**.016**	**.000**	**.000**	**.000**	**.011**	.381	**.034**	.134	.160	.085	**.049**
	Kidney	**.000**	**.000**	.186	**.000**	**.000**	**.000**	**.000**	**.000**	.997	.880	.339	.287	.985	.988
	Soleus	.152	1.000	1.000	.997	.959	.972	**.007**	.801	1.000	.991	1.000	1.000	.985	.925
	VAT	.134	1.000	.994	1.000	1.000	.997	.998	1.000	1.000	1.000	1.000	.999	.952	.946
	SAT	.755	1.000	1.000	.987	.999	1.000	.148	.808	1.000	1.000	.999	.986	.972	.979
Soleus	Liver	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	1.000	.724	.769	.110	**.015**	**.004**	.953	.414	.605	.251	.236	.293	.488	.555
	Kidney	**.031**	**.000**	.180	**.000**	**.000**	**.000**	.110	**.000**	1.000	.999	.484	.448	.718	.540
	Gluteus	.152	1.000	1.000	.997	.959	.972	**.007**	.801	1.000	.991	1.000	1.000	.985	.925
	VAT	**.000**	.998	.989	1.000	.826	.749	**.022**	.912	1.000	.994	1.000	1.000	.578	.364
	SAT	**.005**	1.000	1.000	1.000	.998	.961	.910	1.000	1.000	1.000	1.000	.998	.673	.507
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.278	.988	**.033**	**.000**	**.000**	**.000**	**.019**	.363	**.032**	.197	.332	**.004**	**.002**
	Kidney	**.000**	**.000**	.477	**.000**	**.000**	**.000**	**.000**	**.000**	.998	.898	.455	.512	1.000	1.000
	Gluteus	.134	1.000	.994	1.000	1.000	.997	.998	1.000	1.000	1.000	1.000	.999	.952	.946
	Soleus	**.000**	.998	.989	1.000	.826	.749	**.022**	.912	1.000	.994	1.000	1.000	.578	.364
	SAT	.947	1.000	.988	.999	.985	.999	.328	.916	1.000	1.000	1.000	1.000	1.000	1.000
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.001**	.607	.763	.161	**.003**	**.000**	.291	.406	.617	.123	.431	.663	**.010**	**.006**
	Kidney	**.000**	**.000**	.176	**.000**	**.000**	**.000**	**.005**	**.000**	1.000	.984	.708	.806	1.000	1.000
	Gluteus	.755	1.000	1.000	.987	.999	1.000	.148	.808	1.000	1.000	.999	.986	.972	.979
	Soleus	**.005**	1.000	1.000	1.000	.998	.961	.910	1.000	1.000	1.000	1.000	.998	.673	.507
	VAT	.947	1.000	.988	.999	.985	.999	.328	.916	1.000	1.000	1.000	1.000	1.000	1.000

		p value											
		Lysophosphatidylinositol								*Lysophosphatidylserine*			
		LPI(18:0) [sn2]	LPI(18:0) [sn1]	LPI(18:1) [sn2]	LPI(18:1) [sn1]	LPI(18:2) [sn2]	LPI(18:2) [sn1]	LPI(20:4) [sn2]	LPI(20:4) [sn1]	LPS(16:0)	LPS(18:0)	LPS(18:1)	LPS(18:2)
Liver	Heart	**.000**	**.000**	.200	**.000**	**.000**	**.000**	**.000**	**.000**	**.011**	.887	.850	.823
	Kidney	.762	**.000**	.683	**.000**	**.000**	**.000**	**.000**	**.000**	.580	.522	.245	.909
	Gluteus	**.000**	**.000**	.078	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.024**	.303	.289
	Soleus	**.000**	**.000**	**.004**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	.278	.917	.422
	VAT	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	.148	.193
	SAT	**.000**	**.000**	**.033**	**.000**	**.000**	**.000**	**.000**	**.000**	.068	.280	1.000	1.000
Heart	Liver	**.000**	**.000**	.200	**.000**	**.000**	**.000**	**.000**	**.000**	**.011**	.887	.850	.823
	Kidney	**.000**	**.000**	.992	.996	.738	.999	.996	.564	.649	.991	.914	1.000
	Gluteus	.925	.862	.996	.339	.431	.428	.858	.964	.734	**.001**	.949	.954
	Soleus	1.000	.952	.542	1.000	.503	.809	.926	.982	.991	**.025**	1.000	.984
	VAT	.982	.473	.768	.824	.415	.541	.770	.889	**.014**	**.000**	.825	.904
	SAT	.999	.735	.938	.949	.722	.951	.913	.987	1.000	**.025**	.976	.961
Kidney	Liver	.762	**.000**	.683	**.000**	**.000**	**.000**	**.000**	**.000**	.580	.522	.245	.909
	Heart	**.000**	**.000**	.992	.996	.738	.999	.996	.564	.649	.991	.914	1.000
	Gluteus	**.001**	**.000**	.880	.147	.999	.753	.558	.159	.063	**.000**	1.000	.942
	Soleus	**.000**	**.000**	.241	.961	1.000	.967	.679	.225	.331	**.007**	.937	.976
	VAT	**.000**	**.000**	.400	.512	.999	.851	.444	.084	**.000**	**.000**	1.000	.889
	SAT	**.000**	**.000**	.663	.737	1.000	.998	.655	.247	.888	**.007**	.527	.984
Gluteus	Liver	**.000**	**.000**	.078	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.024**	.303	.289
	Heart	.925	.862	.996	.339	.431	.428	.858	.964	.734	**.001**	.949	.954
	Kidney	**.001**	**.000**	.880	.147	.999	.753	.558	.159	.063	**.000**	1.000	.942
	Soleus	.997	1.000	.898	.712	1.000	.999	1.000	1.000	.992	.971	.962	1.000
	VAT	1.000	.997	.986	.980	1.000	1.000	1.000	1.000	.513	.999	1.000	1.000
	SAT	.998	1.000	.999	.952	1.000	.976	1.000	1.000	.643	.971	.598	.555
Soleus	Liver	**.000**	**.000**	**.004**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	.278	.917	.422
	Heart	1.000	.952	.542	1.000	.503	.809	.926	.982	.991	**.025**	1.000	.984
	Kidney	**.000**	**.000**	.241	.961	1.000	.967	.679	.225	.331	**.007**	.937	.976
	Gluteus	.997	1.000	.898	.712	1.000	.999	1.000	1.000	.992	.971	.962	1.000
	VAT	1.000	.987	.999	.983	1.000	1.000	1.000	1.000	.181	.820	.871	1.000
	SAT	1.000	.999	.992	.998	1.000	1.000	1.000	1.000	.966	1.000	.988	.681
VAT	Liver	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	.148	.193
	Heart	.982	.473	.768	.824	.415	.541	.770	.889	**.014**	**.000**	.825	.904
	Kidney	**.000**	**.000**	.400	.512	.999	.851	.444	.084	**.000**	**.000**	1.000	.889
	Gluteus	1.000	.997	.986	.980	1.000	1.000	1.000	1.000	.513	.999	1.000	1.000
	Soleus	1.000	.987	.999	.983	1.000	1.000	1.000	1.000	.181	.820	.871	1.000
	SAT	1.000	1.000	1.000	1.000	1.000	.994	1.000	1.000	**.017**	.819	.396	.442
SAT	Liver	**.000**	**.000**	**.033**	**.000**	**.000**	**.000**	**.000**	**.000**	.068	.280	1.000	1.000
	Heart	.999	.735	.938	.949	.722	.951	.913	.987	1.000	**.025**	.976	.961
	Kidney	**.000**	**.000**	.663	.737	1.000	.998	.655	.247	.888	**.007**	.527	.984
	Gluteus	.998	1.000	.999	.952	1.000	.976	1.000	1.000	.643	.971	.598	.555
	Soleus	1.000	.999	.992	.998	1.000	1.000	1.000	1.000	.966	1.000	.988	.681
	VAT	1.000	1.000	1.000	1.000	1.000	.994	1.000	1.000	**.017**	.819	.396	.442

p values < 0.05 are represented in bold numbers.

Table S14 Glycerophospholipid concentration detected by targeted lipidomic analysis in all the studied tissues. Lipid species detected were 68 PC, 37 PE, 4 PG, 27 PI and 7 PS.

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Phosphatidylcholine							
PC(28:0)	0.14 ± 0.01	0.17 ± 0.01	0.26 ± 0.01	0.14 ± 0.01	0.15 ± 0.02	0.03 ± 0.002	0.06 ± 0.004
PC(14:0/16:0)	6.40 ± 0.55	11.45 ± 1.15	30.42 ± 1.64	6.31 ± 0.55	6.55 ± 1.12	0.40 ± 0.05	1.98 ± 0.31
PC(31:0) (a)	0.63 ± 0.07	0.57 ± 0.07	1.06 ± 0.09	0.58 ± 0.04	0.48 ± 0.07	0.03 ± 0.01	0.16 ± 0.02
PC(31:0) (b)	3.18 ± 0.29	6.34 ± 0.63	20.12 ± 0.91	2.56 ± 0.08	2.95 ± 0.29	0.64 ± 0.12	2.66 ± 0.42
PC(16:0/16:0)	144.3 ± 11.53	254.2 ± 26.68	753.5 ± 34.63	52.72 ± 2.49	71.65 ± 8.55	13.85 ± 2.30	60.50 ± 8.95
PC(32:1)	68.47 ± 7.20	33.42 ± 3.66	97.88 ± 5.33	46.69 ± 3.21	48.46 ± 7.94	2.24 ± 0.41	12.63 ± 1.42
PC(32:2)	22.58 ± 1.87	4.42 ± 0.50	5.67 ± 0.27	3.60 ± 0.23	4.15 ± 0.76	0.30 ± 0.05	1.38 ± 0.11
PC(33:0) (a)	1.89 ± 0.19	2.24 ± 0.24	4.23 ± 0.25	1.21 ± 0.06	1.25 ± 0.19	0.10 ± 0.02	0.51 ± 0.08
PC(33:0) (b)	1.47 ± 0.12	1.90 ± 0.18	4.11 ± 0.25	0.55 ± 0.02	0.70 ± 0.09	0.15 ± 0.03	0.51 ± 0.09
PC(33:1)	6.80 ± 0.42	4.22 ± 0.43	7.89 ± 0.58	3.97 ± 0.17	4.52 ± 0.61	0.22 ± 0.04	1.08 ± 0.15
PC(33:2)	14.84 ± 0.61	2.89 ± 0.28	3.86 ± 0.35	2.40 ± 0.10	3.40 ± 0.56	0.29 ± 0.05	0.82 ± 0.09
PC(16:0/18:0)	19.81 ± 1.83	35.18 ± 3.71	40.91 ± 2.06	4.83 ± 0.23	6.61 ± 0.79	1.52 ± 0.23	5.06 ± 0.72
PC(16:0/18:1)	389.0 ± 21.51	509.9 ± 51.72	682.7 ± 38.63	249.3 ± 11.45	308.0 ± 42.04	14.63 ± 2.00	65.87 ± 8.60
PC(16:0/18:2)	1,859 ± 86.73	878.7 ± 75.17	945.4 ± 46.49	859.7 ± 46.39	1,280 ± 133.59	136.9 ± 22.60	369.6 ± 39.47
PC(16:1/18:2)	57.34 ± 7.39	8.79 ± 1.28	8.57 ± 0.50	8.02 ± 0.48	13.17 ± 2.33	1.26 ± 0.22	5.64 ± 0.54
PC(16:0/18:3) (a)	20.42 ± 1.20	5.36 ± 0.66	8.69 ± 0.55	4.83 ± 0.22	6.97 ± 1.40	0.47 ± 0.07	1.77 ± 0.21
PC(16:0/18:3) (b)	54.74 ± 6.33	3.82 ± 0.43	5.41 ± 0.43	3.45 ± 0.20	4.56 ± 0.73	0.13 ± 0.02	0.60 ± 0.07
PC(14:0/20:4)	26.65 ± 2.83	7.31 ± 0.67	3.33 ± 0.24	2.25 ± 0.16	1.64 ± 0.35	0.05 ± 0.01	0.25 ± 0.03
PC(34:5)	0.56 ± 0.06	0.11 ± 0.01	0.08 ± 0.01	0.05 ± 0.005	0.05 ± 0.01	0.003 ± 0.001	0.01 ± 0.001
PC(15-MHDA/18:1)	1.20 ± 0.12	1.41 ± 0.18	1.59 ± 0.08	0.75 ± 0.04	0.90 ± 0.10	0.05 ± 0.01	0.25 ± 0.03
PC(17:0/18:1)	2.83 ± 0.17	4.03 ± 0.39	4.87 ± 0.46	1.34 ± 0.04	2.04 ± 0.25	0.23 ± 0.04	0.91 ± 0.15
PC(15-MHDA/18:2)	6.61 ± 0.61	2.67 ± 0.27	2.17 ± 0.17	1.63 ± 0.10	2.68 ± 0.34	0.24 ± 0.04	0.77 ± 0.08
PC(17:0/18:2)	16.06 ± 0.95	7.30 ± 0.75	5.06 ± 0.44	3.48 ± 0.18	6.23 ± 0.68	1.43 ± 0.27	3.34 ± 0.45
PC(17:1/18:2)	1.63 ± 0.12	0.56 ± 0.06	0.46 ± 0.03	0.41 ± 0.02	0.80 ± 0.11	0.07 ± 0.01	0.20 ± 0.03
PC(15:0/20:3)	1.06 ± 0.06	0.32 ± 0.03	0.35 ± 0.02	0.33 ± 0.01	0.49 ± 0.08	0.04 ± 0.01	0.12 ± 0.02
PC(15:0/20:4)	18.74 ± 1.51	5.12 ± 0.55	6.56 ± 0.53	2.83 ± 0.15	2.36 ± 0.46	0.06 ± 0.01	0.30 ± 0.04
PC(35:5)	0.24 ± 0.02	0.05 ± 0.005	0.05 ± 0.003	0.04 ± 0.00	0.03 ± 0.01	0.002 ± 0.0004	0.01 ± 0.001
PC(36:0)	0.34 ± 0.02	0.13 ± 0.01	0.40 ± 0.04	0.03 ± 0.00	0.50 ± 0.13	0.02 ± 0.002	0.12 ± 0.03
PC(18:0/18:1)	47.69 ± 3.28	164.3 ± 16.19	63.47 ± 4.16	10.92 ± 0.57	21.80 ± 2.86	4.02 ± 0.48	16.58 ± 2.74
PC(18:1/18:1)	50.90 ± 4.27	56.02 ± 5.84	46.55 ± 3.06	23.44 ± 1.38	33.87 ± 4.38	3.25 ± 0.56	13.30 ± 1.49
PC(18:0/18:2)	465.4 ± 25.30	445.0 ± 46.74	189.2 ± 11.95	61.59 ± 4.31	147.2 ± 22.52	32.58 ± 4.59	93.36 ± 14.41
PC(18:1/18:2)	279.9 ± 26.45	229.7 ± 23.52	106.8 ± 6.25	71.74 ± 3.65	136.8 ± 17.60	17.85 ± 3.57	54.21 ± 5.75
PC(16:0/20:3) (a)	89.98 ± 5.17	37.98 ± 4.35	55.18 ± 3.79	34.57 ± 1.75	48.66 ± 7.68	3.39 ± 0.47	10.84 ± 1.42
PC(16:0/20:3) (b)	6.12 ± 0.61	3.22 ± 0.34	2.54 ± 0.18	1.51 ± 0.08	2.02 ± 0.32	0.16 ± 0.02	0.52 ± 0.05

PC(18:2/18:2)	83.92 ± 9.20	96.72 ± 13.15	47.68 ± 3.91	33.35 ± 2.30	86.54 ± 15.25	3.71 ± 0.46	11.40 ± 1.44
PC(16:0/20:4)	2,262 ± 179.56	1,433 ± 143.34	1,492 ± 62.23	1,078 ± 45.64	1,008 ± 145.68	35.83 ± 5.51	127.4 ± 12.47
PC(16:1/20:4)	63.78 ± 7.64	17.34 ± 1.97	16.29 ± 1.59	7.90 ± 0.59	7.23 ± 1.44	0.19 ± 0.04	1.19 ± 0.15
PC(16:0/20:5)	17.62 ± 1.41	7.45 ± 0.83	7.71 ± 0.53	6.14 ± 0.28	6.28 ± 1.36	0.14 ± 0.02	0.69 ± 0.06
PC 36:6(a)	0.84 ± 0.06	0.32 ± 0.04	0.23 ± 0.01	0.14 ± 0.01	0.15 ± 0.03	0.01 ± 0.001	0.02 ± 0.002
PC(14:0/22:6)	2.76 ± 0.28	0.71 ± 0.07	0.38 ± 0.02	0.51 ± 0.03	0.51 ± 0.11	0.01 ± 0.001	0.02 ± 0.002
PC(15-MHDA/20:4)	15.35 ± 1.77	3.98 ± 0.45	3.08 ± 0.20	1.59 ± 0.07	1.86 ± 0.31	0.07 ± 0.01	0.33 ± 0.04
PC(17:0/20:4)	46.76 ± 3.93	23.26 ± 2.60	11.45 ± 0.87	4.66 ± 0.13	5.65 ± 0.95	0.37 ± 0.07	1.26 ± 0.16
PC(15:0/22:6)	2.88 ± 0.28	0.56 ± 0.06	0.70 ± 0.07	0.53 ± 0.02	0.63 ± 0.12	0.01 ± 0.001	0.02 ± 0.001
PC(38:2)	6.95 ± 0.49	8.14 ± 0.79	6.03 ± 0.44	0.84 ± 0.04	1.76 ± 0.20	0.24 ± 0.03	0.97 ± 0.12
PC(18:0/20:3)	29.15 ± 1.45	20.23 ± 2.10	15.76 ± 1.01	2.25 ± 0.13	4.48 ± 0.66	0.53 ± 0.07	1.77 ± 0.19
PC(18:1/20:3)	29.73 ± 2.41	10.83 ± 1.09	9.53 ± 0.64	4.88 ± 0.22	7.79 ± 1.24	0.52 ± 0.09	1.82 ± 0.21
PC(38:4) (b)	58.00 ± 6.63	47.63 ± 5.69	18.09 ± 1.14	7.68 ± 0.56	11.86 ± 1.89	0.61 ± 0.10	2.99 ± 0.40
PC(18:0/20:4)	1,508 ± 134.68	1,695 ± 179.92	654.4 ± 36.84	89.53 ± 3.17	151.4 ± 26.08	11.57 ± 1.72	43.92 ± 6.25
PC(38:5) (a)	509.9 ± 44.53	236.6 ± 25.93	179.6 ± 5.60	94.33 ± 4.93	108.6 ± 17.96	3.47 ± 0.65	15.69 ± 1.94
PC(38:5) (b)	63.56 ± 8.43	28.91 ± 3.51	15.59 ± 1.12	11.40 ± 0.80	14.41 ± 2.65	0.35 ± 0.05	1.42 ± 0.14
PC(38:6) (a)	139.0 ± 10.22	267.4 ± 29.25	142.6 ± 5.78	40.26 ± 1.57	62.05 ± 12.44	1.05 ± 0.13	4.50 ± 0.60
PC(16:0/22:6)	356.5 ± 41.04	97.13 ± 12.11	91.48 ± 5.98	139.8 ± 7.43	185.5 ± 34.76	0.58 ± 0.08	2.24 ± 0.21
PC(18:2/20:5)	1.79 ± 0.22	1.38 ± 0.14	1.41 ± 0.06	0.69 ± 0.03	1.07 ± 0.22	0.02 ± 0.003	0.08 ± 0.01
PC(16:1/22:6)	9.17 ± 1.01	2.20 ± 0.26	2.17 ± 0.21	2.43 ± 0.21	2.77 ± 0.59	0.02 ± 0.003	0.08 ± 0.01
PC(38:7) (c)	1.78 ± 0.22	0.36 ± 0.04	0.44 ± 0.02	0.44 ± 0.03	0.55 ± 0.11	0.01 ± 0.001	0.02 ± 0.002
PC (39:5) (a)	0.44 ± 0.03	0.21 ± 0.03	0.08 ± 0.01	0.13 ± 0.01	0.18 ± 0.03	0.00 ± 0.001	0.02 ± 0.002
PC (39:5) (b)	3.85 ± 0.34	1.45 ± 0.17	0.44 ± 0.03	0.32 ± 0.02	0.46 ± 0.08	0.02 ± 0.003	0.08 ± 0.01
PC(15-MHDA/22:6)	2.49 ± 0.29	0.45 ± 0.06	0.28 ± 0.02	0.39 ± 0.02	0.56 ± 0.10	0.01 ± 0.001	0.03 ± 0.004
PC(17:0/22:6)	4.20 ± 0.42	1.12 ± 0.15	0.41 ± 0.04	0.70 ± 0.04	1.04 ± 0.17	0.01 ± 0.001	0.03 ± 0.004
PC(18:0/22:4)	11.17 ± 1.37	33.06 ± 3.57	4.51 ± 0.34	0.93 ± 0.07	2.38 ± 0.40	0.17 ± 0.02	0.80 ± 0.12
PC(20:0/20:4)	4.71 ± 0.41	3.82 ± 0.45	1.92 ± 0.11	0.12 ± 0.01	0.24 ± 0.04	0.04 ± 0.01	0.16 ± 0.02
PC(18:0/22:5) (n3)	67.68 ± 6.87	93.59 ± 11.70	14.11 ± 1.00	5.88 ± 0.38	11.25 ± 2.01	0.33 ± 0.05	1.46 ± 0.16
PC(18:0/22:5) (n6)	15.36 ± 2.72	16.40 ± 1.85	1.89 ± 0.22	0.62 ± 0.05	1.49 ± 0.27	0.06 ± 0.01	0.20 ± 0.02
PC(18:0/22:6)	125.1 ± 12.49	104.0 ± 13.20	21.77 ± 1.64	7.51 ± 0.57	17.46 ± 3.41	0.24 ± 0.03	0.84 ± 0.07
PC(40:7) (a)	3.24 ± 0.36	2.47 ± 0.23	3.48 ± 0.22	1.06 ± 0.06	1.63 ± 0.34	0.02 ± 0.003	0.12 ± 0.02
PC(18:1/22:6) (a)	46.91 ± 4.80	18.27 ± 1.76	5.75 ± 0.24	10.27 ± 0.57	15.77 ± 2.34	0.14 ± 0.02	0.58 ± 0.06
PC(18:1/22:6) (b)	6.30 ± 0.64	2.45 ± 0.33	1.09 ± 0.11	1.55 ± 0.13	2.07 ± 0.41	0.03 ± 0.004	0.09 ± 0.01
PC(40:8)	29.57 ± 2.45	36.85 ± 4.11	28.10 ± 1.63	8.22 ± 0.53	15.09 ± 3.10	0.14 ± 0.02	0.74 ± 0.10
Phosphatidylethanolamine							
PE(16:0/16:0)	2.40 ± 0.14	8.69 ± 0.89	21.41 ± 1.11	0.61 ± 0.03	0.55 ± 0.06	0.29 ± 0.03	0.57 ± 0.07
PE(16:0/16:1)	24.08 ± 2.15	7.16 ± 0.77	34.35 ± 2.84	2.34 ± 0.17	1.93 ± 0.16	0.82 ± 0.18	4.01 ± 0.51
PE(16:0/18:1)	111.5 ± 5.93	126.9 ± 10.94	105.9 ± 5.16	6.19 ± 0.36	11.47 ± 1.65	3.13 ± 0.41	12.03 ± 1.46

PE(16:0/18:2)	862.0 ± 50.65	150.6 ± 16.00	135.0 ± 8.05	19.49 ± 1.41	27.55 ± 3.16	11.79 ± 1.77	35.69 ± 3.02
PE(16:1/18:2)	21.05 ± 2.08	3.83 ± 0.52	9.90 ± 0.79	0.90 ± 0.06	1.64 ± 0.29	1.26 ± 0.20	5.03 ± 0.37
PE(16:0/18:3) (a)	6.12 ± 0.32	1.39 ± 0.14	1.82 ± 0.12	0.16 ± 0.01	0.26 ± 0.04	0.14 ± 0.02	0.40 ± 0.04
PE(16:0/18:3) (b)	20.26 ± 2.39	0.39 ± 0.03	1.77 ± 0.18	0.15 ± 0.02	0.14 ± 0.03	0.05 ± 0.01	0.12 ± 0.02
PE(15-MHDA/18:1)	0.69 ± 0.04	0.54 ± 0.06	0.68 ± 0.03	0.04 ± 0.005	0.09 ± 0.004	0.04 ± 0.01	0.10 ± 0.005
PE(17:0/18:1)	1.29 ± 0.07	1.78 ± 0.15	1.78 ± 0.14	0.17 ± 0.01	0.24 ± 0.03	0.15 ± 0.02	0.42 ± 0.08
PE(15-MHDA/18:2)	4.94 ± 0.34	1.38 ± 0.14	0.92 ± 0.15	0.16 ± 0.01	0.29 ± 0.04	0.17 ± 0.04	0.34 ± 0.07
PE(17:0/18:2)	12.07 ± 0.90	4.94 ± 0.52	2.32 ± 0.15	0.72 ± 0.08	1.30 ± 0.20	0.41 ± 0.08	0.97 ± 0.14
PE(36:0)	0.82 ± 0.06	1.21 ± 0.10	0.65 ± 0.05	0.42 ± 0.02	0.52 ± 0.04	0.33 ± 0.02	0.38 ± 0.02
PE(18:0/18:1)	24.41 ± 1.27	52.67 ± 4.38	47.49 ± 2.27	2.80 ± 0.14	6.17 ± 0.71	2.94 ± 0.35	10.35 ± 1.62
PE(18:1/18:1)	39.05 ± 3.39	60.21 ± 5.77	41.71 ± 1.85	2.82 ± 0.28	11.00 ± 1.67	3.90 ± 0.60	15.06 ± 1.81
PE(18:0/18:2)	546.8 ± 43.27	381.8 ± 46.66	196.0 ± 9.42	75.20 ± 5.93	142.3 ± 22.81	13.92 ± 1.78	44.15 ± 6.29
PE(18:1/18:2)	248.2 ± 22.08	164.1 ± 18.09	125.6 ± 6.71	7.29 ± 0.60	24.19 ± 3.23	10.04 ± 1.58	30.60 ± 3.47
PE(16:0/20:3)	30.26 ± 1.71	10.34 ± 1.43	13.90 ± 1.01	1.54 ± 0.12	2.35 ± 0.35	0.60 ± 0.08	2.02 ± 0.30
PE(16:0/20:4)	1,347 ± 104.59	238.9 ± 25.32	663.8 ± 30.60	48.51 ± 2.73	38.24 ± 5.90	6.10 ± 0.98	22.00 ± 1.70
PE(16:1/20:4)	34.15 ± 3.67	3.51 ± 0.43	40.81 ± 3.29	0.70 ± 0.06	1.85 ± 0.34	0.67 ± 0.10	3.45 ± 0.25
PE(16:0/20:5)	10.25 ± 0.74	1.35 ± 0.13	4.60 ± 0.41	0.36 ± 0.02	0.42 ± 0.09	0.07 ± 0.01	0.19 ± 0.02
PE(15-MHDA/20:4)	11.03 ± 0.76	2.82 ± 0.31	3.26 ± 0.25	0.33 ± 0.04	0.42 ± 0.07	0.06 ± 0.02	0.29 ± 0.04
PE(17:0/20:4)	46.03 ± 2.86	14.69 ± 1.46	21.87 ± 1.79	2.38 ± 0.07	2.74 ± 0.44	0.37 ± 0.07	1.13 ± 0.19
PE(18:0/20:3) (a)	29.64 ± 1.25	12.59 ± 1.23	17.88 ± 1.07	3.42 ± 0.24	4.82 ± 0.83	0.38 ± 0.07	1.56 ± 0.23
PE(18:0/20:3) (b)	1.23 ± 0.09	1.09 ± 0.11	1.21 ± 0.08	0.29 ± 0.03	0.31 ± 0.05	0.04 ± 0.01	0.16 ± 0.02
PE(18:0/20:4)	2,782 ± 205.3	1,624 ± 187.3	2,750 ± 134.1	247.5 ± 11.18	324.8 ± 62.81	12.70 ± 1.75	53.50 ± 7.43
PE(38:5) (a)	701.0 ± 39.21	219.9 ± 21.99	613.1 ± 30.79	17.75 ± 0.81	35.39 ± 5.60	5.09 ± 0.86	20.06 ± 2.26
PE(38:5) (b)	70.39 ± 10.65	72.82 ± 8.73	19.69 ± 1.12	4.95 ± 0.41	5.76 ± 0.86	0.35 ± 0.05	0.94 ± 0.07
PE(16:0/22:6)	1,076 ± 125.0	465.8 ± 53.18	119.1 ± 7.41	58.03 ± 5.49	60.35 ± 8.53	0.79 ± 0.14	2.73 ± 0.31
PE(15-MHDA/22:6)	4.45 ± 0.35	3.22 ± 0.35	0.36 ± 0.04	0.47 ± 0.04	0.80 ± 0.14	0.03 ± 0.01	0.05 ± 0.01
PE(17:0/22:6)	7.08 ± 0.67	9.74 ± 1.16	0.59 ± 0.06	1.37 ± 0.09	2.01 ± 0.44	0.02 ± 0.003	0.06 ± 0.01
PE(18:0/22:4)	29.19 ± 3.47	75.61 ± 6.71	29.86 ± 1.59	5.54 ± 0.46	10.26 ± 1.41	0.77 ± 0.13	4.19 ± 0.64
PE(20:0/20:4)	5.19 ± 0.25	5.70 ± 0.72	5.18 ± 0.30	0.39 ± 0.03	0.73 ± 0.11	0.06 ± 0.01	0.26 ± 0.03
PE(18:0/22:5) (n3)	84.08 ± 6.65	105.0 ± 10.37	11.02 ± 0.61	19.57 ± 1.30	26.47 ± 5.12	0.36 ± 0.07	1.76 ± 0.27
PE(18:0/22:5) (n6)	37.25 ± 6.09	265.3 ± 26.65	5.20 ± 0.45	16.76 ± 1.49	25.09 ± 4.43	0.28 ± 0.06	0.82 ± 0.08
PE(18:0/22:6)	378.4 ± 39.93	1,127 ± 126.8	14.75 ± 0.87	159.6 ± 9.50	272.6 ± 51.71	0.38 ± 0.06	1.66 ± 0.27
PE(18:1/22:6) (a)	149.3 ± 16.98	147.3 ± 15.09	17.75 ± 1.18	16.59 ± 1.20	45.58 ± 7.74	0.28 ± 0.09	1.16 ± 0.18
PE(18:1/22:6) (b)	8.88 ± 1.01	9.18 ± 1.25	1.77 ± 0.12	1.11 ± 0.06	2.62 ± 0.47	0.05 ± 0.01	0.12 ± 0.02
Phosphatidylglycerol							
PG(34:1)	49.67 ± 3.69	252.9 ± 28.69	64.60 ± 4.34	30.06 ± 1.89	32.18 ± 4.35	0.56 ± 0.06	1.77 ± 0.08
PG(36:1)	0.02 ± 0.01	0.07 ± 0.02	0.03 ± 0.01	0.02 ± 0.004	0.04 ± 0.01	0.02 ± 0.01	0.04 ± 0.01
PG(36:2)	13.31 ± 1.13	122.4 ± 10.87	9.08 ± 0.68	15.02 ± 1.20	22.39 ± 2.67	0.49 ± 0.09	1.19 ± 0.16

PG(34:2)	31.59 ± 2.14	73.94 ± 8.25	7.00 ± 0.38	7.41 ± 0.55	11.75 ± 1.74	0.30 ± 0.04	0.78 ± 0.10
Phosphatidylinositol							
PI(16:0/16:0)	2.89 ± 0.24	1.20 ± 0.13	44.97 ± 3.72	0.38 ± 0.03	0.55 ± 0.06	0.07 ± 0.01	0.20 ± 0.04
PI(16:0/16:1)	1.39 ± 0.16	0.62 ± 0.08	3.95 ± 0.30	0.19 ± 0.02	0.28 ± 0.02	0.04 ± 0.01	0.19 ± 0.02
PI(34:0)	15.86 ± 1.20	7.97 ± 0.90	122.1 ± 10.97	10.41 ± 1.63	16.21 ± 1.53	0.28 ± 0.03	1.48 ± 0.32
PI(34:1)	7.62 ± 0.48	11.60 ± 1.18	24.68 ± 1.59	4.04 ± 0.31	6.27 ± 0.69	0.30 ± 0.04	1.23 ± 0.19
PI(17:0/18:1) (a+b)	0.23 ± 0.03	0.25 ± 0.05	0.47 ± 0.05	0.10 ± 0.01	0.18 ± 0.03	0.02 ± 0.01	0.05 ± 0.01
PI(17:0/18:2) (a+b)	5.71 ± 0.27	3.11 ± 0.16	2.69 ± 0.16	2.27 ± 0.07	2.51 ± 0.10	2.11 ± 0.08	2.45 ± 0.17
PI(18:0/18:1)	4.23 ± 0.47	9.18 ± 1.00	8.98 ± 0.83	4.26 ± 0.29	5.93 ± 0.57	0.19 ± 0.03	0.96 ± 0.07
PI(36:2) (a+b)	153.9 ± 11.78	105.3 ± 12.84	31.63 ± 2.18	12.30 ± 0.74	28.99 ± 4.27	1.72 ± 0.27	6.10 ± 0.80
PI(18:1/18:2)	21.01 ± 1.75	34.06 ± 3.87	5.29 ± 0.26	0.92 ± 0.10	2.63 ± 0.41	1.34 ± 0.25	3.78 ± 0.59
PI(16:0/20:3) (a)	9.75 ± 0.93	2.22 ± 0.26	4.16 ± 0.20	0.21 ± 0.03	0.43 ± 0.06	0.26 ± 0.06	0.57 ± 0.07
PI(16:0/20:3) (b)	3.56 ± 0.34	0.60 ± 0.06	0.55 ± 0.04	0.22 ± 0.03	0.49 ± 0.07	0.08 ± 0.02	0.20 ± 0.02
PI(16:0/20:4)	239.6 ± 18.60	26.07 ± 2.20	102.4 ± 5.09	3.85 ± 0.23	5.65 ± 0.68	4.35 ± 0.81	11.80 ± 0.85
PI(17:0/20:4) (a+b)	14.36 ± 1.15	2.25 ± 0.19	3.66 ± 0.14	0.65 ± 0.05	0.87 ± 0.15	0.31 ± 0.06	0.83 ± 0.09
PI(37:6)	0.03 ± 0.01	0.06 ± 0.01	0.06 ± 0.01	0.03 ± 0.01	0.02 ± 0.004	0.02 ± 0.004	0.03 ± 0.01
PI(18:0/20:2)	3.07 ± 0.17	0.71 ± 0.07	2.00 ± 0.16	1.24 ± 0.13	2.18 ± 0.26	0.05 ± 0.01	0.10 ± 0.02
PI(18:0/20:3) (a)	95.12 ± 5.96	11.97 ± 1.36	50.54 ± 3.57	36.72 ± 1.75	50.63 ± 4.30	1.52 ± 0.22	4.45 ± 0.34
PI(18:0/20:3) (b)	7.74 ± 0.47	1.85 ± 0.22	1.86 ± 0.18	2.89 ± 0.25	4.21 ± 0.59	0.16 ± 0.04	0.56 ± 0.03
PI(18:0/20:4)	2,357 ± 185.3	766.8 ± 89.62	988.5 ± 47.56	363.9 ± 18.93	463.2 ± 81.62	20.46 ± 2.82	66.64 ± 9.41
PI(38:5) (a)	71.36 ± 6.24	48.60 ± 5.07	27.95 ± 0.83	5.81 ± 0.35	7.93 ± 1.15	2.08 ± 0.39	7.03 ± 0.84
PI (38:5) (b)	16.81 ± 1.63	5.26 ± 0.52	4.39 ± 0.25	1.25 ± 0.08	1.44 ± 0.24	0.29 ± 0.05	1.06 ± 0.13
PI(38:6)	26.13 ± 2.87	6.06 ± 0.53	17.50 ± 1.31	1.40 ± 0.13	1.73 ± 0.20	0.13 ± 0.02	0.57 ± 0.07
PI(39:6) (a+b)	0.43 ± 0.07	0.15 ± 0.02	0.14 ± 0.01	0.10 ± 0.01	0.10 ± 0.01	0.04 ± 0.01	0.05 ± 0.01
PI(18:0/22:4)	9.64 ± 0.87	3.02 ± 0.36	3.23 ± 0.14	3.21 ± 0.22	5.10 ± 0.74	0.09 ± 0.02	0.34 ± 0.04
PI(20:0/20:4)	1.26 ± 0.10	0.30 ± 0.05	0.45 ± 0.03	0.07 ± 0.01	0.15 ± 0.03	0.04 ± 0.01	0.07 ± 0.01
PI(18:0/22:5) (n3)	18.22 ± 1.92	8.20 ± 0.96	1.86 ± 0.13	12.57 ± 0.67	14.18 ± 2.28	0.06 ± 0.01	0.30 ± 0.05
PI(18:0/22:5) (n6)	15.56 ± 2.45	3.79 ± 0.53	4.81 ± 0.53	8.32 ± 0.42	11.48 ± 0.88	0.07 ± 0.01	0.22 ± 0.04
PI(18:0/22:6)	48.67 ± 6.12	10.92 ± 1.46	9.05 ± 0.57	22.52 ± 1.19	27.72 ± 4.47	0.05 ± 0.01	0.20 ± 0.03
Phosphatidylserine							
PS(36:1)	17.57 ± 1.21	28.15 ± 2.81	74.20 ± 3.66	4.93 ± 0.15	23.85 ± 3.25	5.16 ± 0.76	21.11 ± 3.80
PS(36:2)	22.79 ± 1.26	18.57 ± 1.80	60.37 ± 3.45	11.87 ± 0.79	23.06 ± 2.65	16.98 ± 2.40	49.06 ± 6.87
PS(38:3)	43.27 ± 2.31	28.57 ± 2.78	113.7 ± 5.82	8.67 ± 0.51	11.63 ± 1.11	4.98 ± 0.79	20.07 ± 2.47
PS(38:4)	349.6 ± 23.96	49.07 ± 4.87	851.9 ± 33.56	13.41 ± 0.59	18.74 ± 1.84	7.80 ± 1.31	33.55 ± 4.32
PS(38:5)	13.07 ± 0.94	2.49 ± 0.25	17.21 ± 0.77	2.90 ± 0.25	1.86 ± 0.18	0.79 ± 0.12	2.73 ± 0.33
PS(40:5)	20.11 ± 1.99	89.29 ± 8.69	17.02 ± 1.37	29.05 ± 1.82	31.43 ± 4.55	1.15 ± 0.20	5.13 ± 0.72
PS(40:6)	71.50 ± 5.15	180.1 ± 17.82	12.81 ± 0.67	67.87 ± 3.37	96.43 ± 15.23	0.72 ± 0.11	2.70 ± 0.30

Table S15. Statistic multiple comparison post hoc Tuckey of the glycerophospholipids between all the studied tissues.

		p value													
		Phosphatidylcholine													
		PC(28:0)	PC(14:0/16:0)	PC(31:0) (a)	PC(31:0) (b)	PC(16:0/16:0)	PC(32:1)	PC(32:2)	PC(33:0) (a)	PC(33:0) (b)	PC(33:1)	PC(33:2)	PC(16:0/18:0)	PC(16:0/18:1)	PC(16:0/18:2)
Liver	Heart	.745	**.010**	.990	**.001**	**.003**	**.000**	**.000**	.842	.344	**.001**	**.000**	**.000**	.153	**.000**
	Kidney	**.000**	**.000**	**.001**	**.000**	**.000**	**.008**	**.000**	**.000**	**.000**	.613	**.000**	**.000**	**.000**	**.000**
	Gluteus	1.000	1.000	.997	.984	**.041**	.100	**.000**	.211	**.002**	**.001**	**.000**	**.000**	.098	**.000**
	Soleus	1.000	1.000	.720	1.000	.221	.202	**.000**	.321	**.024**	**.020**	**.000**	**.003**	.712	**.000**
	VAT	**.000**	**.002**	**.000**	**.020**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.001**	.079	**.000**	.995	.104	**.000**	**.000**	**.000**	**.002**	**.000**	**.000**	**.001**	**.000**	**.000**
Heart	Liver	.745	**.010**	.990	**.001**	**.003**	**.000**	**.000**	.842	.344	**.001**	**.000**	**.000**	.153	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.969	**.000**	**.000**	**.000**	.644	.518	**.019**	.997
	Gluteus	.677	**.016**	1.000	**.000**	**.000**	.621	.997	**.011**	**.000**	1.000	.979	**.000**	**.000**	1.000
	Soleus	.868	**.037**	.972	**.002**	**.000**	.528	1.000	**.024**	**.000**	.999	.981	**.000**	**.006**	**.025**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	**.049**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.002**	**.001**	**.000**	.168	.369	**.000**	**.000**	**.000**	**.022**	**.000**	**.000**	**.002**
Kidney	Liver	**.000**	**.000**	**.001**	**.000**	**.000**	**.008**	**.000**	**.000**	**.000**	.613	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.969	**.000**	**.000**	**.000**	.644	.518	**.019**	.997
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.794	**.000**	**.000**	**.000**	.240	**.000**	**.000**	.992
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.953	**.000**	**.000**	**.000**	.991	**.000**	**.000**	.134
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.008**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.095	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
Gluteus	Liver	1.000	1.000	.997	.984	**.041**	.100	**.000**	.211	**.002**	**.001**	**.000**	**.000**	.098	**.000**
	Heart	.677	**.016**	1.000	**.000**	**.000**	.621	.997	**.011**	**.000**	1.000	.979	**.000**	**.000**	1.000
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.794	**.000**	**.000**	**.000**	.240	**.000**	**.000**	.992
	Soleus	1.000	1.000	.963	.999	.997	1.000	1.000	1.000	.995	.986	.717	.998	.935	**.027**
	VAT	**.000**	**.005**	**.000**	.200	.844	**.000**	.253	**.006**	.575	**.000**	**.015**	.941	**.001**	**.000**
	SAT	**.004**	.126	**.003**	1.000	1.000	**.005**	.767	.286	1.000	**.003**	.196	1.000	**.027**	**.006**
Soleus	Liver	1.000	1.000	.720	1.000	.221	.202	**.000**	.321	**.024**	**.020**	**.000**	**.003**	.712	**.000**
	Heart	.868	**.037**	.972	**.002**	**.000**	.528	1.000	**.024**	**.000**	.999	.981	**.000**	**.006**	**.025**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.953	**.000**	**.000**	**.000**	.991	**.000**	**.000**	.134
	Gluteus	1.000	1.000	.963	.999	.997	1.000	1.000	1.000	.995	.986	.717	.998	.935	**.027**
	VAT	**.000**	**.005**	**.001**	.093	.512	**.000**	.149	**.007**	.239	**.000**	**.000**	.722	**.000**	**.000**
	SAT	**.003**	.113	**.049**	1.000	1.000	**.004**	.586	.268	.985	**.000**	**.006**	.999	**.002**	**.000**
VAT	Liver	**.000**	**.002**	**.000**	**.020**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	**.049**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.008**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.005**	**.000**	.200	.844	**.000**	.253	**.006**	.575	**.000**	**.015**	.941	**.001**	**.000**
	Soleus	**.000**	**.005**	**.001**	.093	.512	**.000**	.149	**.007**	.239	**.000**	**.000**	.722	**.000**	**.000**
	SAT	.898	.948	.878	.193	.740	.874	.990	.812	.729	.862	.977	.934	.960	.492
SAT	Liver	**.001**	.079	**.000**	.995	.104	**.000**	**.000**	**.000**	**.002**	**.000**	**.000**	**.001**	**.000**	**.000**
	Heart	**.000**	**.000**	**.002**	**.001**	**.000**	.168	.369	**.000**	**.000**	**.000**	**.022**	**.000**	**.000**	**.002**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.095	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	Gluteus	**.004**	.126	**.003**	1.000	1.000	**.005**	.767	.286	1.000	**.003**	.196	1.000	**.027**	**.006**
	Soleus	**.003**	.113	**.049**	1.000	1.000	**.004**	.586	.268	.985	**.000**	**.006**	.999	**.002**	**.000**
	VAT	.898	.948	.878	.193	.740	.874	.990	.812	.729	.862	.977	.934	.960	.492

		p value													
		Phosphatidylcholine													
		PC(16:1/18:2)	PC(16:0/18:3) (a)	PC(16:0/18:3) (b)	PC(14:0/ 20:4)	PC(34:5)	PC(15-MHDA/18:1)	PC(17:0/18:1)	PC(15-MHDA/18:2)	PC(17:0/18:2)	PC(17:1/ 18:2)	PC(15:0/ 20:3)	PC(15:0 /20:4)	PC(35:5)	PC(36:0)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	.845	.056	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.045**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.240	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.983
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	.114	**.014**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	.583	.552	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.430
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.080
Heart	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.845	.056	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.045**
	Kidney	1.000	.124	1.000	.418	.995	.914	.427	.950	.265	.969	.998	.872	1.000	**.009**
	Gluteus	1.000	.999	1.000	.161	.785	**.005**	**.000**	.378	**.005**	.834	1.000	.439	.982	.858
	Soleus	.984	.874	1.000	.109	.771	.073	**.001**	1.000	.937	.372	.172	.276	.898	**.000**
	VAT	.745	**.003**	.972	**.007**	.100	**.000**	**.000**	**.000**	**.000**	**.001**	**.001**	**.001**	**.010**	.737
	SAT	.997	.104	.991	**.021**	.246	**.000**	**.000**	**.012**	**.006**	**.044**	.086	**.004**	.078	1.000
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.240	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.983
	Heart	1.000	.124	1.000	.418	.995	.914	.427	.950	.265	.969	.998	.872	1.000	**.009**
	Gluteus	1.000	.071	.999	.998	.989	**.000**	**.000**	.947	.728	1.000	1.000	.055	.999	**.000**
	Soleus	.984	.865	1.000	.986	.984	**.007**	**.000**	.966	.929	.096	.483	**.030**	.977	.905
	VAT	.818	**.000**	.891	.669	.430	**.000**	**.000**	**.009**	**.012**	**.018**	**.001**	**.000**	**.038**	**.000**
	SAT	.999	**.000**	.948	.791	.656	**.000**	**.000**	.175	.686	.341	**.038**	**.000**	.190	**.019**
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.114	**.014**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**
	Heart	1.000	.999	1.000	.161	.785	**.005**	**.000**	.378	**.005**	.834	1.000	.439	.982	.858
	Kidney	1.000	.071	.999	.998	.989	**.000**	**.000**	.947	.728	1.000	1.000	.055	.999	**.000**
	Soleus	.972	.707	1.000	1.000	1.000	.983	.730	.485	.166	**.038**	.279	1.000	1.000	**.000**
	VAT	.866	**.021**	.988	.928	.878	**.003**	.155	.123	.401	.052	**.002**	.254	.126	1.000
	SAT	1.000	.296	.996	.968	.966	.115	.965	.716	1.000	.574	.091	.439	.422	.932
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.583	.552	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.430
	Heart	.984	.874	1.000	.109	.771	.073	**.001**	1.000	.937	.372	.172	.276	.898	**.000**
	Kidney	.984	.865	1.000	.986	.984	**.007**	**.000**	.966	.929	.096	.483	**.030**	.977	.905
	Gluteus	.972	.707	1.000	1.000	1.000	.983	.730	.485	.166	**.038**	.279	1.000	1.000	**.000**
	VAT	.354	**.000**	.959	.988	.926	**.000**	**.004**	**.001**	**.001**	**.000**	**.000**	.519	.327	**.000**
	SAT	.866	**.011**	.983	.996	.982	**.022**	.236	**.027**	.156	**.000**	**.000**	.708	.701	**.001**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	Heart	.745	**.003**	.972	**.007**	.100	**.000**	**.000**	**.000**	**.000**	**.001**	**.001**	**.001**	**.010**	.737
	Kidney	.818	**.000**	.891	.669	.430	**.000**	**.000**	**.009**	**.012**	**.018**	**.001**	**.000**	**.038**	**.000**
	Gluteus	.866	**.021**	.988	.928	.878	**.003**	.155	.123	.401	.052	**.002**	.254	.126	1.000
	Soleus	.354	**.000**	.959	.988	.926	**.000**	**.004**	**.001**	**.001**	**.000**	**.000**	.519	.327	**.000**
	SAT	.986	.956	1.000	1.000	1.000	.916	.735	.953	.536	.920	.917	1.000	.999	.860
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.080
	Heart	.997	.104	.991	**.021**	.246	**.000**	**.000**	**.012**	**.006**	**.044**	.086	**.004**	.078	1.000
	Kidney	.999	**.000**	.948	.791	.656	**.000**	**.000**	.175	.686	.341	**.038**	**.000**	.190	**.019**
	Gluteus	1.000	.296	.996	.968	.966	.115	.965	.716	1.000	.574	.091	.439	.422	.932
	Soleus	.866	**.011**	.983	.996	.982	**.022**	.236	**.027**	.156	**.000**	**.000**	.708	.701	**.001**
	VAT	.986	.956	1.000	1.000	1.000	.916	.735	.953	.536	.920	.917	1.000	.999	.860

		p value													
		Phosphatidylcholine													
		PC(18:0/18:1)	PC(18:1/18:1)	PC(18:0/18:2)	PC(18:1/18:2)	PC(16:0/20:3) (a)	PC(16:0/20:3) (b)	PC(18:2/18:2)	PC(16:0/20:4)	PC(16:1/20:4)	PC(16:0/20:5)	PC 36:6(a)	PC(14:0/22:6)	PC(15-MHDA/20:4)	PC(17:0/20:4)
Liver	Heart	**.000**	.963	.998	.398	**.000**	**.000**	.953	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	.817	.988	**.000**	**.000**	**.000**	**.000**	.141	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.040**	**.000**	**.000**	**.000**	**.000**	**.000**	**.011**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	.348	.096	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	.159	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.000**	.963	.998	.398	**.000**	**.000**	.953	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	.662	**.000**	**.000**	.151	.837	**.014**	1.000	1.000	1.000	.600	.645	.990	**.012**
	Gluteus	**.000**	**.000**	**.000**	**.000**	.999	**.025**	**.001**	.437	.600	.960	**.014**	.953	.478	**.000**
	Soleus	**.000**	**.011**	**.000**	**.023**	.718	.292	.992	.277	.573	.981	**.028**	.957	.667	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.032**	**.000**	**.000**	**.013**	**.033**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	.091	**.000**	**.000**	**.034**	.098	**.000**
Kidney	Liver	.817	.988	**.000**	**.000**	**.000**	**.000**	.141	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.662	**.000**	**.000**	.151	.837	**.014**	1.000	1.000	1.000	.600	.645	.990	**.012**
	Gluteus	**.002**	**.008**	.052	.865	.072	.484	.956	.324	.772	.928	.593	.995	.916	.447
	Soleus	**.032**	.440	.958	.942	.972	.966	.164	.200	.740	.961	.700	.997	.973	.672
	VAT	**.000**	**.000**	**.006**	**.028**	**.000**	**.001**	**.047**	**.000**	.082	**.000**	**.001**	.574	.244	**.027**
	SAT	**.011**	**.000**	.309	.542	**.000**	**.014**	.228	**.000**	.180	**.001**	**.005**	.704	.431	.089
Gluteus	Liver	**.040**	**.000**	**.000**	**.000**	**.000**	**.000**	**.011**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	.999	**.025**	**.001**	.437	.600	.960	**.014**	.953	.478	**.000**
	Kidney	**.002**	**.008**	.052	.865	.072	.484	.956	.324	.772	.928	.593	.995	.916	.447
	Soleus	.978	.664	.443	.290	.474	.970	**.017**	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	.997	**.023**	.991	.426	**.001**	.164	.372	**.000**	.810	**.002**	.110	.214	.896	.854
	SAT	.999	.692	.990	.996	**.033**	.594	.775	**.000**	.920	**.012**	.290	.331	.968	.962
Soleus	Liver	.348	.096	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.011**	**.000**	**.023**	.718	.292	.992	.277	.573	.981	**.028**	.957	.667	**.000**
	Kidney	**.032**	.440	.958	.942	.972	.966	.164	.200	.740	.961	.700	.997	.973	.672
	Gluteus	.978	.664	.443	.290	.474	.970	**.017**	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	.780	**.000**	.115	**.002**	**.000**	**.023**	**.000**	**.000**	.888	**.002**	.113	.268	.828	.734
	SAT	1.000	**.048**	.891	.108	**.000**	.166	**.000**	**.002**	.958	**.013**	.283	.387	.933	.898
VAT	Liver	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.032**	**.000**	**.000**	**.013**	**.033**	**.000**
	Kidney	**.000**	**.000**	**.006**	**.028**	**.000**	**.001**	**.047**	**.000**	.082	**.000**	**.001**	.574	.244	**.027**
	Gluteus	.997	**.023**	.991	.426	**.001**	.164	.372	**.000**	.810	**.002**	.110	.214	.896	.854
	Soleus	.780	**.000**	.115	**.002**	**.000**	**.023**	**.000**	**.000**	.888	**.002**	.113	.268	.828	.734
	SAT	.948	.671	.774	.850	.939	.994	.998	.999	1.000	1.000	1.000	1.000	1.000	1.000
SAT	Liver	.159	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	.091	**.000**	**.000**	**.034**	.098	**.000**
	Kidney	**.011**	**.000**	.309	.542	**.000**	**.014**	.228	**.000**	.180	**.001**	**.005**	.704	.431	.089
	Gluteus	.999	.692	.990	.996	**.033**	.594	.775	**.000**	.920	**.012**	.290	.331	.968	.962
	Soleus	1.000	**.048**	.891	.108	**.000**	.166	**.000**	**.002**	.958	**.013**	.283	.387	.933	.898
	VAT	.948	.671	.774	.850	.939	.994	.998	.999	1.000	1.000	1.000	1.000	1.000	1.000

		p value													
		Phosphatidylcholine													
		PC(15:0/22:6)	PC(38:2)	PC(18:0/20:3)	PC(18:1/20:3)	PC(38:4) (b)	PC(18:0/20:4)	PC(38:5) (a)	PC(38:5) (b)	PC(38:6) (a)	PC(16:0/22:6)	PC(18:2/20:5)	PC(16:1/22:6)	PC(38:7) (c)	PC (39:5) (a)
Liver	Heart	**.000**	.524	**.000**	**.000**	.526	.846	**.000**	**.000**	**.000**	**.000**	.378	**.000**	**.000**	**.000**
	Kidney	**.000**	.831	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	.546	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.027**	**.000**	**.033**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.000**	.524	**.000**	**.000**	.526	.846	**.000**	**.000**	**.000**	**.000**	.378	**.000**	**.000**	**.000**
	Kidney	.993	.052	.216	.994	**.000**	**.000**	.699	.371	**.000**	1.000	1.000	1.000	.999	**.005**
	Gluteus	1.000	**.000**	**.000**	.053	**.000**	**.000**	**.005**	.107	**.000**	.877	**.033**	1.000	.999	.295
	Soleus	1.000	**.000**	**.000**	.746	**.000**	**.000**	**.023**	.324	**.000**	.206	.810	.993	.928	.991
	VAT	.114	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	.079	**.000**	.085	.291	**.000**
	SAT	.202	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.003**	**.000**	.144	**.000**	.160	.435	**.000**
Kidney	Liver	**.000**	.831	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	.546	**.000**	**.000**	**.000**
	Heart	.993	.052	.216	.994	**.000**	**.000**	.699	.371	**.000**	1.000	1.000	1.000	.999	**.005**
	Gluteus	.988	**.000**	**.000**	.287	.662	**.018**	.304	.996	**.001**	.841	**.038**	1.000	1.000	.691
	Soleus	1.000	**.000**	**.000**	.983	.964	.065	.570	1.000	**.029**	.199	.782	.993	.997	.081
	VAT	**.034**	**.000**	**.000**	**.001**	.090	**.003**	**.000**	.249	**.000**	.164	**.000**	.136	.152	.382
	SAT	.070	**.000**	**.000**	**.013**	.277	**.013**	**.003**	.415	**.000**	.251	**.000**	.223	.251	.741
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	1.000	**.000**	**.000**	.053	**.000**	**.000**	**.005**	.107	**.000**	.877	**.033**	1.000	.999	.295
	Kidney	.988	**.000**	**.000**	.287	.662	**.018**	.304	.996	**.001**	.841	**.038**	1.000	1.000	.691
	Soleus	1.000	.882	.927	.820	.995	1.000	1.000	.999	.972	.892	.658	1.000	.997	.820
	VAT	.201	.979	.970	.324	.910	.999	.205	.623	.603	**.005**	.051	.067	.148	**.009**
	SAT	.306	1.000	1.000	.785	.991	1.000	.448	.786	.764	**.013**	.152	.123	.245	.058
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.027**	**.000**	**.033**	**.000**	**.000**	**.000**
	Heart	1.000	**.000**	**.000**	.746	**.000**	**.000**	**.023**	.324	**.000**	.206	.810	.993	.928	.991
	Kidney	1.000	**.000**	**.000**	.983	.964	.065	.570	1.000	**.029**	.199	.782	.993	.997	.081
	Gluteus	1.000	.882	.927	.820	.995	1.000	1.000	.999	.972	.892	.658	1.000	.997	.820
	VAT	.104	.389	.432	**.017**	.588	.978	.119	.389	.159	**.000**	**.001**	**.033**	.050	**.000**
	SAT	.172	.949	.858	.126	.853	.996	.295	.564	.280	**.001**	**.003**	.065	.096	**.002**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.114	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	.079	**.000**	.085	.291	**.000**
	Kidney	**.034**	**.000**	**.000**	**.001**	.090	**.003**	**.000**	.249	**.000**	.164	**.000**	.136	.152	.382
	Gluteus	.201	.979	.970	.324	.910	.999	.205	.623	.603	**.005**	.051	.067	.148	**.009**
	Soleus	.104	.389	.432	**.017**	.588	.978	.119	.389	.159	**.000**	**.001**	**.033**	.050	**.000**
	SAT	1.000	.954	.996	.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.202	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.003**	**.000**	.144	**.000**	.160	.435	**.000**
	Kidney	.070	**.000**	**.000**	**.013**	.277	**.013**	**.003**	.415	**.000**	.251	**.000**	.223	.251	.741
	Gluteus	.306	1.000	1.000	.785	.991	1.000	.448	.786	.764	**.013**	.152	.123	.245	.058
	Soleus	.172	.949	.858	.126	.853	.996	.295	.564	.280	**.001**	**.003**	.065	.096	**.002**
	VAT	1.000	.954	.996	.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999

		p value												
		Phosphatidylcholine												
		PC (39:5) (b)	PC(15-MHDA_22:6)	PC(17:0_22:6)	PC(18:0_22:4)	PC(20:0_20:4)	PC(18:0_22:5) (n3)	PC(18:0_22:5) (n6)	PC(18:0_22:6)	PC(40:7) (a)	PC(18:1_22:6) (a)	PC(18:1_22:6) (b)	PC(40:8)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	.273	.060	.999	.541	.279	**.000**	**.000**	.383
	Kidney	**.000**	**.000**	**.000**	.159	**.000**	**.000**	**.000**	**.000**	.994	**.000**	**.000**	1.000
	Gluteus	**.000**	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.034**	**.000**	**.000**	**.000**	**.000**	**.002**	**.000**	**.000**	**.010**
	VAT	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.000**	**.000**	**.000**	**.000**	.273	.060	.999	.541	.279	**.000**	**.000**	.383
	Kidney	**.006**	.978	.272	**.000**	**.001**	**.000**	**.000**	**.000**	.102	**.022**	.174	.251
	Gluteus	**.002**	1.000	.818	**.000**	**.000**	**.000**	**.000**	**.000**	**.006**	.326	.638	**.000**
	Soleus	**.012**	.999	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	.315	.995	.993	**.000**
	VAT	**.000**	.301	**.010**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**
	SAT	**.000**	.455	**.026**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.002**	**.000**
Kidney	Liver	**.000**	**.000**	**.000**	.159	**.000**	**.000**	**.000**	**.000**	.994	**.000**	**.000**	1.000
	Heart	**.006**	.978	.272	**.000**	**.001**	**.000**	**.000**	**.000**	.102	**.022**	.174	.251
	Gluteus	1.000	.999	.975	.847	**.003**	.979	.998	.929	**.000**	.905	.983	**.000**
	Soleus	1.000	.889	.531	.989	**.011**	1.000	1.000	1.000	**.001**	.193	.651	**.043**
	VAT	.706	.863	.874	.665	**.001**	.767	.984	.624	**.000**	.749	.483	**.000**
	SAT	.881	.929	.927	.850	**.007**	.872	.992	.725	**.000**	.859	.640	**.000**
Gluteus	Liver	**.000**	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.002**	1.000	.818	**.000**	**.000**	**.000**	**.000**	**.000**	**.006**	.326	.638	**.000**
	Kidney	1.000	.999	.975	.847	**.003**	.979	.998	.929	**.000**	.905	.983	**.000**
	Soleus	.999	.990	.952	.999	1.000	.998	1.000	.990	.794	.820	.974	.646
	VAT	.911	.573	.347	1.000	1.000	.997	1.000	.997	.106	.125	.110	.371
	SAT	.980	.710	.471	1.000	1.000	.999	1.000	.999	.252	.225	.205	.550
Soleus	Liver	**.000**	**.000**	**.000**	**.034**	**.000**	**.000**	**.000**	**.000**	**.002**	**.000**	**.000**	**.010**
	Heart	**.012**	.999	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	.315	.995	.993	**.000**
	Kidney	1.000	.889	.531	.989	**.011**	1.000	1.000	1.000	**.001**	.193	.651	**.043**
	Gluteus	.999	.990	.952	.999	1.000	.998	1.000	.990	.794	.820	.974	.646
	VAT	.696	.201	.050	.984	.999	.923	.997	.850	**.003**	**.004**	**.015**	**.009**
	SAT	.868	.313	.093	.998	1.000	.966	.999	.901	**.013**	**.012**	**.038**	**.026**
VAT	Liver	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.301	**.010**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**
	Kidney	.706	.863	.874	.665	**.001**	.767	.984	.624	**.000**	.749	.483	**.000**
	Gluteus	.911	.573	.347	1.000	1.000	.997	1.000	.997	.106	.125	.110	.371
	Soleus	.696	.201	.050	.984	.999	.923	.997	.850	**.003**	**.004**	**.015**	**.009**
	SAT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
SAT	Liver	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.455	**.026**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.002**	**.000**
	Kidney	.881	.929	.927	.850	**.007**	.872	.992	.725	**.000**	.859	.640	**.000**
	Gluteus	.980	.710	.471	1.000	1.000	.999	1.000	.999	.252	.225	.205	.550
	Soleus	.868	.313	.093	.998	1.000	.966	.999	.901	**.013**	**.012**	**.038**	**.026**
	VAT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000

		p value													
		Phosphatidylethanolamine													
		PE(16:0/16:0)	PE(16:0/16:1)	PE(16:0/18:1)	PE(16:0/18:2)	PE(16:1/18:2)	PE(16:0/18:3) (a)	PE(16:0/18:3) (b)	PE(15-MHDA/18:1)	PE(17:0/18:1)	PE(15-MHDA/18:2)	PE(17:0/18:2)	PE(36:0)	PE(18:0/18:1)	PE(18:1/18:1)
Liver	Heart	**.000**	**.000**	.530	**.000**	**.000**	**.000**	**.000**	.076	**.012**	**.000**	**.000**	**.001**	**.000**	**.000**
	Kidney	**.000**	**.001**	.996	**.000**	**.000**	**.000**	**.000**	1.000	**.025**	**.000**	**.000**	.427	**.000**	.998
	Gluteus	.417	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**
	Soleus	.435	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.026**	**.000**	**.000**
	VAT	.197	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	.447	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.006**	**.000**
Heart	Liver	**.000**	**.000**	.530	**.000**	**.000**	**.000**	**.000**	.076	**.012**	**.000**	**.000**	**.001**	**.000**	**.000**
	Kidney	**.000**	**.000**	.245	.999	**.005**	.610	.977	.155	1.000	.597	**.012**	**.000**	.748	**.007**
	Gluteus	**.000**	.361	**.000**	**.012**	.485	**.000**	1.000	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	.318	**.000**	**.032**	.816	**.002**	1.000	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	.080	**.000**	**.004**	.596	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	.839	**.000**	.055	.989	**.007**	1.000	**.000**	**.000**	**.009**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	**.000**	**.001**	.996	**.000**	**.000**	**.000**	**.000**	1.000	**.025**	**.000**	**.000**	.427	**.000**	.998
	Heart	**.000**	**.000**	.245	.999	**.005**	.610	.977	.155	1.000	.597	**.012**	**.000**	.748	**.007**
	Gluteus	**.000**	**.000**	**.000**	.059	**.000**	**.000**	.962	**.000**	**.000**	.121	.376	.214	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	.123	**.000**	**.000**	.968	**.000**	**.000**	.333	.855	.826	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.027**	**.000**	**.000**	.942	**.000**	**.000**	.110	.156	**.014**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	.187	.084	**.000**	.966	**.000**	**.000**	.442	.622	.097	**.000**	**.000**
Gluteus	Liver	.417	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**
	Heart	**.000**	.361	**.000**	**.012**	.485	**.000**	1.000	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	.059	**.000**	**.000**	.962	**.000**	**.000**	.121	.376	.214	**.000**	**.000**
	Soleus	1.000	1.000	.998	1.000	.999	1.000	1.000	.976	.999	.999	.990	.956	.974	.722
	VAT	1.000	.995	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.934	1.000	1.000
	SAT	1.000	.994	.997	1.000	.209	.980	1.000	.954	.688	.996	1.000	.999	.449	.267
Soleus	Liver	.435	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.026**	**.000**	**.000**
	Heart	**.000**	.318	**.000**	**.032**	.816	**.002**	1.000	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	.123	**.000**	**.000**	.968	**.000**	**.000**	.333	.855	.826	**.000**	**.000**
	Gluteus	1.000	1.000	.998	1.000	.999	1.000	1.000	.976	.999	.999	.990	.956	.974	.722
	VAT	1.000	.999	.976	1.000	1.000	.999	1.000	.966	.997	1.000	.908	.409	.976	.813
	SAT	1.000	.984	1.000	1.000	.475	.999	1.000	1.000	.919	1.000	1.000	.797	.939	.990
VAT	Liver	.197	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.080	**.000**	**.004**	.596	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.027**	**.000**	**.000**	.942	**.000**	**.000**	.110	.156	**.014**	**.000**	**.000**
	Gluteus	1.000	.995	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.934	1.000	1.000
	Soleus	1.000	.999	.976	1.000	1.000	.999	1.000	.966	.997	1.000	.908	.409	.976	.813
	SAT	1.000	.845	.966	.996	.272	.960	1.000	.938	.564	.997	.990	.998	.435	.337
SAT	Liver	.447	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.006**	**.000**
	Heart	**.000**	.839	**.000**	.055	.989	**.007**	1.000	**.000**	**.000**	**.009**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	.187	.084	**.000**	.966	**.000**	**.000**	.442	.622	.097	**.000**	**.000**
	Gluteus	1.000	.994	.997	1.000	.209	.980	1.000	.954	.688	.996	1.000	.999	.449	.267
	Soleus	1.000	.984	1.000	1.000	.475	.999	1.000	1.000	.919	1.000	1.000	.797	.939	.990
	VAT	1.000	.845	.966	.996	.272	.960	1.000	.938	.564	.997	.990	.998	.435	.337

		p value													
		Phosphatidylethanolamine													
		PE(18:0/18:2)	PE(18:1/18:2)	PE(16:0/20:3)	PE(16:0/20:4)	PE(16:1/20:4)	PE(16:0/20:5)	PE(15-MHDA/20:4)	PE(17:0/20:4)	PE(18:0/20:3) (a)	PE(18:0/20:3) (b)	PE(18:0/20:4)	PE(38:5) (a)	PE(38:5) (b)	PE(16:0/22:6)
Liver	Heart	**.005**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.839	**.000**	**.000**	1.000	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	.360	**.000**	**.000**	**.000**	**.000**	1.000	1.000	.187	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.005**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.839	**.000**	**.000**	1.000	**.000**
	Kidney	**.003**	.461	.326	**.000**	**.000**	**.000**	.988	.065	**.009**	.931	**.000**	**.000**	**.000**	**.008**
	Gluteus	**.000**	**.000**	**.000**	.165	.971	.573	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	Soleus	**.000**	**.000**	**.001**	.159	.999	.689	**.004**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**
	VAT	**.000**	**.000**	**.000**	**.034**	.964	.230	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	.102	1.000	.440	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	.360	**.000**	**.000**	**.000**	**.000**	1.000	1.000	.187	**.000**	**.000**
	Heart	**.003**	.461	.326	**.000**	**.000**	**.000**	.988	.065	**.009**	.931	**.000**	**.000**	**.000**	**.008**
	Gluteus	.174	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.746	.995
	Soleus	.931	**.001**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	.821	.997
	VAT	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.413	.867
	SAT	.054	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.538	.908
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	.165	.971	.573	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**
	Kidney	.174	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.746	.995
	Soleus	.824	.986	.999	1.000	1.000	1.000	1.000	1.000	.971	1.000	1.000	.999	1.000	1.000
	VAT	.837	1.000	.998	.998	1.000	.999	.999	.983	.378	.291	.921	1.000	.999	.996
	SAT	.996	.934	1.000	1.000	.984	1.000	1.000	.999	.896	.924	.977	1.000	1.000	.998
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.001**	.159	.999	.689	**.004**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**
	Kidney	.931	**.001**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	.821	.997
	Gluteus	.824	.986	.999	1.000	1.000	1.000	1.000	1.000	.971	1.000	1.000	.999	1.000	1.000
	VAT	.133	.994	.951	1.000	1.000	.997	.997	.968	.074	.261	.789	.984	.998	.996
	SAT	.489	1.000	1.000	1.000	.999	1.000	1.000	.997	.425	.888	.907	1.000	.999	.998
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.034**	.964	.230	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.413	.867
	Gluteus	.837	1.000	.998	.998	1.000	.999	.999	.983	.378	.291	.921	1.000	.999	.996
	Soleus	.133	.994	.951	1.000	1.000	.997	.997	.968	.074	.261	.789	.984	.998	.996
	SAT	.996	.958	.982	1.000	.981	1.000	1.000	1.000	.986	.947	1.000	1.000	1.000	1.000
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	.102	1.000	.440	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	.054	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.538	.908
	Gluteus	.996	.934	1.000	1.000	.984	1.000	1.000	.999	.896	.924	.977	1.000	1.000	.998
	Soleus	.489	1.000	1.000	1.000	.999	1.000	1.000	.997	.425	.888	.907	1.000	.999	.998
	VAT	.996	.958	.982	1.000	.981	1.000	1.000	1.000	.986	.947	1.000	1.000	1.000	1.000

		p value												
		Phosphatidylethanolamine									*Phosphatidylglycerol*			
		PE(15-MHDA/22:6)	PE(17:0/22:6)	PE(18:0/22:4)	PE(20:0/20:4)	PE(18:0/22:5) (n3)	PE(18:0/22:5) (n6)	PE(18:0 /22:6)	PE(18:1/22:6) (a)	PE(18:1/22:6) (b)	PG(34:1)	PG(36:1)	PG(36:2)	PG(34:2)
Liver	Heart	**.006**	.054	**.000**	.950	.166	**.000**	**.000**	1.000	1.000	**.000**	.106	**.000**	**.000**
	Kidney	**.000**	**.000**	1.000	1.000	**.000**	.601	**.006**	**.000**	**.000**	.988	1.000	.998	**.002**
	Gluteus	**.000**	**.000**	**.001**	**.000**	**.000**	.923	.250	**.000**	**.000**	.953	1.000	1.000	**.003**
	Soleus	**.000**	**.000**	**.019**	**.000**	**.000**	.996	.931	**.000**	**.000**	.979	.983	.907	**.032**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	.389	**.002**	**.000**	**.000**	.158	1.000	.576	**.000**
	SAT	**.000**	**.000**	**.001**	**.000**	**.000**	.504	**.006**	**.000**	**.000**	.259	.996	.719	**.000**
Heart	Liver	**.006**	.054	**.000**	.950	.166	**.000**	**.000**	1.000	1.000	**.000**	.106	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	.958	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.267	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.167	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.642	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.074	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.520	**.000**	**.000**
Kidney	Liver	**.000**	**.000**	1.000	1.000	**.000**	.601	**.006**	**.000**	**.000**	.988	1.000	.998	**.002**
	Heart	**.000**	**.000**	**.000**	.958	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.267	**.000**	**.000**
	Gluteus	1.000	.985	**.001**	**.000**	.967	.997	.767	1.000	.998	.653	1.000	.989	1.000
	Soleus	.909	.807	**.023**	**.000**	.684	.958	.186	.688	.992	.752	.999	.681	.989
	VAT	.960	.997	**.000**	**.000**	.896	1.000	1.000	.932	.741	**.042**	.999	.921	.918
	SAT	.981	.998	**.001**	**.000**	.960	1.000	1.000	.962	.828	.082	1.000	.962	.958
Gluteus	Liver	**.000**	**.000**	**.001**	**.000**	**.000**	.923	.250	**.000**	**.000**	.953	1.000	1.000	**.003**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.167	**.000**	**.000**
	Kidney	1.000	.985	**.001**	**.000**	.967	.997	.767	1.000	.998	.653	1.000	.989	1.000
	Soleus	.978	.996	.982	.998	.991	1.000	.927	.647	.879	1.000	.990	.973	.993
	VAT	.857	.790	.973	.997	.350	.976	.648	.951	.966	.770	1.000	.503	.894
	SAT	.919	.857	1.000	1.000	.527	.986	.727	.973	.983	.850	.998	.641	.944
Soleus	Liver	**.000**	**.000**	**.019**	**.000**	**.000**	.996	.931	**.000**	**.000**	.979	.983	.907	**.032**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.642	**.000**	**.000**
	Kidney	.909	.807	**.023**	**.000**	.684	.958	.186	.688	.992	.752	.999	.681	.989
	Gluteus	.978	.996	.982	.998	.991	1.000	.927	.647	.879	1.000	.990	.973	.993
	VAT	.367	.429	.624	.910	.102	.871	.118	.130	.339	.748	.950	.117	.531
	SAT	.491	.532	.948	.989	.197	.911	.175	.203	.451	.828	1.000	.198	.654
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.389	**.002**	**.000**	**.000**	.158	1.000	.576	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.074	**.000**	**.000**
	Kidney	.960	.997	**.000**	**.000**	.896	1.000	1.000	.932	.741	**.042**	.999	.921	.918
	Gluteus	.857	.790	.973	.997	.350	.976	.648	.951	.966	.770	1.000	.503	.894
	Soleus	.367	.429	.624	.910	.102	.871	.118	.130	.339	.748	.950	.117	.531
	SAT	1.000	1.000	.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.982	1.000	1.000
SAT	Liver	**.000**	**.000**	**.001**	**.000**	**.000**	.504	**.006**	**.000**	**.000**	.259	.996	.719	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.520	**.000**	**.000**
	Kidney	.981	.998	**.001**	**.000**	.960	1.000	1.000	.962	.828	.082	1.000	.962	.958
	Gluteus	.919	.857	1.000	1.000	.527	.986	.727	.973	.983	.850	.998	.641	.944
	Soleus	.491	.532	.948	.989	.197	.911	.175	.203	.451	.828	1.000	.198	.654
	VAT	1.000	1.000	.996	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.982	1.000	1.000

		p value											
		Phosphatidylinositol											
		PI(16:0/16:0)	PI(16:0/16:1)	PI(34:0)	PI(34:1)	PI(17:0/18:1) (a+b)	PI(17:0/18:2) (a+b)	PI(18:0/18:1)	PI(36:2) (a+b)	PI(18:1/18:2)	PI(16:0/20:3) (a)	PI(16:0/20:3) (b)
Liver	Heart	.980	**.006**	.857	**.037**	1.000	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.906	**.000**	.981	.124	.170	**.000**	1.000	**.000**	**.000**	**.000**	**.000**
	Soleus	.944	**.000**	1.000	.959	.944	**.000**	.612	**.000**	**.000**	**.000**	**.000**
	VAT	.827	**.000**	.201	**.000**	**.002**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	SAT	.897	**.000**	.377	**.001**	**.026**	**.000**	**.031**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	.980	**.006**	.857	**.037**	1.000	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.001**	.679	1.000	**.000**	**.000**	.076	1.000
	Gluteus	1.000	.399	1.000	**.000**	.088	**.037**	**.000**	**.000**	**.000**	.059	.700
	Soleus	1.000	.708	.892	**.007**	.835	.333	**.033**	**.000**	**.000**	.158	.999
	VAT	.998	.089	.887	**.000**	**.001**	**.005**	**.000**	**.000**	**.000**	.053	.292
	SAT	.999	.468	.963	**.000**	**.012**	.230	**.000**	**.000**	**.000**	.230	.696
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.001**	.679	1.000	**.000**	**.000**	.076	1.000
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	.736	**.001**	.733	.784	**.000**	.845
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	.997	.079	1.000	.980	**.000**	1.000
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	.348	**.000**	.212	.833	**.000**	.473
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	.984	**.000**	.475	.999	**.000**	.835
Gluteus	Liver	.906	**.000**	.981	.124	.170	**.000**	1.000	**.000**	**.000**	**.000**	**.000**
	Heart	1.000	.399	1.000	**.000**	.088	**.037**	**.000**	**.000**	**.000**	.059	.700
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.736	**.001**	.733	.784	**.000**	.845
	Soleus	1.000	1.000	.984	.729	.838	.977	.691	.867	.998	1.000	.946
	VAT	1.000	.994	.745	.111	.732	.997	**.003**	.977	1.000	1.000	.997
	SAT	1.000	1.000	.880	.479	.976	.995	**.044**	.999	.971	.999	1.000
Soleus	Liver	.944	**.000**	1.000	.959	.944	**.000**	.612	**.000**	**.000**	**.000**	**.000**
	Heart	1.000	.708	.892	**.007**	.835	.333	**.033**	**.000**	**.000**	.158	.999
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.997	.079	1.000	.980	**.000**	1.000
	Gluteus	1.000	1.000	.984	.729	.838	.977	.691	.867	.998	1.000	.946
	VAT	1.000	.943	.287	**.002**	.094	.781	**.000**	.360	1.000	1.000	.680
	SAT	1.000	1.000	.458	**.028**	.366	1.000	**.001**	.643	1.000	1.000	.938
VAT	Liver	.827	**.000**	.201	**.000**	**.002**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	Heart	.998	.089	.887	**.000**	**.001**	**.005**	**.000**	**.000**	**.000**	.053	.292
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.348	**.000**	.212	.833	**.000**	.473
	Gluteus	1.000	.994	.745	.111	.732	.997	**.003**	.977	1.000	1.000	.997
	Soleus	1.000	.943	.287	**.002**	.094	.781	**.000**	.360	1.000	1.000	.680
	SAT	1.000	.994	1.000	.994	.997	.881	.989	1.000	.985	.999	.999
SAT	Liver	.897	**.000**	.377	**.001**	**.026**	**.000**	**.031**	**.000**	**.000**	**.000**	**.000**
	Heart	.999	.468	.963	**.000**	**.012**	.230	**.000**	**.000**	**.000**	.230	.696
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.984	**.000**	.475	.999	**.000**	.835
	Gluteus	1.000	1.000	.880	.479	.976	.995	**.044**	.999	.971	.999	1.000
	Soleus	1.000	1.000	.458	**.028**	.366	1.000	**.001**	.643	1.000	1.000	.938
	VAT	1.000	.994	1.000	.994	.997	.881	.989	1.000	.985	.999	.999

		p value										
		Phosphatidylinositol										
		PI(16:0/20:4)	PI(17:0/20:4) (a+b)	PI(37:6)	PI(18:0/20:2)	PI(18:0/20:3) (a)	PI(18:0/20:3) (b)	PI(18:0/20:4)	PI(38:5) (a)	PI (38:5) (b)	PI(38:6)	PI(39:6) (a+b)
Liver	Heart	**.000**	**.000**	.251	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	.235	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	**.000**
	Gluteus	**.000**	**.000**	.990	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	.886	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	.674	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.000**	**.000**	.251	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**
	Kidney	**.000**	.565	1.000	**.000**	**.000**	1.000	.745	**.008**	.988	**.000**	1.000
	Gluteus	.609	.422	.076	.236	**.000**	.390	.116	**.000**	**.020**	.310	.938
	Soleus	.739	.648	**.029**	**.000**	**.000**	**.001**	.453	**.000**	**.045**	.449	.972
	VAT	.594	.175	**.006**	.052	.390	**.017**	**.000**	**.000**	**.001**	.074	.200
	SAT	.938	.613	.190	.152	.814	.191	**.001**	**.000**	**.020**	.186	.490
Kidney	Liver	**.000**	**.000**	.235	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	**.000**
	Heart	**.000**	.565	1.000	**.000**	**.000**	1.000	.745	**.008**	.988	**.000**	1.000
	Gluteus	**.000**	**.014**	.074	**.035**	.189	.467	**.004**	**.007**	.173	**.000**	.980
	Soleus	**.000**	**.039**	**.029**	.991	1.000	**.002**	**.036**	**.029**	.274	**.000**	.993
	VAT	**.000**	**.003**	**.007**	**.000**	**.000**	**.029**	**.000**	**.001**	**.022**	**.000**	.349
	SAT	**.000**	**.034**	.176	**.000**	**.000**	.241	**.000**	**.019**	.157	**.000**	.655
Gluteus	Liver	**.000**	**.000**	.990	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.609	.422	.076	.236	**.000**	.390	.116	**.000**	**.020**	.310	.938
	Kidney	**.000**	**.014**	.074	**.035**	.189	.467	**.004**	**.007**	.173	**.000**	.980
	Soleus	1.000	1.000	.999	**.007**	.221	.223	.996	1.000	1.000	1.000	1.000
	VAT	1.000	1.000	.983	**.000**	**.000**	**.000**	.286	.994	.984	.997	.858
	SAT	.998	1.000	1.000	**.001**	**.000**	**.002**	.543	1.000	1.000	1.000	.979
Soleus	Liver	**.000**	**.000**	.886	**.007**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.739	.648	**.029**	**.000**	**.000**	**.001**	.453	**.000**	**.045**	.449	.972
	Kidney	**.000**	**.039**	**.029**	.991	1.000	**.002**	**.036**	**.029**	.274	**.000**	.993
	Gluteus	1.000	1.000	.999	**.007**	.221	.223	.996	1.000	1.000	1.000	1.000
	VAT	1.000	.994	1.000	**.000**	**.000**	**.000**	.100	.953	.968	.991	.830
	SAT	1.000	1.000	.989	**.000**	**.000**	**.000**	.249	1.000	1.000	.999	.967
VAT	Liver	**.000**	**.000**	.674	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.594	.175	**.006**	.052	.390	**.017**	**.000**	**.000**	**.001**	.074	.200
	Kidney	**.000**	**.003**	**.007**	**.000**	**.000**	**.029**	**.000**	**.001**	**.022**	**.000**	.349
	Gluteus	1.000	1.000	.983	**.000**	**.000**	**.000**	.286	.994	.984	.997	.858
	Soleus	1.000	.994	1.000	**.000**	**.000**	**.000**	.100	.953	.968	.991	.830
	SAT	.998	.996	.935	1.000	.998	.990	1.000	.979	.996	1.000	1.000
SAT	Liver	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.938	.613	.190	.152	.814	.191	**.001**	**.000**	**.020**	.186	.490
	Kidney	**.000**	**.034**	.176	**.000**	**.000**	.241	**.000**	**.019**	.157	**.000**	.655
	Gluteus	.998	1.000	1.000	**.001**	**.000**	**.002**	.543	1.000	1.000	1.000	.979
	Soleus	1.000	1.000	.989	**.000**	**.000**	**.000**	.249	1.000	1.000	.999	.967
	VAT	.998	.996	.935	1.000	.998	.990	1.000	.979	.996	1.000	1.000

		p value											
		Phosphatidylinositol					*Phosphatidylserine*						
		PI(18:0/22:4)	PI(20:0/20:4)	PI(18:0/22:5) (n3)	PI(18:0/22:5) (n6)	PI(18:0/22:6)	PS(36:1)	PS(36:2)	PS(38:3)	PS(38:4)	PS(38:5)	PS(40:5)	PS(40:6)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	.092	.967	**.015**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.999	**.005**
	Gluteus	**.000**	**.000**	.072	**.004**	**.000**	**.042**	.302	**.000**	**.000**	**.000**	.823	1.000
	Soleus	**.000**	**.000**	.425	.326	**.003**	.743	1.000	**.000**	**.000**	**.000**	.659	.689
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.036**	.879	**.000**	**.000**	**.000**	.065	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	.978	**.000**	**.000**	**.000**	**.000**	.333	**.001**
Heart	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.092	.967	**.015**	**.000**	**.000**	**.000**	**.000**
	Kidney	1.000	.499	**.030**	.997	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	1.000	.069	.281	.171	.239	**.000**	.816	**.001**	.804	.999	**.000**	**.000**
	Soleus	.148	.479	.067	**.003**	**.031**	.945	.974	**.011**	.915	.990	**.000**	**.000**
	VAT	**.004**	**.015**	**.001**	.338	.269	**.000**	1.000	**.000**	.640	.364	**.000**	**.000**
	SAT	**.024**	.092	**.005**	.487	.378	.632	**.000**	.536	.997	1.000	**.000**	**.000**
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.999	**.005**
	Heart	1.000	.499	**.030**	.997	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	1.000	**.001**	**.000**	.521	.155	**.000**	**.000**	**.000**	**.000**	**.000**	.609	**.019**
	Soleus	.305	**.016**	**.000**	**.024**	**.020**	**.000**	**.000**	**.000**	**.000**	**.000**	.444	**.000**
	VAT	**.004**	**.000**	.969	.156	.565	**.000**	**.000**	**.000**	**.000**	**.000**	.248	.985
	SAT	**.020**	**.001**	.990	.255	.663	**.000**	.375	**.000**	**.000**	**.000**	.664	.996
Gluteus	Liver	**.000**	**.000**	.072	**.004**	**.000**	**.042**	.302	**.000**	**.000**	**.000**	.823	1.000
	Heart	1.000	.069	.281	.171	.239	**.000**	.816	**.001**	.804	.999	**.000**	**.000**
	Kidney	1.000	**.001**	**.000**	.521	.155	**.000**	**.000**	**.000**	**.000**	**.000**	.609	**.019**
	Soleus	.292	.977	.988	.685	.960	**.002**	.388	.996	1.000	.913	1.000	.603
	VAT	**.004**	.999	**.000**	**.001**	**.001**	1.000	.948	.983	1.000	.196	**.003**	**.001**
	SAT	**.022**	1.000	**.000**	**.003**	**.003**	**.011**	**.000**	.256	.991	1.000	**.031**	**.005**
Soleus	Liver	**.000**	**.000**	.425	.326	**.003**	.743	1.000	**.000**	**.000**	**.000**	.659	.689
	Heart	.148	.479	.067	**.003**	**.031**	.945	.974	**.011**	.915	.990	**.000**	**.000**
	Kidney	.305	**.016**	**.000**	**.024**	**.020**	**.000**	**.000**	**.000**	**.000**	**.000**	.444	**.000**
	Gluteus	.292	.977	.988	.685	.960	**.002**	.388	.996	1.000	.913	1.000	.603
	VAT	**.000**	.836	**.000**	**.000**	**.000**	**.001**	.906	.800	1.000	.893	**.002**	**.000**
	SAT	**.000**	.981	**.000**	**.000**	**.000**	.997	**.001**	.647	.999	.969	**.018**	**.000**
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.036**	.879	**.000**	**.000**	**.000**	.065	**.000**
	Heart	**.004**	**.015**	**.001**	.338	.269	**.000**	1.000	**.000**	.640	.364	**.000**	**.000**
	Kidney	**.004**	**.000**	.969	.156	.565	**.000**	**.000**	**.000**	**.000**	**.000**	.248	.985
	Gluteus	**.004**	.999	**.000**	**.001**	**.001**	1.000	.948	.983	1.000	.196	**.003**	**.001**
	Soleus	**.000**	.836	**.000**	**.000**	**.000**	**.001**	.906	.800	1.000	.893	**.002**	**.000**
	SAT	1.000	.999	1.000	1.000	1.000	**.009**	**.000**	**.041**	.964	.332	.998	1.000
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.978	**.000**	**.000**	**.000**	**.000**	.333	**.001**
	Heart	**.024**	.092	**.005**	.487	.378	.632	**.000**	.536	.997	1.000	**.000**	**.000**
	Kidney	**.020**	**.001**	.990	.255	.663	**.000**	.375	**.000**	**.000**	**.000**	.664	.996
	Gluteus	**.022**	1.000	**.000**	**.003**	**.003**	**.011**	**.000**	.256	.991	1.000	**.031**	**.005**
	Soleus	**.000**	.981	**.000**	**.000**	**.000**	.997	**.001**	.647	.999	.969	**.018**	**.000**
	VAT	1.000	.999	1.000	1.000	1.000	**.009**	**.000**	**.041**	.964	.332	.998	1.000

p values < 0.05 are represented in bold numbers.

Table S16. Ether glycerophospholipid concentration detected by targeted lipidomic analysis in all the studied tissues. Lipid species detected were 10 LPC(O-), 6 LPC(P-), 4 LPE(P-), 22 PC(O-), 26 PC(P-), 14 PE(O-) and 55 PE(P-).

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Alkyl lysophosphatidylcholine							
LPC(O-16:0)	0.32 ± 0.05	0.21 ± 0.03	1.25 ± 0.09	0.13 ± 0.02	0.27 ± 0.03	0.07 ± 0.01	0.28 ± 0.04
LPC(O-18:0)	0.12 ± 0.02	0.07 ± 0.01	0.29 ± 0.02	0.04 ± 0.00	0.05 ± 0.01	0.02 ± 0.003	0.07 ± 0.01
LPC(O-18:1)	0.25 ± 0.03	0.12 ± 0.02	0.52 ± 0.03	0.07 ± 0.01	0.11 ± 0.02	0.04 ± 0.01	0.21 ± 0.03
LPC(O-20:0)	0.03 ± 0.005	0.02 ± 0.003	0.06 ± 0.003	0.01 ± 0.0004	0.01 ± 0.002	0.01 ± 0.001	0.02 ± 0.003
LPC(O-20:1)	0.01 ± 0.002	0.002 ± 0.0003	0.004 ± 0.001	0.002 ± 0.0003	0.002 ± 0.0004	0.001 ± 0.0003	0.004 ± 0.001
LPC(O-22:0)	0.03 ± 0.002	0.02 ± 0.002	0.04 ± 0.003	0.01 ± 0.0004	0.01 ± 0.002	0.005 ± 0.001	0.01 ± 0.001
LPC(O-22:1)	0.02 ± 0.002	0.01 ± 0.001	0.01 ± 0.002	0.01 ± 0.001	0.01 ± 0.001	0.003 ± 0.001	0.01 ± 0.001
LPC(O-24:0)	0.03 ± 0.002	0.02 ± 0.002	0.03 ± 0.003	0.01 ± 0.001	0.02 ± 0.002	0.01 ± 0.001	0.02 ± 0.001
LPC(O-24:1)	0.04 ± 0.003	0.02 ± 0.002	0.03 ± 0.002	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.002	0.02 ± 0.002
LPC(O-24:2)	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.003 ± 0.0004	0.003 ± 0.0004	0.002 ± 0.0002	0.005 ± 0.001
Alkenyl lysophosphatidylcholine							
LPC(P-16:0)	0.04 ± 0.01	0.69 ± 0.08	0.83 ± 0.05	0.46 ± 0.03	0.58 ± 0.07	0.03 ± 0.005	0.13 ± 0.02
LPC(P-17:0) (a)	0.003 ± 0.0004	0.01 ± 0.002	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.002 ± 0.0005	0.00 ± 0.001
LPC(P-17:0) (b)	0.004 ± 0.0003	0.01 ± 0.002	0.01 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.002 ± 0.0005	0.005 ± 0.0001
LPC(P-18:0)	0.01 ± 0.001	0.04 ± 0.005	0.06 ± 0.004	0.06 ± 0.006	0.05 ± 0.008	0.01 ± 0.001	0.02 ± 0.002
LPC(P-18:1)	0.01 ± 0.002	0.08 ± 0.01	0.07 ± 0.005	0.06 ± 0.006	0.06 ± 0.008	0.004 ± 0.001	0.02 ± 0.004
LPC(P-20:0)	0.004 ± 0.001	0.003 ± 0.001	0.01 ± 0.001	0.003 ± 0.0005	0.003 ± 0.001	0.002 ± 0.0004	0.004 ± 0.001
Alkenyl lysophosphatidylethanolamine							
LPE(P-16:0)	0.16 ± 0.02	4.18 ± 0.48	6.33 ± 0.44	1.01 ± 0.09	2.16 ± 0.32	0.21 ± 0.03	0.81 ± 0.15
LPE(P-18:0)	0.23 ± 0.03	1.92 ± 0.25	3.87 ± 0.37	0.63 ± 0.05	1.13 ± 0.13	0.12 ± 0.02	0.47 ± 0.06
LPE(P-18:1)	0.10 ± 0.02	1.79 ± 0.17	1.62 ± 0.11	0.25 ± 0.03	0.69 ± 0.07	0.08 ± 0.01	0.36 ± 0.04
LPE(P-20:0)	0.08 ± 0.01	0.09 ± 0.01	0.17 ± 0.02	0.05 ± 0.01	0.08 ± 0.01	0.05 ± 0.01	0.09 ± 0.01
Alkyl phosphatidylcholine							
PC(O-16:0/16:0)	7.32 ± 0.59	4.46 ± 0.51	9.09 ± 0.57	2.15 ± 0.10	3.03 ± 0.50	0.27 ± 0.04	1.59 ± 0.28
PC(O-32:1)	0.71 ± 0.07	0.35 ± 0.03	1.30 ± 0.09	0.54 ± 0.02	0.84 ± 0.14	0.05 ± 0.01	0.31 ± 0.06
PC(O-32:2)	0.06 ± 0.004	0.05 ± 0.004	0.11 ± 0.01	0.06 ± 0.001	0.06 ± 0.01	0.02 ± 0.001	0.04 ± 0.002
PC(O-34:1)	8.91 ± 0.66	4.32 ± 0.48	17.70 ± 0.94	5.05 ± 0.20	6.23 ± 1.02	0.32 ± 0.05	2.46 ± 0.47
PC(O-34:2)	1.86 ± 0.11	1.26 ± 0.13	4.88 ± 0.30	1.42 ± 0.06	1.40 ± 0.23	0.16 ± 0.02	0.68 ± 0.11
PC(O-34:4)	0.17 ± 0.01	0.16 ± 0.01	0.38 ± 0.02	0.15 ± 0.001	0.15 ± 0.01	0.08 ± 0.00	0.13 ± 0.01
PC(O-35:4)	0.15 ± 0.02	0.08 ± 0.01	0.30 ± 0.02	0.04 ± 0.004	0.04 ± 0.01	0.01 ± 0.002	0.04 ± 0.004
PC(O-36:0)	0.16 ± 0.01	0.09 ± 0.01	0.18 ± 0.02	0.03 ± 0.002	0.06 ± 0.01	0.02 ± 0.003	0.05 ± 0.01
PC(O-18:0/18:1)	0.32 ± 0.02	0.12 ± 0.01	0.27 ± 0.02	0.09 ± 0.01	0.19 ± 0.03	0.01 ± 0.002	0.07 ± 0.01

PC(O-18:1/18:1)	0.41 ± 0.02	0.18 ± 0.02	0.44 ± 0.03	0.23 ± 0.01	0.29 ± 0.04	0.02 ± 0.003	0.14 ± 0.02
PC(O-18:0/18:2)	0.27 ± 0.02	0.11 ± 0.01	0.33 ± 0.03	0.11 ± 0.01	0.11 ± 0.02	0.02 ± 0.003	0.06 ± 0.01
PC(O-18:1/18:2)	0.56 ± 0.02	0.29 ± 0.04	0.87 ± 0.06	0.25 ± 0.01	0.25 ± 0.03	0.05 ± 0.01	0.21 ± 0.04
PC(O-16:0/20:3)	0.35 ± 0.02	0.22 ± 0.02	0.41 ± 0.03	0.14 ± 0.01	0.14 ± 0.01	0.07 ± 0.004	0.17 ± 0.01
PC(O-16:0/20:4)	16.62 ± 1.48	11.54 ± 1.28	33.60 ± 2.06	5.22 ± 0.13	5.72 ± 0.84	1.16 ± 0.17	5.24 ± 0.86
PC(O-36:5)	0.43 ± 0.03	0.63 ± 0.06	0.87 ± 0.04	1.09 ± 0.03	1.00 ± 0.16	0.11 ± 0.01	0.31 ± 0.03
PC(O-18:0/20:4)	1.72 ± 0.14	0.69 ± 0.09	2.22 ± 0.19	0.23 ± 0.02	0.27 ± 0.04	0.07 ± 0.01	0.32 ± 0.04
PC(O-38:5)	8.15 ± 0.75	5.15 ± 0.57	9.98 ± 0.55	4.10 ± 0.19	3.46 ± 0.67	0.40 ± 0.07	2.80 ± 0.53
PC(O-16:0/22:6)	1.05 ± 0.08	3.65 ± 0.52	7.29 ± 0.58	10.22 ± 0.35	9.31 ± 2.15	0.10 ± 0.01	0.30 ± 0.02
PC(O-40:5)	0.19 ± 0.01	0.13 ± 0.02	0.47 ± 0.04	0.13 ± 0.01	0.11 ± 0.02	0.01 ± 0.001	0.06 ± 0.01
PC(O-18:0/22:6)	0.38 ± 0.02	0.64 ± 0.07	0.71 ± 0.04	0.85 ± 0.04	0.81 ± 0.17	0.07 ± 0.003	0.15 ± 0.01
PC(O-40:7) (a)	0.28 ± 0.01	0.38 ± 0.05	0.58 ± 0.04	0.50 ± 0.02	0.48 ± 0.12	0.01 ± 0.002	0.08 ± 0.01
PC(O-40:7) (b)	0.72 ± 0.05	1.58 ± 0.19	1.54 ± 0.16	0.92 ± 0.05	1.00 ± 0.20	0.07 ± 0.005	0.17 ± 0.01
Alkenyl phosphatidylcholine							
PC(P-16:0/14:0)	0.06 ± 0.01	0.09 ± 0.01	0.12 ± 0.01	0.72 ± 0.06	0.41 ± 0.08	0.01 ± 0.002	0.05 ± 0.01
PC(P-16:0/16:0)	4.05 ± 0.26	4.59 ± 0.49	4.25 ± 0.31	10.12 ± 0.58	7.59 ± 1.49	0.23 ± 0.04	1.05 ± 0.17
PC(P-16:0/16:1)	0.29 ± 0.03	0.25 ± 0.03	0.47 ± 0.04	1.33 ± 0.11	0.83 ± 0.16	0.02 ± 0.01	0.12 ± 0.03
PC(P-16:0/18:0)	0.15 ± 0.01	0.20 ± 0.02	0.16 ± 0.01	2.73 ± 0.18	1.53 ± 0.37	0.01 ± 0.002	0.06 ± 0.01
PC(P-16:0/18:1)	0.94 ± 0.06	1.68 ± 0.18	5.41 ± 0.47	11.07 ± 0.52	8.75 ± 1.54	0.10 ± 0.01	0.42 ± 0.06
PC(P-16:0/18:2)	1.01 ± 0.05	6.54 ± 0.75	4.78 ± 0.44	12.73 ± 0.45	11.66 ± 2.12	0.25 ± 0.05	0.68 ± 0.09
PC(P-16:0/18:3)	0.17 ± 0.01	0.25 ± 0.02	0.34 ± 0.02	0.54 ± 0.02	0.46 ± 0.06	0.12 ± 0.01	0.17 ± 0.01
PC(P-35:2)(a)	0.09 ± 0.01	0.14 ± 0.01	0.10 ± 0.01	0.26 ± 0.02	0.25 ± 0.05	0.01 ± 0.002	0.03 ± 0.002
PC(P-35:2)(b)	0.06 ± 0.01	0.08 ± 0.01	0.07 ± 0.01	0.16 ± 0.01	0.16 ± 0.03	0.01 ± 0.001	0.02 ± 0.003
PC(P-15:0/20:4) (a)	0.003 ± 0.001	0.01 ± 0.002	0.02 ± 0.001	0.01 ± 0.001	0.01 ± 0.001	0.001 ± 0.0002	0.003 ± 0.0005
PC(P-15:0/20:4) (b)	0.03 ± 0.00	0.42 ± 0.04	0.39 ± 0.03	0.12 ± 0.01	0.11 ± 0.02	0.01 ± 0.002	0.04 ± 0.01
PC(P-18:1/18:1)	0.32 ± 0.01	0.34 ± 0.04	0.61 ± 0.04	0.44 ± 0.01	0.54 ± 0.07	0.06 ± 0.003	0.13 ± 0.01
PC(P-18:0/18:2)	0.17 ± 0.01	0.31 ± 0.03	0.38 ± 0.03	1.04 ± 0.05	0.91 ± 0.19	0.02 ± 0.003	0.08 ± 0.01
PC(P-36:3)	0.83 ± 0.05	1.35 ± 0.13	2.36 ± 0.19	1.22 ± 0.05	1.12 ± 0.20	0.13 ± 0.01	0.37 ± 0.05
PC(P-16:0/20:4)	10.18 ± 0.76	136.4 ± 14.69	57.03 ± 4.19	24.92 ± 1.81	22.61 ± 6.16	1.25 ± 0.23	5.51 ± 0.96
PC(P-16:0/20:5)	0.11 ± 0.01	0.48 ± 0.05	0.39 ± 0.03	0.36 ± 0.02	0.27 ± 0.06	0.01 ± 0.00	0.06 ± 0.01
PC(P-17:0/20:4) (a)	0.28 ± 0.02	3.35 ± 0.41	1.01 ± 0.10	0.61 ± 0.05	0.62 ± 0.17	0.04 ± 0.01	0.17 ± 0.03
PC(P-17:0/20:4) (b)	0.18 ± 0.01	1.39 ± 0.13	0.71 ± 0.07	0.35 ± 0.03	0.33 ± 0.09	0.02 ± 0.004	0.09 ± 0.02
PC(P-18:0/20:4)	1.48 ± 0.11	5.65 ± 0.58	3.08 ± 0.31	2.30 ± 0.24	1.95 ± 0.60	0.11 ± 0.02	0.50 ± 0.10
PC(P-38:5) (a)	3.25 ± 0.19	45.44 ± 5.37	16.03 ± 1.04	35.28 ± 2.06	28.09 ± 6.35	0.44 ± 0.06	1.94 ± 0.34
PC(P-38:5) (b)	0.42 ± 0.04	4.24 ± 0.49	1.28 ± 0.12	3.05 ± 0.22	2.55 ± 0.57	0.06 ± 0.01	0.19 ± 0.03
PC(P-16:0/22:6)	0.48 ± 0.02	14.65 ± 1.93	1.71 ± 0.12	44.78 ± 2.35	42.59 ± 9.35	0.05 ± 0.01	0.17 ± 0.02
PC(P-20:0/20:4)	0.08 ± 0.01	0.05 ± 0.01	0.12 ± 0.01	0.01 ± 0.001	0.02 ± 0.003	0.01 ± 0.001	0.02 ± 0.003
PC(P-18:0/22:5)	0.27 ± 0.02	0.72 ± 0.08	0.36 ± 0.02	1.24 ± 0.07	1.05 ± 0.20	0.09 ± 0.005	0.16 ± 0.01

PC(P-18:0/22:6)	0.14 ± 0.01	0.56 ± 0.07	0.10 ± 0.01	2.29 ± 0.12	2.12 ± 0.50	0.01 ± 0.001	0.02 ± 0.003
PC(P-18:1/22:6)	0.20 ± 0.01	1.55 ± 0.18	0.22 ± 0.02	2.18 ± 0.13	2.54 ± 0.62	0.01 ± 0.002	0.05 ± 0.01
Alkyl phosphatidylethanolamine							
PE(O-34:1)	0.66 ± 0.04	3.54 ± 0.34	8.63 ± 0.54	0.87 ± 0.07	2.61 ± 0.46	0.06 ± 0.01	0.31 ± 0.05
PE(O-16:0/18:2)	0.31 ± 0.03	1.49 ± 0.17	5.52 ± 0.36	0.22 ± 0.02	0.59 ± 0.13	0.03 ± 0.01	0.09 ± 0.01
PE(O-18:1/18:2)	0.17 ± 0.03	0.99 ± 0.12	2.07 ± 0.11	0.09 ± 0.01	0.30 ± 0.06	0.02 ± 0.004	0.05 ± 0.01
PE(O-16:0/20:3)	0.10 ± 0.02	0.16 ± 0.02	0.36 ± 0.02	0.04 ± 0.01	0.06 ± 0.01	0.01 ± 0.01	0.02 ± 0.003
PE(O-16:0/20:4)	2.92 ± 0.25	10.23 ± 0.98	24.55 ± 1.27	0.71 ± 0.06	2.10 ± 0.36	0.17 ± 0.03	0.84 ± 0.16
PE(O-36:5)	0.06 ± 0.01	0.53 ± 0.06	0.41 ± 0.05	0.07 ± 0.01	0.19 ± 0.05	0.02 ± 0.003	0.07 ± 0.01
PE(O-16:0/22:4)	2.16 ± 0.16	4.97 ± 0.50	2.60 ± 0.15	0.58 ± 0.06	1.80 ± 0.34	0.05 ± 0.01	0.30 ± 0.05
PE(O-18:0/20:4)	1.70 ± 0.10	1.83 ± 0.25	8.52 ± 0.56	0.12 ± 0.01	0.34 ± 0.07	0.11 ± 0.01	0.31 ± 0.02
PE(O-38:5) (a)	3.35 ± 0.22	23.89 ± 2.24	12.16 ± 0.56	4.67 ± 0.27	8.57 ± 1.85	0.17 ± 0.03	0.86 ± 0.19
PE(O-38:5) (b)	0.35 ± 0.03	1.85 ± 0.17	0.74 ± 0.04	0.38 ± 0.05	0.65 ± 0.13	0.04 ± 0.01	0.09 ± 0.01
PE(O-16:0/22:6)	0.78 ± 0.07	13.05 ± 1.39	4.12 ± 0.36	4.98 ± 0.31	8.91 ± 1.86	0.05 ± 0.01	0.16 ± 0.02
PE(O-18:0/22:5) (a)	0.37 ± 0.03	2.14 ± 0.24	0.32 ± 0.04	1.12 ± 0.09	1.55 ± 0.30	0.02 ± 0.01	0.08 ± 0.01
PE(O-18:0/22:6)	0.81 ± 0.06	4.35 ± 0.47	1.59 ± 0.12	2.12 ± 0.17	3.30 ± 0.65	0.04 ± 0.005	0.24 ± 0.03
PE(O-18:1/22:6)	0.47 ± 0.09	3.76 ± 0.50	0.67 ± 0.03	1.02 ± 0.04	1.86 ± 0.38	0.01 ± 0.002	0.05 ± 0.01
Alkenyl phosphatidylethanolamine							
PE(P-15:0/20:4) (a)	0.21 ± 0.07	0.19 ± 0.02	0.38 ± 0.03	0.10 ± 0.01	0.11 ± 0.02	0.07 ± 0.01	0.10 ± 0.02
PE(P-15:0/20:4) (b)	0.54 ± 0.06	2.23 ± 0.28	4.33 ± 0.28	0.12 ± 0.01	0.29 ± 0.06	0.10 ± 0.02	0.46 ± 0.06
PE(P-15:0/22:6) (a)	0.08 ± 0.03	0.33 ± 0.22	0.09 ± 0.05	0.47 ± 0.24	0.14 ± 0.04	0.04 ± 0.01	0.06 ± 0.02
PE(P-15:0/22:6) (b)	0.14 ± 0.03	2.37 ± 0.29	0.40 ± 0.07	1.51 ± 0.14	1.68 ± 0.33	0.05 ± 0.01	0.11 ± 0.02
PE(P-16:0/18:1)	6.94 ± 0.35	17.32 ± 1.62	73.27 ± 3.93	6.37 ± 0.42	34.42 ± 6.13	2.26 ± 0.31	12.52 ± 3.14
PE(P-16:0/18:2)	6.07 ± 0.22	96.23 ± 9.92	61.04 ± 4.45	13.06 ± 0.76	25.05 ± 4.06	2.37 ± 0.36	6.18 ± 1.13
PE(P-16:0/18:3)	0.17 ± 0.03	0.60 ± 0.06	1.80 ± 0.18	0.25 ± 0.05	0.25 ± 0.05	0.11 ± 0.02	0.14 ± 0.02
PE(P-16:0/20:3) (a)	1.47 ± 0.10	2.49 ± 0.27	3.92 ± 0.25	0.34 ± 0.05	0.56 ± 0.08	0.13 ± 0.02	0.36 ± 0.10
PE(P-16:0/20:3) (b)	0.91 ± 0.08	1.08 ± 0.10	2.27 ± 0.27	0.30 ± 0.05	0.44 ± 0.08	0.31 ± 0.10	0.52 ± 0.06
PE(P-16:0/20:4)	117.6 ± 8.89	958.0 ± 92.18	768.7 ± 49.28	29.06 ± 0.93	61.19 ± 11.19	17.00 ± 2.97	77.62 ± 13.97
PE(P-16:0/20:5)	0.91 ± 0.05	3.34 ± 0.39	3.42 ± 0.29	0.50 ± 0.04	0.57 ± 0.12	0.10 ± 0.02	0.55 ± 0.11
PE(P-16:0/22:4)	58.28 ± 4.13	161.7 ± 16.13	80.25 ± 4.30	24.90 ± 1.66	38.23 ± 5.94	2.61 ± 0.42	16.70 ± 2.43
PE(P-16:0/22:5) (n3)	33.43 ± 1.71	539.4 ± 56.78	98.24 ± 5.22	136.7 ± 9.67	144.2 ± 26.99	2.41 ± 0.36	15.69 ± 3.58
PE(P-16:0/22:5) (n6)	6.46 ± 0.60	108.0 ± 13.55	12.88 ± 1.15	28.19 ± 2.61	25.99 ± 5.11	0.62 ± 0.05	2.23 ± 0.22
PE(P-16:0/22:6)	8.93 ± 0.65	542.2 ± 73.94	41.23 ± 2.60	365.0 ± 22.31	387.0 ± 73.17	1.35 ± 0.22	5.27 ± 0.78
PE(P-17:0/20:4) (a)	3.64 ± 0.31	15.92 ± 1.58	13.33 ± 0.71	1.05 ± 0.08	1.96 ± 0.38	0.51 ± 0.09	2.87 ± 0.65
PE(P-17:0/20:4) (b)	4.27 ± 0.29	30.03 ± 3.27	25.25 ± 2.28	1.06 ± 0.09	2.18 ± 0.44	0.45 ± 0.11	1.57 ± 0.30
PE(P-17:0/22:6) (a)	0.84 ± 0.05	18.49 ± 2.63	1.65 ± 0.16	19.21 ± 1.04	20.80 ± 4.44	0.15 ± 0.03	0.46 ± 0.09
PE(P-17:0/22:6) (b)	0.48 ± 0.07	23.24 ± 3.47	1.35 ± 0.09	16.80 ± 0.67	16.93 ± 2.96	0.15 ± 0.04	0.20 ± 0.02
PE(P-18:0/18:1)	2.79 ± 0.14	4.79 ± 0.39	17.13 ± 1.11	4.89 ± 0.39	43.25 ± 9.67	0.60 ± 0.05	8.85 ± 3.09

PE(P-18:0/18:2)	2.93 ± 0.13	30.27 ± 2.95	20.03 ± 1.38	9.97 ± 0.70	16.34 ± 2.77	0.54 ± 0.07	1.68 ± 0.29
PE(P-18:0/18:3)	1.36 ± 0.08	20.76 ± 2.32	10.00 ± 0.54	3.40 ± 0.31	6.60 ± 0.98	1.07 ± 0.08	2.25 ± 0.30
PE(P-18:0/20:3) (a)	1.41 ± 0.11	2.00 ± 0.16	3.00 ± 0.18	0.49 ± 0.07	0.96 ± 0.16	0.13 ± 0.02	0.41 ± 0.05
PE(P-18:0/20:3) (b)	0.40 ± 0.03	0.52 ± 0.05	0.90 ± 0.07	0.16 ± 0.02	0.22 ± 0.05	0.07 ± 0.02	0.20 ± 0.02
PE(P-18:0/20:4)	83.13 ± 5.81	499.2 ± 43.51	499.8 ± 39.93	28.37 ± 1.45	50.97 ± 9.54	6.21 ± 1.09	29.60 ± 5.55
PE(P-18:0/20:5)	0.57 ± 0.06	1.50 ± 0.17	1.39 ± 0.12	0.52 ± 0.07	0.63 ± 0.16	0.07 ± 0.01	0.18 ± 0.04
PE(P-18:0/22:4)	13.98 ± 0.90	26.32 ± 2.50	15.84 ± 1.20	8.09 ± 0.68	11.28 ± 1.93	0.57 ± 0.08	2.64 ± 0.42
PE(P-18:0/22:5) (n3)	3.97 ± 0.15	43.19 ± 5.19	3.58 ± 0.28	49.91 ± 3.62	43.14 ± 8.21	0.27 ± 0.04	1.66 ± 0.39
PE(P-18:0/22:5) (n6)	2.12 ± 0.18	21.20 ± 2.57	3.13 ± 0.28	12.69 ± 1.37	10.95 ± 2.15	0.21 ± 0.04	0.53 ± 0.05
PE(P-18:0/22:6)	5.29 ± 0.32	177.5 ± 22.44	13.88 ± 0.98	191.6 ± 9.49	193.8 ± 37.38	0.35 ± 0.04	1.72 ± 0.24
PE(P-18:1/18:1) (a)	2.23 ± 0.13	6.33 ± 0.62	21.73 ± 1.09	3.18 ± 0.34	53.80 ± 11.64	0.74 ± 0.14	10.49 ± 3.43
PE(P-18:1/18:1) (b)	0.15 ± 0.01	0.80 ± 0.09	3.25 ± 0.23	0.28 ± 0.03	2.55 ± 0.52	0.08 ± 0.02	0.55 ± 0.16
PE(P-18:1/18:2) (a)	1.83 ± 0.14	46.06 ± 5.61	16.85 ± 0.95	4.97 ± 0.31	9.77 ± 1.48	0.50 ± 0.07	2.20 ± 0.47
PE(P-18:1/18:2) (b)	0.12 ± 0.02	2.39 ± 0.36	2.37 ± 0.32	0.30 ± 0.04	0.58 ± 0.10	0.05 ± 0.01	0.13 ± 0.03
PE(P-18:1/18:3)	0.28 ± 0.03	3.98 ± 0.38	3.52 ± 0.27	0.67 ± 0.06	1.34 ± 0.23	0.19 ± 0.02	0.48 ± 0.03
PE(P-18:1/20:3) (a)	0.66 ± 0.09	1.14 ± 0.11	1.76 ± 0.08	0.20 ± 0.02	0.36 ± 0.06	0.06 ± 0.02	0.22 ± 0.05
PE(P-18:1/20:3) (b)	0.88 ± 0.06	2.40 ± 0.26	1.58 ± 0.12	0.29 ± 0.02	0.55 ± 0.12	0.06 ± 0.01	0.37 ± 0.04
PE(P-18:1/20:4) (a)	66.03 ± 4.11	806.7 ± 67.77	381.2 ± 18.44	11.46 ± 0.26	26.12 ± 4.27	5.04 ± 0.90	32.78 ± 6.66
PE(P-18:1/20:4) (b)	1.00 ± 0.09	16.25 ± 1.74	12.92 ± 1.20	0.40 ± 0.04	0.79 ± 0.13	0.16 ± 0.03	0.97 ± 0.16
PE(P-18:1/20:5) (a)	0.43 ± 0.08	1.02 ± 0.11	1.22 ± 0.09	0.08 ± 0.02	0.11 ± 0.02	0.03 ± 0.01	0.11 ± 0.02
PE(P-18:1/20:5) (b)	0.04 ± 0.01	0.11 ± 0.02	0.17 ± 0.02	0.03 ± 0.01	0.05 ± 0.01	0.01 ± 0.003	0.05 ± 0.01
PE(P-18:1/22:4)	20.07 ± 1.16	51.83 ± 5.47	23.67 ± 0.93	23.52 ± 1.07	25.83 ± 3.49	5.23 ± 0.19	10.55 ± 0.73
PE(P-18:1/22:5) (a)	4.46 ± 0.22	79.08 ± 9.88	4.96 ± 0.29	20.95 ± 1.06	27.05 ± 4.69	0.35 ± 0.05	2.46 ± 0.46
PE(P-18:1/22:5) (b)	0.93 ± 0.10	14.41 ± 1.80	1.02 ± 0.07	3.37 ± 0.32	3.59 ± 0.69	0.09 ± 0.02	0.32 ± 0.03
PE(P-18:1/22:6) (a)	2.80 ± 0.17	187.8 ± 23.08	7.18 ± 0.46	42.13 ± 2.42	61.47 ± 10.13	0.24 ± 0.05	1.58 ± 0.26
PE(P-18:1/22:6) (b)	0.13 ± 0.02	7.97 ± 1.22	0.39 ± 0.04	2.77 ± 0.20	3.63 ± 0.57	0.03 ± 0.01	0.09 ± 0.01
PE(P-19:0/20:4) (a)	3.08 ± 0.27	14.67 ± 1.38	9.91 ± 0.82	1.80 ± 0.22	3.54 ± 0.85	0.36 ± 0.06	2.54 ± 0.49
PE(P-19:0/20:4) (b)	0.28 ± 0.03	1.97 ± 0.16	1.87 ± 0.15	0.14 ± 0.02	0.28 ± 0.08	0.06 ± 0.01	0.27 ± 0.05
PE(P-20:0/18:1)	0.48 ± 0.04	0.50 ± 0.06	0.99 ± 0.09	0.42 ± 0.05	1.22 ± 0.22	0.38 ± 0.05	0.59 ± 0.05
PE(P-20:0/18:2)	0.22 ± 0.02	0.75 ± 0.09	0.64 ± 0.08	0.16 ± 0.02	0.15 ± 0.03	0.06 ± 0.01	0.21 ± 0.05
PE(P-20:0/20:4)	1.60 ± 0.12	6.83 ± 0.69	9.54 ± 1.43	0.35 ± 0.01	0.78 ± 0.15	0.18 ± 0.04	1.04 ± 0.19
PE(P-20:0/22:6)	0.34 ± 0.04	1.67 ± 0.22	0.23 ± 0.02	0.29 ± 0.02	0.39 ± 0.07	0.03 ± 0.01	0.11 ± 0.01
PE(P-20:1/20:4)	0.71 ± 0.08	4.39 ± 0.47	3.20 ± 0.24	0.21 ± 0.03	0.56 ± 0.13	0.12 ± 0.03	0.71 ± 0.10
PE(P-20:1/22:6) (a)	0.09 ± 0.02	1.39 ± 0.22	0.08 ± 0.01	0.45 ± 0.05	0.74 ± 0.09	0.03 ± 0.01	0.06 ± 0.01
PE(P-20:1/22:6) (b)	0.04 ± 0.01	0.07 ± 0.01	0.04 ± 0.01	0.03 ± 0.01	0.04 ± 0.01	0.02 ± 0.003	0.03 0.005

Table S17. Statistic multiple comparison post hoc Tuckey of the ether glycerolipids between all the studied tissues.

		p value									
		Alkyl lysophosphatidylcholine									
		LPC(O-16:0)	LPC(O-18:0)	LPC(O-18:1)	LPC(O-20:0)	LPC(O-20:1)	LPC(O-22:0)	LPC(O-22:1)	LPC(O-24:0)	LPC(O-24:1)	LPC(O-24:2)
Liver	Heart	.678	.061	**.004**	.059	**.000**	**.003**	**.001**	.367	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.005**	.092	.674	.979	**.024**	**.003**
	Gluteus	.113	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.043**	**.000**	**.000**
	Soleus	.990	**.033**	**.007**	**.000**	**.000**	**.000**	**.000**	.276	**.000**	**.000**
	VAT	**.011**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**
	SAT	.997	.144	.926	.380	**.015**	**.000**	**.036**	.226	**.001**	**.000**
Heart	Liver	.678	.061	**.004**	.059	**.000**	**.003**	**.001**	.367	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	.897	**.000**	.197	.096	.541	.698
	Gluteus	.878	.724	.849	**.046**	1.000	**.004**	.832	.900	.328	.226
	Soleus	.992	.998	1.000	.364	1.000	**.036**	.840	1.000	.422	.171
	VAT	.364	.253	.355	**.026**	.969	**.000**	.121	.160	.058	**.010**
	SAT	.975	1.000	.195	.996	.818	.724	.993	.999	1.000	.744
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.005**	.092	.674	.979	**.024**	**.003**
	Heart	**.000**	**.000**	**.000**	**.000**	.897	**.000**	.197	.096	.541	.698
	Gluteus	**.000**	**.000**	**.000**	**.000**	.812	**.000**	**.014**	**.008**	**.008**	**.009**
	Soleus	**.000**	**.000**	**.000**	**.000**	.897	**.000**	**.018**	.075	**.015**	**.007**
	VAT	**.000**	**.000**	**.000**	**.000**	.423	**.000**	**.000**	**.000**	**.001**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	.694	.058	.870	.088
Gluteus	Liver	.113	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.043**	**.000**	**.000**
	Heart	.878	.724	.849	**.046**	1.000	**.004**	.832	.900	.328	.226
	Kidney	**.000**	**.000**	**.000**	**.000**	.812	**.000**	**.014**	**.008**	**.008**	**.009**
	Soleus	.565	.977	.965	.981	1.000	.998	1.000	.993	1.000	1.000
	VAT	.985	.992	.990	1.000	.997	.979	.875	.862	.991	.911
	SAT	.466	.770	**.016**	**.022**	.719	.340	.517	.997	.234	.989
Soleus	Liver	.990	**.033**	**.007**	**.000**	**.000**	**.000**	**.000**	.276	**.000**	**.000**
	Heart	.992	.998	1.000	.364	1.000	**.036**	.840	1.000	.422	.171
	Kidney	**.000**	**.000**	**.000**	**.000**	.897	**.000**	**.018**	.075	**.015**	**.007**
	Gluteus	.565	.977	.965	.981	1.000	.998	1.000	.993	1.000	1.000
	VAT	.154	.713	.643	.963	.991	.804	.910	.475	.988	.978
	SAT	1.000	.997	.187	.188	.824	.724	.535	1.000	.305	.962
VAT	Liver	**.011**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**
	Heart	.364	.253	.355	**.026**	.969	**.000**	.121	.160	.058	**.010**
	Kidney	**.000**	**.000**	**.000**	**.000**	.423	**.000**	**.000**	**.000**	**.001**	**.000**
	Gluteus	.985	.992	.990	1.000	.997	.979	.875	.862	.991	.911
	Soleus	.154	.713	.643	.963	.991	.804	.910	.475	.988	.978
	SAT	.110	.336	**.002**	**.013**	.341	.058	**.048**	.545	**.044**	.513
SAT	Liver	.997	.144	.926	.380	**.015**	**.000**	**.036**	.226	**.001**	**.000**
	Heart	.975	1.000	.195	.996	.818	.724	.993	.999	1.000	.744
	Kidney	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	.694	.058	.870	.088
	Gluteus	.466	.770	**.016**	**.022**	.719	.340	.517	.997	.234	.989
	Soleus	1.000	.997	.187	.188	.824	.724	.535	1.000	.305	.962
	VAT	.110	.336	**.002**	**.013**	.341	.058	**.048**	.545	**.044**	.513

		p value									
		Alkenyl lysophosphatidylcholine						*Alkenyl lysophosphatidylethanolamine*			
		LPC(P-16:0)	LPC(P-17:0) (a)	LPC(P-17:0) (b)	LPC(P-18:0)	LPC(P-18:1)	LPC(P-20:0)	LPE(P-16:0)	LPE(P-18:0)	LPE(P-18:1)	LPE(P-20:0)
Liver	Heart	**.000**	**.000**	**.010**	**.005**	**.000**	.866	**.000**	**.000**	**.000**	.982
	Kidney	**.000**	**.000**	**.009**	**.000**	**.000**	.830	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.049**	**.000**	**.000**	.659	.521	.808	.926	.864
	Soleus	**.000**	**.031**	.345	**.000**	**.000**	.947	**.002**	.063	**.004**	1.000
	VAT	1.000	.999	.855	.980	1.000	.123	1.000	1.000	1.000	.685
	SAT	.916	.995	.999	.951	.944	.995	.821	.985	.562	.960
Heart	Liver	**.000**	**.000**	**.010**	**.005**	**.000**	.866	**.000**	**.000**	**.000**	.982
	Kidney	.459	1.000	1.000	**.046**	1.000	.177	**.000**	**.000**	.907	**.001**
	Gluteus	.052	.732	1.000	.149	.655	.999	**.000**	**.001**	**.000**	.410
	Soleus	.813	.095	.908	.639	.885	1.000	**.002**	.130	**.000**	.994
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	.759	**.000**	**.000**	**.000**	.227
	SAT	**.000**	**.000**	.090	.169	**.000**	.999	**.000**	**.000**	**.000**	1.000
Kidney	Liver	**.000**	**.000**	**.009**	**.000**	**.000**	.830	**.000**	**.000**	**.000**	**.000**
	Heart	.459	1.000	1.000	**.046**	1.000	.177	**.000**	**.000**	.907	**.001**
	Gluteus	**.000**	.918	.997	.999	.862	.096	**.000**	**.000**	**.000**	**.000**
	Soleus	.052	.237	.832	.873	.974	.328	**.000**	**.000**	**.000**	**.001**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	.072	**.000**	**.000**	.546	**.000**	**.000**	**.000**	**.009**
Gluteus	Liver	**.000**	**.000**	**.049**	**.000**	**.000**	.659	.521	.808	.926	.864
	Heart	.052	.732	1.000	.149	.655	.999	**.000**	**.001**	**.000**	.410
	Kidney	**.000**	.918	.997	.999	.862	.096	**.000**	**.000**	**.000**	**.000**
	Soleus	.754	.854	.987	.986	1.000	.998	.277	.694	.090	.885
	VAT	**.000**	**.000**	**.002**	**.000**	**.000**	.964	.615	.603	.893	1.000
	SAT	**.005**	**.008**	.236	**.000**	**.004**	.973	1.000	.999	.992	.396
Soleus	Liver	**.000**	**.031**	.345	**.000**	**.000**	.947	**.002**	.063	**.004**	1.000
	Heart	.813	.095	.908	.639	.885	1.000	**.002**	.130	**.000**	.994
	Kidney	.052	.237	.832	.873	.974	.328	**.000**	**.000**	**.000**	**.001**
	Gluteus	.754	.854	.987	.986	1.000	.998	.277	.694	.090	.885
	VAT	**.000**	**.012**	**.033**	**.000**	**.000**	.781	**.004**	**.030**	**.003**	.740
	SAT	**.000**	.223	.720	**.006**	**.002**	1.000	.158	.423	.395	.983
VAT	Liver	1.000	.999	.855	.980	1.000	.123	1.000	1.000	1.000	.685
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	.759	**.000**	**.000**	**.000**	.227
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.002**	**.000**	**.000**	.964	.615	.603	.893	1.000
	Soleus	**.000**	**.012**	**.033**	**.000**	**.000**	.781	**.004**	**.030**	**.003**	.740
	SAT	.872	.937	.680	.601	.838	.550	.879	.914	.512	.234
SAT	Liver	.916	.995	.999	.951	.944	.995	.821	.985	.562	.960
	Heart	**.000**	**.000**	.090	.169	**.000**	.999	**.000**	**.000**	**.000**	1.000
	Kidney	**.000**	**.000**	.072	**.000**	**.000**	.546	**.000**	**.000**	**.000**	**.009**
	Gluteus	**.005**	**.008**	.236	**.000**	**.004**	.973	1.000	.999	.992	.396
	Soleus	**.000**	.223	.720	**.006**	**.002**	1.000	.158	.423	.395	.983
	VAT	.872	.937	.680	.601	.838	.550	.879	.914	.512	.234

		p value										
		Alkyl phosphatidylcholine										
		PC(O-16:0/16:0)	PC(O-32:1)	PC(O-32:2)	PC(O-34:1)	PC(O-34:2)	PC(O-34:4)	PC(O-35:4)	PC(O-36:0)	PC(O-18:0/18:1)	PC(O-18:1/18:1)	PC(O-18:0/18:2)
Liver	Heart	**.001**	**.020**	.758	**.000**	.172	1.000	**.006**	**.002**	**.000**	**.000**	**.000**
	Kidney	.167	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.914	.295	.983	.143
	Gluteus	**.000**	.718	1.000	**.005**	.600	.905	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	.896	.968	.153	.597	.961	**.000**	**.000**	**.000**	.056	**.000**
	VAT	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.018**	.456	**.000**	**.001**	.507	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.001**	**.020**	.758	**.000**	.172	1.000	**.006**	**.002**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.027**	.634	.710	.990	.995	.984	.583	**.011**	.855	.835	1.000
	Soleus	.446	**.002**	.298	.521	.998	.996	.702	.580	.083	.086	1.000
	VAT	**.000**	.079	.076	**.002**	**.001**	**.001**	**.014**	**.001**	**.000**	**.001**	**.005**
	SAT	**.005**	1.000	.995	.551	.327	.730	.491	.183	.441	.842	.549
Kidney	Liver	.167	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.914	.295	.983	.143
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.008**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	.073	**.013**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	**.000**	.718	1.000	**.005**	.600	.905	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.027**	.634	.710	.990	.995	.984	.583	**.011**	.855	.835	1.000
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	.910	.177	.991	.928	1.000	1.000	1.000	.660	**.006**	.742	1.000
	VAT	.144	**.001**	**.002**	**.001**	**.000**	**.022**	.655	.998	**.032**	**.000**	**.009**
	SAT	.991	.487	.422	.232	.137	.990	1.000	.965	.991	.203	.602
Soleus	Liver	**.000**	.896	.968	.153	.597	.961	**.000**	**.000**	**.000**	.056	**.000**
	Heart	.446	**.002**	.298	.521	.998	.996	.702	.580	.083	.086	1.000
	Kidney	**.000**	**.008**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	.073	**.013**	**.000**
	Gluteus	.910	.177	.991	.928	1.000	1.000	1.000	.660	**.006**	.742	1.000
	VAT	**.010**	**.000**	**.000**	**.000**	**.001**	**.022**	.629	.304	**.000**	**.000**	**.009**
	SAT	.556	**.002**	.144	**.026**	.193	.979	1.000	.993	**.001**	**.007**	.538
VAT	Liver	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.079	.076	**.002**	**.001**	**.001**	**.014**	**.001**	**.000**	**.001**	**.005**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.144	**.001**	**.002**	**.001**	**.000**	**.022**	.655	.998	**.032**	**.000**	**.009**
	Soleus	**.010**	**.000**	**.000**	**.000**	**.001**	**.022**	.629	.304	**.000**	**.000**	**.009**
	SAT	.574	.314	.430	.416	.505	.180	.819	.743	.223	.077	.561
SAT	Liver	**.000**	**.018**	.456	**.000**	**.001**	.507	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.005**	1.000	.995	.551	.327	.730	.491	.183	.441	.842	.549
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.991	.487	.422	.232	.137	.990	1.000	.965	.991	.203	.602
	Soleus	.556	**.002**	.144	**.026**	.193	.979	1.000	.993	**.001**	**.007**	.538
	VAT	.574	.314	.430	.416	.505	.180	.819	.743	.223	.077	.561

		p value										
		Alkyl phosphatidylcholine										
		PC(O-18:1/18:2)	PC(O-16:0/20:3)	PC(O-16:0/20:4)	PC(O-36:5)	PC(O-18:0/20:4)	PC(O-38:5)	PC(O-16:0/22:6)	PC(O-40:5)	PC(O-18:0/22:6)	PC(O-40:7) (a)	PC(O-40:7) (b)
Liver	Heart	**.000**	**.000**	.083	.331	**.000**	**.008**	.310	.398	.148	.818	**.000**
	Kidney	**.000**	.584	**.000**	**.001**	**.039**	.339	**.000**	**.000**	.052	**.006**	**.002**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.434	**.001**	.101	.943
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.236	**.007**	.200	.794
	VAT	**.000**	**.000**	**.000**	**.031**	**.000**	**.000**	.985	**.000**	.063	**.015**	**.019**
	SAT	**.000**	**.000**	**.000**	.927	**.000**	**.000**	.997	**.003**	.366	.180	.123
Heart	Liver	**.000**	**.000**	.083	.331	**.000**	**.008**	.310	.398	.148	.818	**.000**
	Kidney	**.000**	**.000**	**.000**	.212	**.000**	**.000**	.079	**.000**	.995	.151	1.000
	Gluteus	.980	.084	**.026**	**.001**	.078	.879	**.000**	1.000	.494	.737	**.021**
	Soleus	.988	.135	.070	**.017**	.183	.491	**.002**	.998	.747	.875	.086
	VAT	**.000**	**.000**	**.000**	**.000**	**.004**	**.000**	.072	**.003**	**.000**	**.000**	**.000**
	SAT	.752	.515	**.039**	.056	.317	.138	.166	.280	**.001**	**.009**	**.000**
Kidney	Liver	**.000**	.584	**.000**	**.001**	**.039**	.339	**.000**	**.000**	.052	**.006**	**.002**
	Heart	**.000**	**.000**	**.000**	.212	**.000**	**.000**	.079	**.000**	.995	.151	1.000
	Gluteus	**.000**	**.000**	**.000**	.412	**.000**	**.000**	.315	**.000**	.894	.946	.058
	Soleus	**.000**	**.000**	**.000**	.917	**.000**	**.000**	.767	**.000**	.979	.899	.182
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.434	**.001**	.101	.943
	Heart	.980	.084	**.026**	**.001**	.078	.879	**.000**	1.000	.494	.737	**.021**
	Kidney	**.000**	**.000**	**.000**	.412	**.000**	**.000**	.315	**.000**	.894	.946	.058
	Soleus	1.000	1.000	1.000	.981	1.000	.993	.994	.999	1.000	1.000	1.000
	VAT	**.008**	.299	.376	**.000**	.962	**.002**	**.000**	**.008**	**.000**	**.000**	**.002**
	SAT	.994	.980	1.000	**.000**	.998	.804	**.000**	.378	**.000**	**.000**	**.018**
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.236	**.007**	.200	.794
	Heart	.988	.135	.070	**.017**	.183	.491	**.002**	.998	.747	.875	.086
	Kidney	**.000**	**.000**	**.000**	.917	**.000**	**.000**	.767	**.000**	.979	.899	.182
	Gluteus	1.000	1.000	1.000	.981	1.000	.993	.994	.999	1.000	1.000	1.000
	VAT	**.011**	.302	.290	**.000**	.902	**.025**	**.000**	**.042**	**.000**	**.000**	**.001**
	SAT	.994	.991	1.000	**.000**	1.000	.993	**.000**	.692	**.000**	**.001**	**.009**
VAT	Liver	**.000**	**.000**	**.000**	**.031**	**.000**	**.000**	.985	**.000**	.063	**.015**	**.019**
	Heart	**.000**	**.000**	**.000**	**.000**	**.004**	**.000**	.072	**.003**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.008**	.299	.376	**.000**	.962	**.002**	**.000**	**.008**	**.000**	**.000**	**.002**
	Soleus	**.011**	.302	.290	**.000**	.902	**.025**	**.000**	**.042**	**.000**	**.000**	**.001**
	SAT	.071	.062	.419	.504	.762	.141	1.000	.766	.995	.989	.999
SAT	Liver	**.000**	**.000**	**.000**	.927	**.000**	**.000**	.997	**.003**	.366	.180	.123
	Heart	.752	.515	**.039**	.056	.317	.138	.166	.280	**.001**	**.009**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.994	.980	1.000	**.000**	.998	.804	**.000**	.378	**.000**	**.000**	**.018**
	Soleus	.994	.991	1.000	**.000**	1.000	.993	**.000**	.692	**.000**	**.001**	**.009**
	VAT	.071	.062	.419	.504	.762	.141	1.000	.766	.995	.989	.999

		p value												
		Alkenyl phosphatidylcholine												
		PC(P-16:0/14:0)	PC(P-16:0/16:0)	PC(P-16:0/16:1)	PC(P-16:0/18:0)	PC(P-16:0/18:1)	PC(P-16:0/18:2)	PC(P-16:0/18:3)	PC(P-35:2)(a)	PC(P-35:2)(b)	PC(P-15:0/20:4) (a)	PC(P-15:0/20:4) (b)	PC(P-18:1/18:1)	PC(P-18:0/18:2)
Liver	Heart	.991	.996	1.000	1.000	.976	**.001**	.234	.644	.963	**.002**	**.000**	.999	.769
	Kidney	.897	1.000	.644	1.000	**.000**	.073	**.001**	1.000	.999	**.000**	**.000**	**.000**	.424
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.937	.174	.219	**.000**
	Soleus	**.000**	**.015**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.915	.261	**.003**	**.000**
	VAT	.989	**.003**	.181	.995	.965	.996	.786	.084	**.019**	.639	.998	**.000**	.802
	SAT	1.000	.063	.759	1.000	.998	1.000	1.000	.352	.145	1.000	1.000	**.027**	.985
Heart	Liver	.991	.996	1.000	1.000	.976	**.001**	.234	.644	.963	**.002**	**.000**	.999	.769
	Kidney	.998	1.000	.426	1.000	**.004**	.818	.279	.900	.999	**.001**	.936	**.000**	.995
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	**.001**	.063	**.000**	.431	**.000**
	Soleus	**.000**	.062	**.000**	**.000**	**.000**	**.007**	**.000**	**.026**	**.002**	.113	**.000**	**.009**	**.000**
	VAT	.781	**.000**	.342	.979	.572	**.000**	**.009**	**.001**	**.001**	**.000**	**.000**	**.000**	.096
	SAT	.988	**.016**	.911	.996	.846	**.001**	.437	**.012**	**.019**	**.006**	**.000**	**.009**	.377
Kidney	Liver	.897	1.000	.644	1.000	**.000**	.073	**.001**	1.000	.999	**.000**	**.000**	**.000**	.424
	Heart	.998	1.000	.426	1.000	**.004**	.818	.279	.900	.999	**.001**	.936	**.000**	.995
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.039**	**.000**
	Soleus	**.001**	**.041**	.061	**.000**	**.031**	**.000**	.091	**.002**	**.001**	**.000**	**.000**	.839	**.001**
	VAT	.522	**.003**	**.004**	.995	**.000**	**.021**	**.000**	.053	**.011**	**.000**	**.000**	**.000**	**.032**
	SAT	.897	.058	.078	.999	**.000**	.081	**.005**	.237	.082	**.000**	**.000**	**.000**	.162
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.937	.174	.219	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.004**	**.001**	.063	**.000**	.431	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.039**	**.000**
	Soleus	**.000**	.225	**.003**	**.000**	.283	.988	.463	.999	1.000	1.000	1.000	.593	.930
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.152	.063	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.957	.451	**.000**	**.000**
Soleus	Liver	**.000**	**.015**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.915	.261	**.003**	**.000**
	Heart	**.000**	.062	**.000**	**.000**	**.000**	**.007**	**.000**	**.026**	**.002**	.113	**.000**	**.009**	**.000**
	Kidney	**.001**	**.041**	.061	**.000**	**.031**	**.000**	.091	**.002**	**.001**	**.000**	**.000**	.839	**.001**
	Gluteus	**.000**	.225	**.003**	**.000**	.283	.988	.463	.999	1.000	1.000	1.000	.593	.930
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.148	.106	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.939	.558	**.000**	**.000**
VAT	Liver	.989	**.003**	.181	.995	.965	.996	.786	.084	**.019**	.639	.998	**.000**	.802
	Heart	.781	**.000**	.342	.979	.572	**.000**	**.009**	**.001**	**.001**	**.000**	**.000**	**.000**	.096
	Kidney	.522	**.003**	**.004**	.995	**.000**	**.021**	**.000**	.053	**.011**	**.000**	**.000**	**.000**	**.032**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.152	.063	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.148	.106	**.000**	**.000**
	SAT	.998	.983	.982	1.000	1.000	1.000	.791	.999	.998	.754	.979	.791	.999
SAT	Liver	1.000	.063	.759	1.000	.998	1.000	1.000	.352	.145	1.000	1.000	**.027**	.985
	Heart	.988	**.016**	.911	.996	.846	**.001**	.437	**.012**	**.019**	**.006**	**.000**	**.009**	.377
	Kidney	.897	.058	.078	.999	**.000**	.081	**.005**	.237	.082	**.000**	**.000**	**.000**	.162
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.957	.451	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.939	.558	**.000**	**.000**
	VAT	.998	.983	.982	1.000	1.000	1.000	.791	.999	.998	.754	.979	.791	.999

		p value												
		Alkenyl phosphatidylcholine												
		PC(P-18:0/18:2)	PC(P-16:0/20:4)	PC(P-16:0/20:5)	PC(P-17:0/20:4) (a)	PC(P-17:0/20:4) (b)	PC(P-18:0/20:4)	PC(P-38:5) (a)	PC(P-38:5) (b)	PC(P-16:0/22:6)	PC(P-20:0/20:4)	PC(P-18:0/22:5)	PC(P-18:0/22:6)	PC(P-18:1/22:6)
Liver	Heart	.054	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.087	**.002**	**.008**	.668	**.004**
	Kidney	**.000**	**.001**	**.000**	.198	**.000**	.089	.186	.534	1.000	**.004**	.989	1.000	1.000
	Gluteus	.361	.815	**.000**	.919	.757	.769	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	.726	.924	.051	.932	.866	.985	**.001**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.004**	.977	.426	.979	.723	.170	.997	.985	1.000	**.000**	.780	.999	.998
	SAT	.223	1.000	.955	1.000	.983	.636	1.000	.999	1.000	**.000**	.980	1.000	1.000
Heart	Liver	.054	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.087	**.002**	**.008**	.668	**.004**
	Kidney	**.000**	**.000**	.592	**.000**	**.000**	**.001**	**.000**	**.000**	.208	**.000**	.100	.653	**.010**
	Gluteus	.989	**.000**	.243	**.000**	**.000**	**.000**	.439	.168	**.000**	**.000**	**.002**	**.000**	.591
	Soleus	.889	**.000**	**.003**	**.000**	**.000**	**.000**	**.034**	**.019**	**.000**	**.007**	.178	**.000**	.143
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.087	**.000**	**.000**	.391	**.001**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.149	**.016**	**.002**	.526	**.004**
Kidney	Liver	**.000**	**.001**	**.000**	.198	**.000**	.089	.186	.534	1.000	**.004**	.989	1.000	1.000
	Heart	**.000**	**.000**	.592	**.000**	**.000**	**.001**	**.000**	**.000**	.208	**.000**	.100	.653	**.010**
	Gluteus	**.000**	.095	.997	.864	.053	.845	**.015**	**.014**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	.078	.278	.887	**.050**	.540	.352	.199	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.038**	**.000**	**.000**	.067	.175	1.000	**.000**	.389	1.000	.998
	SAT	**.000**	**.001**	**.000**	.162	**.000**	**.003**	.187	.368	1.000	**.000**	.768	1.000	.999
Gluteus	Liver	.361	.815	**.000**	.919	.757	.769	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.989	**.000**	.243	**.000**	**.000**	**.000**	.439	.168	**.000**	**.000**	**.002**	**.000**	.591
	Kidney	**.000**	.095	.997	.864	.053	.845	**.015**	**.014**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	.999	1.000	.604	1.000	1.000	.997	.861	.957	1.000	.993	.806	.997	.970
	VAT	**.000**	.347	**.000**	.501	.082	**.007**	**.000**	**.000**	**.000**	.947	**.000**	**.000**	**.000**
	SAT	**.002**	.662	**.000**	.825	.370	.077	**.000**	**.000**	**.000**	.963	**.000**	**.000**	**.000**
Soleus	Liver	.726	.924	.051	.932	.866	.985	**.001**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.889	**.000**	**.003**	**.000**	**.000**	**.000**	**.034**	**.019**	**.000**	**.007**	.178	**.000**	.143
	Kidney	**.000**	.078	.278	.887	**.050**	.540	.352	.199	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.999	1.000	.604	1.000	1.000	.997	.861	.957	1.000	.993	.806	.997	.970
	VAT	**.000**	.521	**.000**	.547	.147	.054	**.000**	**.000**	**.000**	.636	**.000**	**.000**	**.000**
	SAT	**.013**	.806	**.009**	.846	.499	.289	**.001**	**.001**	**.000**	1.000	**.000**	**.000**	**.000**
VAT	Liver	**.004**	.977	.426	.979	.723	.170	.997	.985	1.000	**.000**	.780	.999	.998
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.087	**.000**	**.000**	.391	**.001**
	Kidney	**.000**	**.000**	**.000**	**.038**	**.000**	**.000**	.067	.175	1.000	**.000**	.389	1.000	.998
	Gluteus	**.000**	.347	**.000**	.501	.082	**.007**	**.000**	**.000**	**.000**	.947	**.000**	**.000**	**.000**
	Soleus	**.000**	.521	**.000**	.547	.147	.054	**.000**	**.000**	**.000**	.636	**.000**	**.000**	**.000**
	SAT	.879	1.000	.979	1.000	.997	.995	1.000	1.000	1.000	.460	.999	1.000	1.000
SAT	Liver	.223	1.000	.955	1.000	.983	.636	1.000	.999	1.000	**.000**	.980	1.000	1.000
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.149	**.016**	**.002**	.526	**.004**
	Kidney	**.000**	**.001**	**.000**	.162	**.000**	**.003**	.187	.368	1.000	**.000**	.768	1.000	.999
	Gluteus	**.002**	.662	**.000**	.825	.370	.077	**.000**	**.000**	**.000**	.963	**.000**	**.000**	**.000**
	Soleus	**.013**	.806	**.009**	.846	.499	.289	**.001**	**.001**	**.000**	1.000	**.000**	**.000**	**.000**
	VAT	.879	1.000	.979	1.000	.997	.995	1.000	1.000	1.000	.460	.999	1.000	1.000

		p value													
		Alkenyl phosphatidylethanolamine													
		PE(O-34:1)	PE(O-16:0/18:2)	PE(O-18:1/18:2)	PE(O-16:0/20:3)	PE(O-16:0/20:4)	PE(O-36:5)	PE(O-16:0/22:4)	PE(O-18:0/20:4)	PE(O-38:5) (a)	PE(O-38:5) (b)	PE(O-16:0/22:6)	PE(O-18:0/22:5) (a)	PE(O-18:0/22:6)	PE(O-18:1/22:6)
Liver	Heart	**.000**	**.000**	**.000**	.060	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.939	**.000**	**.000**	.110	.220	1.000	.671	.999
	Gluteus	.999	1.000	.991	.292	.338	1.000	**.006**	**.002**	.991	1.000	.057	**.039**	.121	.813
	Soleus	**.003**	.927	.907	.728	.987	.347	.979	**.017**	.119	.391	**.000**	**.000**	**.000**	**.026**
	VAT	.831	.906	.836	**.012**	.102	.988	**.000**	**.001**	.562	.286	.998	.719	.651	.890
	SAT	.991	.976	.962	.056	.469	1.000	**.001**	**.014**	.853	.580	1.000	.898	.919	.946
Heart	Liver	**.000**	**.000**	**.000**	.060	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.334	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.002**	**.001**	**.000**
	Soleus	.464	**.019**	**.000**	**.002**	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	.087	.221	.390	**.001**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.939	**.000**	**.000**	.110	.220	1.000	.671	.999
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	.334	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.007**	.238	.997	**.035**	.946	.980
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	.589	**.000**	.579	.998	**.045**	**.000**	**.037**	.116
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.087	.885	**.045**	.682
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	.157	.970	.174	.794
Gluteus	Liver	.999	1.000	.991	.292	.338	1.000	**.006**	**.002**	.991	1.000	.057	**.039**	.121	.813
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.002**	**.001**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.007**	.238	.997	**.035**	.946	.980
	Soleus	**.022**	.812	.598	.997	.879	.538	.122	.998	.481	.595	.162	.656	.303	.477
	VAT	.607	.990	.998	.885	.999	.967	.870	1.000	.230	.242	**.019**	**.001**	**.002**	.197
	SAT	.921	.999	1.000	.979	1.000	1.000	.996	.999	.507	.501	**.043**	**.004**	**.017**	.310
Soleus	Liver	**.003**	.927	.907	.728	.987	.347	.979	**.017**	.119	.391	**.000**	**.000**	**.000**	**.026**
	Heart	.464	**.019**	**.000**	**.002**	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	.087	.221	.390	**.001**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	.589	**.000**	.579	.998	**.045**	**.000**	**.037**	.116
	Gluteus	**.022**	.812	.598	.997	.879	.538	.122	.998	.481	.595	.162	.656	.303	.477
	VAT	**.000**	.365	.258	.574	.585	.105	**.004**	.997	**.002**	**.004**	**.000**	**.000**	**.000**	**.001**
	SAT	**.001**	.564	.478	.808	.934	.546	**.038**	1.000	**.011**	**.017**	**.000**	**.000**	**.000**	**.004**
VAT	Liver	.831	.906	.836	**.012**	.102	.988	**.000**	**.001**	.562	.286	.998	.719	.651	.890
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.087	.885	**.045**	.682
	Gluteus	.607	.990	.998	.885	.999	.967	.870	1.000	.230	.242	**.019**	**.001**	**.002**	.197
	Soleus	**.000**	.365	.258	.574	.585	.105	**.004**	.997	**.002**	**.004**	**.000**	**.000**	**.000**	**.001**
	SAT	.999	1.000	1.000	1.000	.996	.981	.998	.999	1.000	1.000	1.000	1.000	1.000	1.000
SAT	Liver	.991	.976	.962	.056	.469	1.000	**.001**	**.014**	.853	.580	1.000	.898	.919	.946
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.005**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.003**	.157	.970	.174	.794
	Gluteus	.921	.999	1.000	.979	1.000	1.000	.996	.999	.507	.501	**.043**	**.004**	**.017**	.310
	Soleus	**.001**	.564	.478	.808	.934	.546	**.038**	1.000	**.011**	**.017**	**.000**	**.000**	**.000**	**.004**
	VAT	.999	1.000	1.000	1.000	.996	.981	.998	.999	1.000	1.000	1.000	1.000	1.000	1.000

		p value										
		Alkenyl phosphatidylethanolamine										
		PE(P-15:0/20:4) (a)	PE(P-15:0/20:4) (b)	PE(P-15:0/22:6) (a)	PE(P-15:0/22:6) (b)	PE(P-16:0/18:1)	PE(P-16:0/18:2)	PE(P-16:0/18:3)	PE(P-16:0/20:3) (a)	PE(P-16:0/20:3) (b)	PE(P-16:0/20:4)	PE(P-16:0/20:5)
Liver	Heart	.999	**.000**	.855	**.000**	.190	**.000**	**.007**	**.002**	.967	**.000**	**.000**
	Kidney	.065	**.000**	1.000	.967	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.407	.656	.452	**.000**	1.000	.966	.996	**.001**	**.047**	.858	.867
	Soleus	.614	.967	1.000	**.000**	**.000**	.216	.995	**.022**	.289	.986	.955
	VAT	.124	.556	1.000	1.000	.929	.999	.997	**.000**	**.040**	.739	.166
	SAT	.504	1.000	1.000	1.000	.893	1.000	1.000	**.003**	.499	.998	.935
Heart	Liver	.999	**.000**	.855	**.000**	.190	**.000**	**.007**	**.002**	.967	**.000**	**.000**
	Kidney	**.024**	**.000**	.899	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.113	1.000
	Gluteus	.660	**.000**	.988	.051	.202	**.000**	.065	**.000**	**.004**	**.000**	**.000**
	Soleus	.836	**.000**	.976	.237	**.011**	**.000**	.096	**.000**	.051	**.000**	**.000**
	VAT	.278	**.000**	.778	**.000**	**.017**	**.000**	**.002**	**.000**	**.003**	**.000**	**.000**
	SAT	.745	**.000**	.875	**.000**	.945	**.000**	**.011**	**.000**	.118	**.000**	**.000**
Kidney	Liver	.065	**.000**	1.000	.967	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.024**	**.000**	.899	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.113	1.000
	Gluteus	**.000**	**.000**	.537	**.008**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.002**	**.000**	1.000	**.002**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	1.000	.890	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.001**	**.000**	1.000	.963	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	.407	.656	.452	**.000**	1.000	.966	.996	**.001**	**.047**	.858	.867
	Heart	.660	**.000**	.988	.051	.202	**.000**	.065	**.000**	**.004**	**.000**	**.000**
	Kidney	**.000**	**.000**	.537	**.008**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	1.000	.996	.739	.998	**.000**	.774	1.000	.984	.993	1.000	1.000
	VAT	.998	1.000	.376	**.000**	.971	.807	.910	.984	1.000	1.000	.902
	SAT	1.000	.886	.515	**.001**	.871	.981	.986	1.000	.945	.995	1.000
Soleus	Liver	.614	.967	1.000	**.000**	**.000**	.216	.995	**.022**	.289	.986	.955
	Heart	.836	**.000**	.976	.237	**.011**	**.000**	.096	**.000**	.051	**.000**	**.000**
	Kidney	**.002**	**.000**	1.000	**.002**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	1.000	.996	.739	.998	**.000**	.774	1.000	.984	.993	1.000	1.000
	VAT	.988	.991	.999	**.000**	**.000**	.094	.913	.691	.994	.997	.832
	SAT	1.000	.997	1.000	**.000**	**.002**	.320	.985	.992	1.000	1.000	1.000
VAT	Liver	.124	.556	1.000	1.000	.929	.999	.997	**.000**	**.040**	.739	.166
	Heart	.278	**.000**	.778	**.000**	**.017**	**.000**	**.002**	**.000**	**.003**	**.000**	**.000**
	Kidney	**.000**	**.000**	1.000	.890	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.998	1.000	.376	**.000**	.971	.807	.910	.984	1.000	1.000	.902
	Soleus	.988	.991	.999	**.000**	**.000**	.094	.913	.691	.994	.997	.832
	SAT	.997	.832	1.000	1.000	.346	.999	1.000	.978	.947	.982	.868
SAT	Liver	.504	1.000	1.000	1.000	.893	1.000	1.000	**.003**	.499	.998	.935
	Heart	.745	**.000**	.875	**.000**	.945	**.000**	**.011**	**.000**	.118	**.000**	**.000**
	Kidney	**.001**	**.000**	1.000	.963	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	1.000	.886	.515	**.001**	.871	.981	.986	1.000	.945	.995	1.000
	Soleus	1.000	.997	1.000	**.000**	**.002**	.320	.985	.992	1.000	1.000	1.000
	VAT	.997	.832	1.000	1.000	.346	.999	1.000	.978	.947	.982	.868

		p value										
		Alkenyl phosphatidylethanolamine										
		PE(P-16:0/22:4)	PE(P-16:0/22:5) (n3)	PE(P-16:0/22:5) (n6)	PE(P-16:0/22:6)	PE(P-17:0/20:4) (a)	PE(P-17:0/20:4) (b)	PE(P-17:0/22:6) (a)	PE(P-17:0/22:6) (b)	PE(P-18:0/18:1)	PE(P-18:0/18:2)	PE(P-18:0/18:3)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**
	Kidney	.535	.702	.994	.999	**.000**	**.000**	1.000	1.000	.140	**.000**	**.000**
	Gluteus	.102	.184	.290	**.000**	.366	.875	**.000**	**.000**	1.000	.130	.887
	Soleus	.684	.162	.470	**.000**	.847	.987	**.000**	**.000**	**.000**	**.000**	.067
	VAT	**.000**	.986	.996	1.000	.138	.726	1.000	1.000	1.000	.964	1.000
	SAT	**.028**	1.000	1.000	1.000	.997	.952	1.000	1.000	.935	.999	.999
Heart	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	.363	.526	**.000**	**.000**	.282	**.006**	**.000**
	Gluteus	**.000**	**.000**	**.000**	.109	**.000**	**.000**	1.000	.283	1.000	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	.265	**.000**	**.000**	.990	.358	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.984	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.991	**.000**	**.000**
Kidney	Liver	.535	.702	.994	.999	**.000**	**.000**	1.000	1.000	.140	**.000**	**.000**
	Heart	**.000**	**.000**	**.000**	**.000**	.363	.526	**.000**	**.000**	.282	**.006**	**.000**
	Gluteus	**.001**	.974	.746	**.000**	**.000**	**.000**	**.000**	**.000**	.358	**.013**	**.010**
	Soleus	**.040**	.950	.879	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	.863	.539
	VAT	**.000**	.286	.876	.996	**.000**	**.000**	.999	1.000	.068	**.000**	**.000**
	SAT	**.000**	.549	.951	.999	**.000**	**.000**	1.000	1.000	.811	**.000**	**.003**
Gluteus	Liver	.102	.184	.290	**.000**	.366	.875	**.000**	**.000**	1.000	.130	.887
	Heart	**.000**	**.000**	**.000**	.109	**.000**	**.000**	1.000	.283	1.000	**.000**	**.000**
	Kidney	**.001**	.974	.746	**.000**	**.000**	**.000**	**.000**	**.000**	.358	**.013**	**.010**
	Soleus	.950	1.000	1.000	1.000	.993	1.000	.999	1.000	**.000**	.321	.611
	VAT	.549	**.041**	.102	**.000**	.999	1.000	**.000**	**.000**	.987	**.018**	.829
	SAT	.996	.134	.208	**.000**	.828	1.000	**.000**	**.000**	.994	.088	.996
Soleus	Liver	.684	.162	.470	**.000**	.847	.987	**.000**	**.000**	**.000**	**.000**	.067
	Heart	**.000**	**.000**	**.000**	.265	**.000**	**.000**	.990	.358	**.000**	**.000**	**.000**
	Kidney	**.040**	.950	.879	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	.863	.539
	Gluteus	.950	1.000	1.000	1.000	.993	1.000	.999	1.000	**.000**	.321	.611
	VAT	.105	**.037**	.201	**.000**	.923	.996	**.000**	**.000**	**.000**	**.000**	.055
	SAT	.704	.118	.343	**.000**	.995	1.000	**.000**	**.000**	**.000**	**.000**	.294
VAT	Liver	**.000**	.986	.996	1.000	.138	.726	1.000	1.000	1.000	.964	1.000
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.984	**.000**	**.000**
	Kidney	**.000**	.286	.876	.996	**.000**	**.000**	.999	1.000	.068	**.000**	**.000**
	Gluteus	.549	**.041**	.102	**.000**	.999	1.000	**.000**	**.000**	.987	**.018**	.829
	Soleus	.105	**.037**	.201	**.000**	.923	.996	**.000**	**.000**	**.000**	**.000**	.055
	SAT	.926	1.000	1.000	1.000	.558	1.000	1.000	1.000	.791	1.000	.995
SAT	Liver	**.028**	1.000	1.000	1.000	.997	.952	1.000	1.000	.935	.999	.999
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.991	**.000**	**.000**
	Kidney	**.000**	.549	.951	.999	**.000**	**.000**	1.000	1.000	.811	**.000**	**.003**
	Gluteus	.996	.134	.208	**.000**	.828	1.000	**.000**	**.000**	.994	.088	.996
	Soleus	.704	.118	.343	**.000**	.995	1.000	**.000**	**.000**	**.000**	**.000**	.294
	VAT	.926	1.000	1.000	1.000	.558	1.000	1.000	1.000	.791	1.000	.995

		p value										
		Alkenyl phosphatidylethanolamine										
		PE(P-18:0/20:3) (a)	PE(P-18:0/20:3) (b)	PE(P-18:0/20:4)	PE(P-18:0/20:5)	PE(P-18:0/22:4)	PE(P-18:0/22:5) (n3)	PE(P-18:0/22:5) (n6)	PE(P-18:0/22:6)	PE(P-18:1/18:1) (a)	PE(P-18:1/18:1) (b)	PE(P-18:1/18:2) (a)
Liver	Heart	**.030**	.479	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.993	.335	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	.980	1.000	.999	1.000	.061	**.000**	**.006**
	Gluteus	**.000**	**.015**	.777	1.000	.134	**.000**	**.000**	**.000**	1.000	.999	.983
	Soleus	.293	.153	.983	1.000	.904	**.000**	**.008**	**.000**	**.000**	**.000**	.464
	VAT	**.000**	**.000**	.371	.054	**.000**	.995	.972	1.000	1.000	1.000	1.000
	SAT	**.000**	.084	.826	.302	**.000**	1.000	.993	1.000	.884	.887	1.000
Heart	Liver	**.030**	.479	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.993	.335	**.000**
	Kidney	**.000**	**.000**	1.000	.995	**.000**	**.000**	**.000**	**.000**	.235	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	.917	**.007**	.998	.999	.687	**.000**
	Soleus	**.000**	**.002**	**.000**	**.000**	**.000**	1.000	**.001**	.996	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.972	.254	**.000**
	SAT	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.996	.990	**.000**
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	.980	1.000	.999	1.000	.061	**.000**	**.006**
	Heart	**.000**	**.000**	1.000	.995	**.000**	**.000**	**.000**	**.000**	.235	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.030**	**.000**	**.004**	**.000**	.124	**.000**	.084
	Soleus	**.000**	**.000**	**.000**	**.003**	.519	**.000**	**.039**	**.000**	**.001**	.452	.657
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	.998	.860	.998	**.043**	**.000**	**.003**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.938	.999	.703	**.000**	**.022**
Gluteus	Liver	**.000**	**.015**	.777	1.000	.134	**.000**	**.000**	**.000**	1.000	.999	.983
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	.917	**.007**	.998	.999	.687	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.030**	**.000**	**.004**	**.000**	.124	**.000**	.084
	Soleus	.310	.987	.998	.995	.846	.945	.991	1.000	**.000**	**.000**	.921
	VAT	.530	.811	.997	.165	**.029**	**.000**	**.000**	**.000**	1.000	.995	.921
	SAT	1.000	.999	1.000	.542	.306	**.000**	**.000**	**.000**	.947	.988	.995
Soleus	Liver	.293	.153	.983	1.000	.904	**.000**	**.008**	**.000**	**.000**	**.000**	.464
	Heart	**.000**	**.002**	**.000**	**.000**	**.000**	1.000	**.001**	.996	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.003**	.519	**.000**	**.039**	**.000**	**.001**	.452	.657
	Gluteus	.310	.987	.998	.995	.846	.945	.991	1.000	**.000**	**.000**	.921
	VAT	**.004**	.365	.925	**.048**	**.001**	**.000**	**.001**	**.000**	**.000**	**.000**	.309
	SAT	.184	1.000	.999	.237	**.023**	**.000**	**.003**	**.000**	**.000**	**.000**	.624
VAT	Liver	**.000**	**.000**	.371	.054	**.000**	.995	.972	1.000	1.000	1.000	1.000
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.972	.254	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.998	.860	.998	**.043**	**.000**	**.003**
	Gluteus	.530	.811	.997	.165	**.029**	**.000**	**.000**	**.000**	1.000	.995	.921
	Soleus	**.004**	.365	.925	**.048**	**.001**	**.000**	**.001**	**.000**	**.000**	**.000**	.309
	SAT	.816	.529	.997	.997	.975	1.000	1.000	1.000	.798	.807	1.000
SAT	Liver	**.000**	.084	.826	.302	**.000**	1.000	.993	1.000	.884	.887	1.000
	Heart	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.996	.990	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.938	.999	.703	**.000**	**.022**
	Gluteus	1.000	.999	1.000	.542	.306	**.000**	**.000**	**.000**	.947	.988	.995
	Soleus	.184	1.000	.999	.237	**.023**	**.000**	**.003**	**.000**	**.000**	**.000**	.624
	VAT	.816	.529	.997	.997	.975	1.000	1.000	1.000	.798	.807	1.000

		p value										
		Alkenyl phosphatidylethanolamine										
		PE(P-18:1/18:2) (b)	PE(P-18:1/18:3)	PE(P-18:1/20:3) (a)	PE(P-18:1/20:3) (b)	PE(P-18:1/20:4) (a)	PE(P-18:1/20:4) (b)	PE(P-18:1/20:5) (a)	PE(P-18:1/20:5) (b)	PE(P-18:1/22:4)	PE(P-18:1/22:5) (a)	PE(P-18:1/22:5) (b)
Liver	Heart	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.010**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.018**	**.000**	**.000**	**.000**	**.000**	.979	1.000	1.000
	Gluteus	.997	.889	**.005**	.080	.905	.999	**.037**	1.000	.983	.259	.484
	Soleus	.794	**.049**	.182	.712	.983	1.000	.089	.997	.855	.057	.436
	VAT	1.000	1.000	**.000**	**.002**	.827	.995	**.007**	.916	**.013**	.997	.993
	SAT	1.000	.997	**.012**	.227	.993	1.000	.097	.999	.357	1.000	.999
Heart	Liver	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.010**	**.000**	**.000**	**.000**
	Kidney	1.000	.809	**.000**	**.003**	**.000**	.210	.542	.271	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.115	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.084	**.000**	**.000**	**.000**
Kidney	Liver	**.000**	**.000**	**.000**	**.018**	**.000**	**.000**	**.000**	**.000**	.979	1.000	1.000
	Heart	1.000	.809	**.000**	**.003**	**.000**	.210	.542	.271	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.361	.596
	Soleus	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.001**	.999	.096	.541
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	.995	.991
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.104	1.000	.999
Gluteus	Liver	.997	.889	**.005**	.080	.905	.999	**.037**	1.000	.983	.259	.484
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.361	.596
	Soleus	.984	.527	.885	.910	1.000	1.000	1.000	.997	.999	.986	1.000
	VAT	.985	.785	.872	.922	1.000	1.000	.999	.947	**.003**	.094	.183
	SAT	.999	.998	1.000	1.000	1.000	1.000	1.000	.999	.111	.243	.334
Soleus	Liver	.794	**.049**	.182	.712	.983	1.000	.089	.997	.855	.057	.436
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.115	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.001**	.999	.096	.541
	Gluteus	.984	.527	.885	.910	1.000	1.000	1.000	.997	.999	.986	1.000
	VAT	.696	**.032**	.204	.294	1.000	.999	.995	.693	**.001**	**.017**	.165
	SAT	.868	.267	.947	.987	1.000	1.000	1.000	1.000	**.047**	.060	.298
VAT	Liver	1.000	1.000	**.000**	**.002**	.827	.995	**.007**	.916	**.013**	.997	.993
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.002**	.995	.991
	Gluteus	.985	.785	.872	.922	1.000	1.000	.999	.947	**.003**	.094	.183
	Soleus	.696	**.032**	.204	.294	1.000	.999	.995	.693	**.001**	**.017**	.165
	SAT	1.000	.983	.822	.784	.998	.998	.993	.774	.907	1.000	1.000
SAT	Liver	1.000	.997	**.012**	.227	.993	1.000	.097	.999	.357	1.000	.999
	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.084	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.104	1.000	.999
	Gluteus	.999	.998	1.000	1.000	1.000	1.000	1.000	.999	.111	.243	.334
	Soleus	.868	.267	.947	.987	1.000	1.000	1.000	1.000	**.047**	.060	.298
	VAT	1.000	.983	.822	.784	.998	.998	.993	.774	.907	1.000	1.000

		p value										
		Alkenyl phosphatidylethanolamine										
		PE(P-18:1/22:6) (a)	PE(P-18:1/22:6) (b)	PE(P-19:0/20:4) (a)	PE(P-19:0/20:4) (b)	PE(P-20:0/18:1)	PE(P-20:0/18:2)	PE(P-20:0/20:4)	PE(P-20:0/22:6)	PE(P-20:1/20:4)	PE(P-20:1/22:6) (a)	PE(P-20:1/22:6) (b)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.041**
	Kidney	1.000	1.000	**.000**	**.000**	**.019**	**.000**	**.000**	.993	**.000**	1.000	.999
	Gluteus	.228	.062	.930	.973	1.000	.990	.853	1.000	.816	.288	1.000
	Soleus	**.022**	**.007**	1.000	1.000	**.000**	.983	.982	1.000	1.000	**.006**	1.000
	VAT	1.000	1.000	.231	.736	.989	.505	.731	.401	.628	1.000	.624
	SAT	1.000	1.000	.999	1.000	.992	1.000	.998	.816	1.000	1.000	.997
Heart	Liver	**.000**	**.000**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.041**
	Kidney	**.000**	**.000**	**.004**	.994	**.027**	.849	.097	**.000**	**.029**	**.000**	.199
	Gluteus	**.000**	**.000**	**.000**	**.000**	.998	**.000**	**.000**	**.000**	**.000**	**.000**	**.031**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.007**	.149
	VAT	**.000**	**.000**	**.000**	**.000**	.973	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	**.000**	**.000**	.997	**.000**	**.000**	**.000**	**.000**	**.000**	**.022**
Kidney	Liver	1.000	1.000	**.000**	**.000**	**.019**	**.000**	**.000**	.993	**.000**	1.000	.999
	Heart	**.000**	**.000**	**.004**	.994	**.027**	.849	.097	**.000**	**.029**	**.000**	.199
	Gluteus	.429	.168	**.000**	**.000**	**.011**	**.000**	**.000**	1.000	**.000**	.326	.986
	Soleus	.064	**.027**	**.000**	**.000**	.792	**.000**	**.000**	.971	**.000**	**.009**	1.000
	VAT	1.000	1.000	**.000**	**.000**	**.003**	**.000**	**.000**	.866	**.000**	1.000	.384
	SAT	1.000	1.000	**.000**	**.000**	.194	**.001**	**.000**	.993	**.000**	1.000	.953
Gluteus	Liver	.228	.062	.930	.973	1.000	.990	.853	1.000	.816	.288	1.000
	Heart	**.000**	**.000**	**.000**	**.000**	.998	**.000**	**.000**	**.000**	**.000**	**.000**	**.031**
	Kidney	.429	.168	**.000**	**.000**	**.011**	**.000**	**.000**	1.000	**.000**	.326	.986
	Soleus	.935	.974	.835	.980	**.000**	1.000	1.000	.997	.974	.662	.999
	VAT	.193	.058	.898	.998	1.000	.936	1.000	.683	1.000	.154	.859
	SAT	.301	.106	.997	.988	.942	.997	.995	.952	.874	.293	1.000
Soleus	Liver	**.022**	**.007**	1.000	1.000	**.000**	.983	.982	1.000	1.000	**.006**	1.000
	Heart	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.007**	.149
	Kidney	.064	**.027**	**.000**	**.000**	.792	**.000**	**.000**	.971	**.000**	**.009**	1.000
	Gluteus	.935	.974	.835	.980	**.000**	1.000	1.000	.997	.974	.662	.999
	VAT	**.019**	**.007**	.184	.800	**.000**	.970	.997	.353	.909	**.002**	.593
	SAT	**.040**	**.016**	.990	1.000	**.009**	.994	1.000	.732	1.000	**.009**	.990
VAT	Liver	1.000	1.000	.231	.736	.989	.505	.731	.401	.628	1.000	.624
	Heart	**.000**	**.000**	**.000**	**.000**	.973	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	1.000	1.000	**.000**	**.000**	**.003**	**.000**	**.000**	.866	**.000**	1.000	.384
	Gluteus	.193	.058	.898	.998	1.000	.936	1.000	.683	1.000	.154	.859
	Soleus	**.019**	**.007**	.184	.800	**.000**	.970	.997	.353	.909	**.002**	.593
	SAT	1.000	1.000	.609	.842	.822	.676	.981	.999	.731	1.000	.959
SAT	Liver	1.000	1.000	.999	1.000	.992	1.000	.998	.816	1.000	1.000	.997
	Heart	**.000**	**.000**	**.000**	**.000**	.997	**.000**	**.000**	**.000**	**.000**	**.000**	**.022**
	Kidney	1.000	1.000	**.000**	**.000**	.194	**.001**	**.000**	.993	**.000**	1.000	.953
	Gluteus	.301	.106	.997	.988	.942	.997	.995	.952	.874	.293	1.000
	Soleus	**.040**	**.016**	.990	1.000	**.009**	.994	1.000	.732	1.000	**.009**	.990
	VAT	1.000	1.000	.609	.842	.822	.676	.981	.999	.731	1.000	.959

p values < 0.05 are represented in bold numbers.

8.3.4. Sphingolipids

Table S18. Sphingolipid concentration detected by targeted lipidomic analysis in all the studied tissues. Lipid species detected were 8 sphingosines (five of them sph-1P), 6 dihydroceramides, 54 ceramides (one cer-1P), 44 sphingomylins, 14 MHC, 10 DHC, 6 THC, 8 gangliosides and 6 sulfatides.

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Sphingosine							
Sph(d16:1)	7.40±0.36	6.99±0.29	7.30±0.44	6.41±0.10	6.71±0.30	6.87±0.32	7.40±0.43
Sph(d18:1)	59.95±3.52	42.36±3.28	62.35±3.54	17.74±0.36	19.48±1.06	16.46±0.50	20.14±1.46
Sph(d18:2)	8.53±0.41	12.03±0.71	20.18±0.89	5.26±0.21	5.75±0.25	6.22±0.31	7.92±0.54
Sphingosine1phosphate							
S1P(d16:1)	0.41±0.04	0.51±0.05	0.46±0.03	0.42±0.06	0.45±0.03	0.40±0.05	0.62±0.10
S1P(d17:1)	0.37±0.06	0.40±0.08	0.37±0.06	0.31±0.02	0.33±0.03	0.31±0.03	0.44±0.07
S1P(d18:0)	0.27±0.04	0.29±0.04	0.28±0.03	0.19±0.02	0.28±0.05	0.21±0.05	0.32±0.03
S1P(d18:1)	0.85±0.09	0.87±0.05	0.98±0.11	0.93±0.04	0.82±0.08	0.87±0.09	1.18±0.32
S1P(d18:2)	0.44±0.06	0.47±0.07	0.46±0.04	0.34±0.02	0.39±0.04	0.38±0.04	0.46±0.06
Dihydroceramides							
Cer(d18:0/16:0)	1.57±0.07	0.14±0.02	0.87±0.06	0.05±0.01	0.07±0.01	0.11±0.02	0.31±0.06
Cer(d18:0/18:0)	0.31±0.04	0.12±0.02	0.20±0.02	0.13±0.02	0.15±0.01	0.11±0.05	0.08±0.01
Cer(d18:0/20:0)	0.49±0.04	0.46±0.04	0.45±0.03	0.24±0.02	0.30±0.03	0.19±0.02	0.25±0.02
Cer(d18:0/22:0)	1.71±0.09	0.52±0.05	0.66±0.03	0.25±0.03	0.30±0.03	0.21±0.03	0.26±0.02
Cer(d18:0/24:0)	6.64±0.39	1.07±0.06	3.07±0.23	0.51±0.03	0.56±0.05	0.38±0.05	0.64±0.06
Cer(d20:1/22:0)	1.65±0.08	1.49±0.08	1.29±0.07	1.40±0.06	1.39±0.06	0.86±0.11	1.29±0.14
Ceramides							
Cer(d16:1/16:0)	0.26±0.02	0.02±0.003	0.04±0.005	0.04±0.01	0.02±0.003	0.22±0.03	0.27±0.05
Cer(d16:1/18:0)	0.04±0.01	0.02±0.003	0.02±0.003	0.02±0.003	0.02±0.003	0.01±0.002	0.01±0.002
Cer(d16:1/20:0)	0.04±0.004	0.04±0.004	0.02±0.003	0.03±0.002	0.03±0.003	0.02±0.002	0.03±0.002
Cer(d16:1/22:0)	0.24±0.02	0.11±0.01	0.10±0.02	0.09±0.01	0.10±0.02	0.06±0.01	0.09±0.01
Cer(d16:1/23:0)	0.28±0.02	0.16±0.01	0.15±0.02	0.15±0.01	0.16±0.01	0.14±0.01	0.15±0.02
Cer(d16:1/24:0)	1.19±0.08	0.30±0.02	0.40±0.05	0.35±0.04	0.30±0.05	0.22±0.02	0.28±0.04
Cer(d16:1/24:1)	0.28±0.01	0.04±0.004	0.05±0.004	0.04±0.01	0.03±0.004	0.03±0.004	0.04±0.01
Cer(d17:1/16:0)	0.71±0.04	0.08±0.01	0.34±0.04	0.03±0.002	0.06±0.01	0.10±0.02	0.19±0.03
Cer(d17:1/18:0)	0.12±0.02	0.09±0.01	0.10±0.004	0.25±0.01	0.18±0.01	0.10±0.01	0.10±0.01
Cer(d17:1/20:0)	0.04±0.01	0.06±0.01	0.03±0.002	0.03±0.002	0.03±0.01	0.02±0.003	0.03±0.004
Cer(d17:1/22:0)	0.56±0.03	0.21±0.02	0.15±0.01	0.08±0.01	0.11±0.01	0.07±0.01	0.13±0.02
Cer(d17:1/23:0)	0.45±0.03	0.13±0.01	0.09±0.01	0.10±0.01	0.10±0.01	0.06±0.01	0.10±0.003
Cer(d17:1/24:0)	2.96±0.15	0.64±0.05	1.04±0.09	0.39±0.03	0.38±0.05	0.31±0.03	0.51±0.04
Cer(d17:1/24:1)	1.27±0.07	0.47±0.05	0.39±0.04	0.11±0.01	0.14±0.02	0.47±0.07	0.99±0.11
Cer(d18:1/14:0)	0.58±0.05	0.07±0.005	0.15±0.02	0.04±0.01	0.05±0.01	0.05±0.01	0.13±0.004
Cer(d18:1/16:0)	67.82±3.88	5.36±0.68	50.86±4.67	1.52±0.05	2.41±0.15	4.94±0.84	14.28±2.06
Cer(d18:1/18:0)(a)	5.10±0.30	3.74±0.37	2.51±0.21	22.92±0.84	20.04±2.26	0.55±0.06	1.33±0.15
Cer(d18:1/19:0)	0.46±0.01	0.40±0.02	0.29±0.01	0.53±0.01	0.58±0.04	0.32±0.01	0.44±0.02
Cer(d18:1/20:0)(a)	7.95±0.35	11.66±0.90	5.68±0.56	1.75±0.07	4.17±0.57	0.98±0.14	2.26±0.17

Cer(d18:1/21:0)	1.20±0.06	1.21±0.11	0.57±0.04	0.13±0.01	0.29±0.04	0.14±0.02	0.24±0.02
Cer(d18:1/22:0)(a)	58.37±2.90	15.26±1.44	17.71±1.60	2.26±0.12	4.45±0.50	3.97±0.57	7.67±0.70
Cer(d18:1/23:0)	50.55±3.14	7.85±0.96	5.26±0.38	1.90±0.14	3.20±0.46	3.16±0.49	6.02±0.68
Cer(d18:1/24:0)(a)	423.2±22.66	41.46±4.37	216.3±15.46	11.38±0.64	20.98±3.48	14.13±2.29	30.89±3.88
Cer(d18:1/24:1)(a)	103.7±6.87	10.10±1.08	44.75±3.52	4.94±0.22	7.23±0.76	3.78±0.58	13.25±0.64
Cer(d18:1/26:0)	5.75±0.39	1.13±0.10	5.87±0.58	0.64±0.04	0.70±0.10	0.64±0.05	1.00±0.10
Cer(d18:1/18:0)(b)	9.88±1.03	8.96±1.27	10.64±1.42	10.09±0.86	11.40±3.12	10.75±2.01	9.33±0.87
Cer(d18:1/20:0)(b)	0.19±0.01	0.19±0.02	0.20±0.03	0.21±0.01	0.17±0.01	0.15±0.02	0.15±0.02
Cer(d18:1/22:0)(b)	0.13±0.02	0.10±0.01	0.13±0.01	0.06±0.01	0.08±0.01	0.05±0.01	0.10±0.01
Cer(d18:1/24:0)(b)	0.35±0.02	0.12±0.01	0.23±0.01	0.11±0.01	0.12±0.01	0.10±0.02	0.16±0.02
Cer(d18:1/24:1)(b)	0.20±0.03	0.05±0.01	0.09±0.01	0.04±0.01	0.04±0.01	0.03±0.01	0.06±0.01
Cer(d18:2/14:0)	0.04±0.01	0.01±0.002	0.03±0.005	0.003±0.001	0.004±0.001	0.01±0.002	0.02±0.004
Cer(d18:2/16:0)	2.97±0.20	0.52±0.05	6.93±0.53	0.25±0.01	0.39±0.02	1.75±0.27	5.05±0.67
Cer(d18:2/17:0)	0.15±0.01	0.12±0.01	0.15±0.01	0.12±0.01	0.13±0.01	0.13±0.01	0.13±0.01
Cer(d18:2/18:0)	0.34±0.03	0.79±0.06	0.55±0.06	1.67±0.09	1.48±0.20	0.16±0.03	0.42±0.05
Cer(d18:2/20:0)	0.28±0.02	1.55±0.13	0.42±0.04	0.08±0.01	0.17±0.03	0.20±0.03	0.56±0.08
Cer(d18:2/21:0)	0.10±0.01	0.46±0.03	0.09±0.01	0.02±0.002	0.04±0.004	0.07±0.01	0.15±0.02
Cer(d18:2/22:0)	4.87±0.29	5.69±0.41	8.31±1.05	0.34±0.03	0.58±0.04	3.01±0.42	6.94±0.95
Cer(d18:2/23:0)	4.91±0.34	3.46±0.27	1.87±0.18	0.35±0.02	0.47±0.06	4.10±0.58	8.97±1.12
Cer(d18:2/24:0)	31.00±2.20	11.98±1.07	94.37±6.37	1.62±0.15	2.31±0.27	23.50±3.46	52.93±7.13
Cer(d18:2/24:1)	6.58±0.52	2.85±0.21	15.88±1.23	0.58±0.03	0.91±0.07	3.03±0.50	8.30±0.79
Cer(d18:2/26:0)	0.63±0.05	0.27±0.02	3.55±0.30	0.07±0.004	0.08±0.01	0.50±0.08	1.11±0.16
Cer(d19:1/16:0)	0.05±0.01	0.01±0.002	0.02±0.002	0.01±0.002	0.01±0.002	0.01±0.001	0.02±0.003
Cer(d19:1/18:0)	0.02±0.003	0.01±0.003	0.01±0.003	0.03±0.005	0.03±0.005	0.01±0.001	0.01±0.002
Cer(d19:1/20:0)	0.07±0.01	0.06±0.01	0.05±0.01	0.05±0.01	0.06±0.01	0.05±0.004	0.05±0.005
Cer(d19:1/22:0)	0.24±0.02	0.08±0.01	0.09±0.01	0.06±0.01	0.07±0.01	0.04±0.01	0.06±0.01
Cer(d19:1/23:0)	0.20±0.01	0.06±0.01	0.06±0.01	0.04±0.003	0.05±0.005	0.03±0.003	0.05±0.01
Cer(d19:1/24:0)	1.27±0.05	0.24±0.02	0.51±0.04	0.16±0.01	0.14±0.01	0.11±0.01	0.20±0.01
Cer(d19:1/24:1)	0.43±0.02	0.11±0.01	0.15±0.01	0.07±0.01	0.07±0.01	0.09±0.01	0.22±0.01
Cer(d19:1/26:0)	0.14±0.01	0.10±0.01	0.09±0.01	0.10±0.01	0.10±0.01	0.08±0.01	0.11±0.01
Cer(d20:1/23:0)	0.08±0.01	0.05±0.004	0.08±0.01	0.05±0.004	0.03±0.004	0.03±0.004	0.04±0.01
Cer(d20:1/24:0)	0.50±0.03	0.32±0.02	0.44±0.03	0.28±0.02	0.27±0.03	0.21±0.02	0.28±0.02
Cer(d20:1/24:1)	0.12±0.01	0.05±0.01	0.09±0.01	0.04±0.004	0.03±0.003	0.02±0.001	0.04±0.002
Cer(d20:1/26:0)	0.39±0.04	0.30±0.01	0.28±0.03	0.33±0.03	0.32±0.04	0.24±0.02	0.27±0.03
Cer(d18:0/24:1)	2.39±0.11	0.33±0.04	0.76±0.07	0.09±0.02	0.11±0.02	0.05±0.01	0.18±0.02
Ceramide1phosphate							
Cer1P(d18:1/16:0)	0.05±0.01	0.05±0.01	0.06±0.01	0.04±0.003	0.04±0.004	0.04±0.01	0.05±0.01
Sphingomyelins							
SM(d17:1/14:0)	0.12±0.004	0.11±0.01	0.12±0.002	0.09±0.002	0.10±0.002	0.08±0.002	0.09±0.001
SM(d18:0/14:0)	0.12±0.01	0.04±0.01	0.08±0.005	0.02±0.002	0.02±0.002	0.01±0.001	0.03±0.004
SM(d18:1/14:0)/SM(d16:1/16:0)	2.49±0.17	1.55±0.15	3.16±0.14	0.52±0.05	0.69±0.08	0.35±0.05	0.99±0.07
SM(d18:2/14:0)	0.11±0.01	0.11±0.01	0.25±0.01	0.05±0.004	0.06±0.003	0.03±0.003	0.08±0.01
SM(d17:1/16:0)	3.74±0.19	1.46±0.19	6.63±0.55	0.34±0.03	0.51±0.07	0.50±0.08	1.44±0.18
SM(d18:0/16:0)	11.07±0.53	2.12±0.27	22.52±1.39	0.48±0.02	1.08±0.07	0.98±0.16	3.17±0.52
SM(d18:1/16:0)	282.10±20.81	111.1±12.62	1,132±72.43	20.76±0.70	39.91±2.62	42.77±6.87	133.0±18.21
SM(d18:2/16:0)	6.76±0.50	5.55±0.54	80.50±5.28	1.32±0.09	2.42±0.18	4.05±0.64	10.84±1.51

SM(34:3)	0.03±0.002	0.02±0.002	0.12±0.01	0.01±0.001	0.02±0.003	0.01±0.001	0.03±0.003
SM(d16:1/19:0)	0.33±0.03	0.13±0.02	0.61±0.06	0.04±0.01	0.07±0.01	0.03±0.01	0.11±0.01
SM(d18:1/17:0)/SM(d17:1/18:0)	2.48±0.20	3.23±0.40	9.33±0.82	1.59±0.05	1.88±0.18	0.62±0.12	1.88±0.24
SM(d18:2/17:0)	0.09±0.01	0.17±0.02	0.81±0.10	0.05±0.002	0.08±0.01	0.06±0.01	0.14±0.02
SM(35:2)(b)	0.05±0.005	0.02±0.004	0.81±0.13	0.03±0.002	0.03±0.01	0.01±0.002	0.02±0.004
SM(d18:1/18:0)/SM(d16:1/20:0)	47.35±3.28	101.5±10.83	75.10±7.49	147.1±5.47	141.5±20.39	3.79±0.56	13.48±1.56
SM(d18:2/18:0)	2.15±0.13	11.30±1.08	9.08±1.19	6.00±0.31	6.44±0.92	0.66±0.10	1.99±0.20
SM(d18:2/18:1)	0.22±0.02	0.16±0.02	0.32±0.02	0.11±0.004	0.09±0.01	0.03±0.004	0.12±0.01
SM(37:1)	1.86±0.09	1.55±0.17	5.11±0.37	1.67±0.06	1.72±0.26	0.16±0.02	0.70±0.11
SM(37:2)	0.12±0.01	0.62±0.05	0.30±0.03	0.19±0.01	0.23±0.03	0.05±0.01	0.14±0.02
SM(d18:1/20:0)/SM(d16:1/22:0)	19.58±1.11	91.37±9.09	42.51±3.75	3.94±0.14	11.91±1.58	2.31±0.38	8.46±1.20
SM(d18:2/20:0)	1.77±0.11	23.07±2.28	5.55±0.52	0.62±0.04	1.32±0.13	0.61±0.10	1.91±0.26
SM(38:3)(a)	0.22±0.01	0.21±0.02	0.20±0.02	0.04±0.003	0.06±0.01	0.02±0.004	0.08±0.004
SM(38:3)(b)	0.14±0.01	0.11±0.01	0.26±0.02	0.04±0.001	0.05±0.01	0.02±0.002	0.06±0.01
SM(d16:1/23:0)/SM(d17:1/22:0)	2.51±0.10	5.67±0.56	3.34±0.29	0.37±0.03	0.82±0.06	0.23±0.04	0.85±0.09
SM(d18:0/22:0)	1.45±0.08	0.52±0.05	1.73±0.16	0.09±0.01	2.12±0.54	0.06±0.01	0.52±0.15
SM(d18:1/22:0)/SM(d16:1/24:0)	89.21±4.36	61.09±6.56	123.0±12.16	4.46±0.19	17.57±2.65	5.20±0.77	17.41±2.14
SM(d16:1/24:1)	10.79±0.85	5.03±0.68	6.23±0.88	0.57±0.03	1.44±0.10	0.58±0.10	2.23±0.21
SM(d18:2/22:0)	5.02±0.28	16.48±1.59	36.62±5.00	0.78±0.07	1.62±0.15	1.97±0.27	5.58±0.67
SM(40:3)(a)	2.83±0.23	2.42±0.25	3.80±0.32	0.75±0.04	0.96±0.14	0.19±0.02	0.68±0.07
SM(40:3)(b)	1.58±0.14	1.06±0.10	1.34±0.08	0.57±0.02	0.59±0.09	0.06±0.01	0.22±0.03
SM(41:0)	1.47±0.08	0.29±0.04	0.75±0.06	0.06±0.01	0.36±0.07	0.06±0.01	0.20±0.04
SM(41:1)(a)	5.72±0.50	3.04±0.34	1.46±0.16	0.19±0.02	0.43±0.06	0.19±0.03	0.67±0.06
SM(d18:1/23:0)/SM(d17:1/24:0)	50.78±2.98	15.94±1.81	28.93±2.73	2.13±0.10	5.11±0.61	2.53±0.40	8.07±0.97
SM(d17:1/24:1)	2.68±0.15	2.02±0.21	2.12±0.15	0.24±0.02	0.51±0.04	0.20±0.03	0.68±0.07
SM(d18:2/23:0)	2.50±0.17	4.50±0.43	6.36±0.85	0.32±0.03	0.59±0.06	1.17±0.16	3.27±0.49
SM(d18:1/24:0)	340.4±21.44	67.71±7.89	1,067±50.72	10.84±0.56	30.81±4.24	8.46±1.30	28.23±3.24
SM(d18:1/24:1)	94.61±6.04	29.32±3.17	204.1±8.48	6.42±0.19	21.20±2.70	3.93±0.52	17.94±2.20
SM(d18:2/24:0)	19.21±1.29	16.11±1.57	373.8±23.40	1.67±0.12	3.45±0.33	5.01±0.69	14.87±2.02
SM(43:1)	38.54±2.89	5.24±0.59	16.99±0.94	0.92±0.05	1.77±0.27	0.58±0.09	1.79±0.18
SM(d19:1/24:1)	0.25±0.02	0.07±0.01	0.22±0.01	0.04±0.01	0.07±0.01	0.02±0.00	0.07±0.01
SM(43:2)(b)	1.87±0.17	0.85±0.09	2.16±0.12	0.11±0.01	0.30±0.03	0.22±0.03	0.73±0.07
SM(43:2)(c)	1.24±0.10	0.72±0.07	5.19±0.32	0.08±0.01	0.17±0.02	0.31±0.04	0.84±0.14
SM(44:1)	6.95±0.51	2.83±0.31	41.72±2.71	0.29±0.01	0.81±0.13	0.16±0.02	0.56±0.06
SM(44:2)	4.34±0.52	1.40±0.18	15.08±0.49	0.21±0.02	0.54±0.06	0.19±0.03	0.53±0.06
SM(44:3)	0.49±0.05	0.49±0.05	2.58±0.09	0.06±0.005	0.17±0.02	0.08±0.01	0.25±0.03
Monohexosylceramides							
Hex1Cer(d16:1/18:0)	0.12±0.02	0.08±0.03	0.11±0.02	0.09±0.02	0.11±0.01	0.12±0.03	0.16±0.04
Hex1Cer(d16:1/20:0)	0.10±0.02	0.08±0.03	0.09±0.01	0.19±0.04	0.09±0.01	0.13±0.03	0.10±0.01
Hex1Cer(d16:1/22:0)	0.24±0.03	0.22±0.02	0.24±0.03	0.24±0.02	0.19±0.01	0.21±0.02	0.23±0.04
Hex1Cer(d16:1/24:0)	0.17±0.02	0.07±0.02	0.06±0.01	0.10±0.02	0.08±0.01	0.08±0.02	0.10±0.02
Hex1Cer(d18:1/16:0)	43.18±4.02	5.17±0.77	35.63±3.45	1.83±0.19	5.77±0.73	2.62±0.27	11.20±1.59
Hex1Cer(d18:1/18:0)	2.57±0.28	1.68±0.21	2.48±0.32	1.14±0.13	5.33±0.69	0.31±0.05	1.53±0.28
Hex1Cer(d18:1/20:0)	1.24±0.06	0.92±0.10	1.40±0.15	0.25±0.05	3.35±0.69	0.14±0.03	1.17±0.22
Hex1Cer(d18:1/22:0)	9.97±0.89	1.39±0.13	3.48±0.30	0.62±0.08	18.23±4.44	0.31±0.06	4.26±1.37
Hex1Cer(d18:1/24:0)	45.97±4.86	3.88±0.91	23.39±1.94	1.36±0.23	65.87±15.30	0.54±0.09	14.79±4.93
Hex1Cer(d18:1/24:1)	7.70±0.77	1.40±0.24	7.93±0.87	1.08±0.12	35.35±6.42	0.36±0.03	8.49±2.69

Hex1Cer(d18:2/18:0)	0.36±0.04	0.38±0.07	0.54±0.09	0.34±0.03	0.72±0.11	0.31±0.04	0.31±0.03
Hex1Cer(d18:2/20:0)	0.12±0.01	0.18±0.02	0.56±0.08	0.07±0.01	0.50±0.05	0.08±0.02	0.14±0.03
Hex1Cer(d18:2/22:0)	0.56±0.05	0.49±0.05	1.47±0.16	0.41±0.04	2.16±0.24	0.42±0.05	0.73±0.09
Hex1Cer(d18:2/24:0)	1.49±0.10	0.35±0.03	11.61±1.15	0.25±0.04	9.24±1.38	0.29±0.05	2.43±0.81
Dihexosylceramides							
Hex2Cer(d16:1/16:0)	0.18±0.02	0.14±0.01	0.14±0.01	0.22±0.03	0.14±0.01	0.19±0.02	0.19±0.02
Hex2Cer(d16:1/24:1)	0.07±0.02	0.06±0.01	0.05±0.01	0.05±0.01	0.04±0.01	0.05±0.01	0.09±0.02
Hex2Cer(d18:1/16:0)	2.94±0.48	1.56±0.20	2.31±0.21	0.94±0.08	1.01±0.11	0.30±0.03	0.76±0.09
Hex2Cer(d18:1/18:0)	0.16±0.04	0.18±0.05	1.01±0.14	0.32±0.07	8.47±1.87	0.09±0.03	1.65±0.68
Hex2Cer(d18:1/20:0)	0.64±0.10	6.36±0.58	0.64±0.09	0.67±0.07	1.36±0.30	0.08±0.03	0.20±0.04
Hex2Cer(d18:1/22:0)	1.74±0.14	3.69±0.32	0.94±0.09	0.68±0.07	0.94±0.19	0.19±0.03	0.30±0.03
Hex2Cer(d18:1/24:0)	9.79±0.86	6.60±0.86	6.27±0.42	3.03±0.16	4.20±0.58	0.35±0.05	0.96±0.07
Hex2Cer(d18:1/24:1)	1.69±0.24	1.06±0.13	0.92±0.06	0.70±0.06	1.04±0.12	0.18±0.03	0.35±0.03
Hex2Cer(d18:2/16:0)	0.14±0.02	0.12±0.01	0.17±0.02	0.18±0.03	0.11±0.02	0.15±0.03	0.17±0.03
Hex2Cer(d18:2/24:1)	0.08±0.02	0.43±0.05	0.20±0.02	0.08±0.02	0.14±0.02	0.10±0.02	0.13±0.03
Trihexosylceramides							
Hex3Cer(d18:1/16:0)	0.20±0.04	0.18±0.03	0.24±0.04	0.17±0.03	0.17±0.04	0.13±0.02	0.26±0.04
Hex3Cer(d18:1/18:0)	0.43±0.05	0.50±0.06	0.53±0.07	0.42±0.06	0.33±0.05	0.46±0.04	0.68±0.06
Hex3Cer(d18:1/20:0)	0.08±0.02	0.07±0.02	0.10±0.02	0.06±0.01	0.05±0.02	0.09±0.02	0.11±0.02
Hex3Cer(d18:1/22:0)	0.11±0.02	0.13±0.03	0.15±0.02	0.11±0.02	0.07±0.01	0.12±0.03	0.14±0.02
Hex3Cer(d18:1/24:0)	0.17±0.03	0.18±0.02	0.17±0.02	0.13±0.03	0.09±0.01	0.13±0.02	0.24±0.03
Hex3Cer(d18:1/24:1)	0.10±0.02	0.10±0.01	0.14±0.02	0.10±0.02	0.08±0.01	0.08±0.02	0.17±0.04
Gangliosides							
GM1(d18:1/16:0)	0.15±0.02	0.09±0.02	0.11±0.02	0.10±0.01	0.10±0.01	0.10±0.01	0.15±0.02
GM3(d18:1/16:0)	3.04±0.20	1.79±0.19	4.23±0.33	0.31±0.03	0.62±0.04	0.50±0.06	1.54±0.28
GM3(d18:1/18:0)	1.52±0.10	3.44±0.36	1.32±0.10	4.48±0.40	8.03±1.04	0.13±0.04	0.29±0.03
GM3(d18:1/20:0)	1.16±0.09	10.68±0.73	1.45±0.13	0.34±0.06	1.39±0.18	0.19±0.03	0.42±0.04
GM3(d18:1/22:0)	2.83±0.17	7.02±0.61	2.16±0.20	0.30±0.04	0.89±0.10	0.39±0.07	1.27±0.16
GM3(d18:1/24:0)	6.21±0.38	5.07±0.40	5.05±0.31	0.78±0.07	1.78±0.19	0.67±0.10	2.04±0.32
GM3(d18:1/24:1)	2.24±0.15	1.82±0.21	1.71±0.15	0.20±0.04	0.71±0.06	0.11±0.02	0.66±0.08
GM3(d18:2/24:1)	0.30±0.06	1.61±0.18	0.99±0.15	0.23±0.02	0.39±0.06	0.34±0.05	1.08±0.18
Sulfatides							
Sulfatide(d18:1:/16:0(OH))	0.02±0.005	0.01±0.004	0.03±0.002	0.02±0.002	0.01±0.001	0.01±0.002	0.01±0.002
Sulfatide(d18:1:/16:0)	0.02±0.004	0.01±0.003	0.08±0.02	0.01±0.002	0.04±0.005	0.01±0.001	0.02±0.002
Sulfatide(d18:1:/24:0(OH))	0.06±0.01	0.10±0.02	2.55±0.54	0.08±0.02	1.10±0.20	0.03±0.01	0.19±0.06
Sulfatide(d18:1:/24:0)	0.06±0.01	0.05±0.01	0.23±0.09	0.06±0.01	1.69±0.23	0.03±0.005	0.28±0.10
Sulfatide(d18:1:/24:1(OH))	0.09±0.01	0.07±0.01	0.40±0.05	0.06±0.01	0.26±0.04	0.03±0.002	0.07±0.01
Sulfatide(d18:1:/24:1)	0.08±0.01	0.05±0.01	0.18±0.02	0.05±0.01	1.63±0.36	0.02±0.003	0.16±0.06

Table S19. Statistic multiple comparison post hoc Tuckey of the sphingolipid species between all the studied tissues.

		p value													
		Sphingosine			*Sphigosine 1P*					*Dihydroceramides*					
		Sph(d16:1)	Sph(d18:1)	Sph(d18:2)	S1P(d16:1)	S1P(d17:1)	S1P(d18:0)	S1P(d18:1)	S1P(d18:2)	Cer(d18:0/16:0)	Cer(d18:0/18:0)	Cer(d18:0/20:0)	Cer(d18:0/22:0)	Cer(d18:0/24:0)	Cer(d20:1/22:0)
Liver	Heart	.980	**.000**	**.001**	.868	1.000	1.000	1.000	1.000	**.000**	**.001**	.990	**.000**	**.000**	.891
	Kidney	1.000	.996	**.000**	.994	1.000	1.000	.996	1.000	**.000**	.258	.980	**.000**	**.000**	.176
	Gluteus	.520	**.000**	**.007**	1.000	.992	.828	1.000	.889	**.000**	**.005**	**.000**	**.000**	**.000**	.599
	Soleus	.873	**.000**	**.046**	.999	1.000	1.000	1.000	.994	**.000**	**.035**	**.015**	**.000**	**.000**	.586
	VAT	.940	**.000**	.096	1.000	.990	.948	1.000	.989	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	SAT	1.000	**.000**	.993	.238	.984	.990	.728	1.000	**.000**	**.001**	**.001**	**.000**	**.000**	.210
Heart	Liver	.980	**.000**	**.001**	.868	1.000	1.000	1.000	1.000	**.000**	**.001**	.990	**.000**	**.000**	.891
	Kidney	.997	**.000**	**.000**	.999	1.000	1.000	.998	1.000	**.000**	.565	1.000	.545	**.000**	.799
	Gluteus	.931	**.000**	**.000**	.958	.946	.694	1.000	.693	.837	1.000	**.003**	**.025**	.518	.996
	Soleus	.999	**.000**	**.000**	.994	.989	1.000	1.000	.946	.965	.992	.082	.173	.667	.993
	VAT	1.000	**.000**	**.000**	.824	.935	.866	1.000	.914	.999	1.000	**.000**	**.004**	.222	**.001**
	SAT	.989	**.000**	**.001**	.875	.999	.999	.776	1.000	.266	.990	**.007**	.051	.812	.820
Kidney	Liver	1.000	.996	**.000**	.994	1.000	1.000	.996	1.000	**.000**	.258	.980	**.000**	**.000**	.176
	Heart	.997	**.000**	**.000**	.999	1.000	1.000	.998	1.000	**.000**	.565	1.000	.545	**.000**	.799
	Gluteus	.707	**.000**	**.000**	.999	.991	.844	1.000	.836	**.000**	.742	**.008**	**.000**	**.000**	.989
	Soleus	.952	**.000**	**.000**	1.000	.999	1.000	.992	.983	**.000**	.960	.152	**.004**	**.000**	.996
	VAT	.985	**.000**	**.000**	.987	.989	.952	.998	.972	**.000**	.473	**.000**	**.000**	**.000**	.074
	SAT	1.000	**.000**	**.000**	.658	.992	.995	.973	1.000	**.000**	.262	**.019**	**.001**	**.000**	1.000
Gluteus	Liver	.520	**.000**	**.007**	1.000	.992	.828	1.000	.889	**.000**	**.005**	**.000**	**.000**	**.000**	.599
	Heart	.931	**.000**	**.000**	.958	.946	.694	1.000	.693	.837	1.000	**.003**	**.025**	.518	.996
	Kidney	.707	**.000**	**.000**	.999	.991	.844	1.000	.836	**.000**	.742	**.008**	**.000**	**.000**	.989
	Soleus	.999	1.000	.999	1.000	1.000	.828	.999	.999	1.000	.999	.948	.995	1.000	1.000
	VAT	.981	1.000	.928	1.000	1.000	1.000	1.000	.999	.978	1.000	.942	.999	.999	**.010**
	SAT	.636	.998	.094	.398	.808	.485	.923	.878	**.024**	.976	1.000	1.000	1.000	.990
Soleus	Liver	.873	**.000**	**.046**	.999	1.000	1.000	1.000	.994	**.000**	**.035**	**.015**	**.000**	**.000**	.586
	Heart	.999	**.000**	**.000**	.994	.989	1.000	1.000	.946	.965	.992	.082	.173	.667	.993
	Kidney	.952	**.000**	**.000**	1.000	.999	1.000	.992	.983	**.000**	.960	.152	**.004**	**.000**	.996
	Gluteus	.999	1.000	.999	1.000	1.000	.828	.999	.999	1.000	.999	.948	.995	1.000	1.000
	VAT	1.000	.991	.999	.997	1.000	.941	1.000	1.000	.999	.977	.405	.921	.997	**.020**
	SAT	.915	1.000	.304	.600	.920	.998	.724	.989	.069	.848	.979	.999	1.000	.996
VAT	Liver	.940	**.000**	.096	1.000	.990	.948	1.000	.989	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**
	Heart	1.000	**.000**	**.000**	.824	.935	.866	1.000	.914	.999	1.000	**.000**	**.004**	.222	**.001**
	Kidney	.985	**.000**	**.000**	.987	.989	.952	.998	.972	**.000**	.473	**.000**	**.000**	**.000**	.074
	Gluteus	.981	1.000	.928	1.000	1.000	1.000	1.000	.999	.978	1.000	.942	.999	.999	**.010**
	Soleus	1.000	.991	.999	.997	1.000	.941	1.000	1.000	.999	.977	.405	.921	.997	**.020**
	SAT	.965	.976	.516	.212	.783	.668	.787	.982	.131	.998	.911	.997	.982	.102
SAT	Liver	1.000	**.000**	.993	.238	.984	.990	.728	1.000	**.000**	**.001**	**.001**	**.000**	**.000**	.210
	Heart	.989	**.000**	**.001**	.875	.999	.999	.776	1.000	.266	.990	**.007**	.051	.812	.820
	Kidney	1.000	**.000**	**.000**	.658	.992	.995	.973	1.000	**.000**	.262	**.019**	**.001**	**.000**	1.000
	Gluteus	.636	.998	.094	.398	.808	.485	.923	.878	**.024**	.976	1.000	1.000	1.000	.990
	Soleus	.915	1.000	.304	.600	.920	.998	.724	.989	.069	.848	.979	.999	1.000	.996
	VAT	.965	.976	.516	.212	.783	.668	.787	.982	.131	.998	.911	.997	.982	.102

		p value										
		Ceramides										
		Cer(d16:1/16:0)	Cer(d16:1/18:0)	Cer(d16:1/20:0)	Cer(d16:1/22:0)	Cer(d16:1/23:0)	Cer(d16:1/24:0)	Cer(d16:1/24:1)	Cer(d17:1/16:0)	Cer(d17:1/18:0)	Cer(d17:1/20:0)	Cer(d17:1/22:0)
Liver	Heart	**.000**	**.001**	.665	**.000**	**.000**	**.000**	**.000**	**.000**	.308	.094	**.000**
	Kidney	**.000**	**.003**	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	.876	.954	**.000**
	Gluteus	**.000**	**.015**	.063	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.433	**.000**
	Soleus	**.000**	**.003**	.377	**.000**	**.000**	**.000**	**.000**	**.000**	**.019**	.398	**.000**
	VAT	.918	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	.733	.211	**.000**
	SAT	1.000	**.000**	.072	**.000**	**.000**	**.000**	**.000**	**.000**	.868	.395	**.000**
Heart	Liver	**.000**	**.001**	.665	**.000**	**.000**	**.000**	**.000**	**.000**	.308	.094	**.000**
	Kidney	1.000	1.000	.138	1.000	.997	.750	.943	**.000**	.980	**.012**	.267
	Gluteus	.996	.986	.761	.993	.998	.990	1.000	.890	**.000**	**.001**	**.000**
	Soleus	1.000	1.000	.995	.998	1.000	1.000	.975	.999	**.000**	**.001**	**.021**
	VAT	**.000**	.863	.078	.302	.990	.912	.899	.999	.995	**.000**	**.000**
	SAT	**.000**	.816	.755	.970	1.000	1.000	1.000	.136	.990	**.001**	.151
Kidney	Liver	**.000**	**.003**	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	.876	.954	**.000**
	Heart	1.000	1.000	.138	1.000	.997	.750	.943	**.000**	.980	**.012**	.267
	Gluteus	1.000	.997	.924	1.000	1.000	.991	.983	**.000**	**.000**	.962	.279
	Soleus	1.000	1.000	.559	1.000	.999	.876	.579	**.000**	**.001**	.939	.906
	VAT	**.000**	.820	1.000	.596	1.000	.176	.362	**.000**	1.000	.839	.082
	SAT	**.000**	.771	.954	.998	1.000	.726	.961	**.021**	1.000	.938	1.000
Gluteus	Liver	**.000**	**.015**	.063	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.433	**.000**
	Heart	.996	.986	.761	.993	.998	.990	1.000	.890	**.000**	**.001**	**.000**
	Kidney	1.000	.997	.924	1.000	1.000	.991	.983	**.000**	**.000**	.962	.279
	Soleus	.998	.991	.990	1.000	.999	.998	.955	.996	**.016**	1.000	.945
	VAT	**.000**	.460	.853	.781	1.000	.570	.858	.663	**.000**	1.000	.998
	SAT	**.000**	.428	1.000	1.000	1.000	.980	1.000	**.013**	**.000**	1.000	.550
Soleus	Liver	**.000**	**.003**	.377	**.000**	**.000**	**.000**	**.000**	**.000**	**.019**	.398	**.000**
	Heart	1.000	1.000	.995	.998	1.000	1.000	.975	.999	**.000**	**.001**	**.021**
	Kidney	1.000	1.000	.559	1.000	.999	.876	.579	**.000**	**.001**	.939	.906
	Gluteus	.998	.991	.990	1.000	.999	.998	.955	.996	**.016**	1.000	.945
	VAT	**.000**	.915	.434	.761	.995	.912	1.000	.964	**.000**	1.000	.703
	SAT	**.000**	.875	.986	1.000	1.000	1.000	.986	.081	**.002**	1.000	.988
VAT	Liver	.918	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	.733	.211	**.000**
	Heart	**.000**	.863	.078	.302	.990	.912	.899	.999	.995	**.000**	**.000**
	Kidney	**.000**	.820	1.000	.596	1.000	.176	.362	**.000**	1.000	.839	.082
	Gluteus	**.000**	.460	.853	.781	1.000	.570	.858	.663	**.000**	1.000	.998
	Soleus	**.000**	.915	.434	.761	.995	.912	1.000	.964	**.000**	1.000	.703
	SAT	.907	1.000	.904	.919	.999	.979	.941	.347	1.000	1.000	.235
SAT	Liver	1.000	**.000**	.072	**.000**	**.000**	**.000**	**.000**	**.000**	.868	.395	**.000**
	Heart	**.000**	.816	.755	.970	1.000	1.000	1.000	.136	.990	**.001**	.151
	Kidney	**.000**	.771	.954	.998	1.000	.726	.961	**.021**	1.000	.938	1.000
	Gluteus	**.000**	.428	1.000	1.000	1.000	.980	1.000	**.013**	**.000**	1.000	.550
	Soleus	**.000**	.875	.986	1.000	1.000	1.000	.986	.081	**.002**	1.000	.988
	VAT	.907	1.000	.904	.919	.999	.979	.941	.347	1.000	1.000	.235

		p value											
		Ceramides											
		Cer(d17:1/23:0)	Cer(d17:1/24:0)	Cer(d17:1/24:1)	Cer(d18:1/14:0)	Cer(d18:1/16:0)	Cer(d18:1/18:0) (a)	Cer(d18:1/19:0)	Cer(d18:1/20:0) (a)	Cer(d18:1/21:0)	Cer(d18:1/22:0) (a)	Cer(d18:1/23:0)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	**.000**	.929	.546	**.000**	1.000	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.002**	.473	**.000**	.088	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.229	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.009**	**.001**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	**.001**	**.000**	**.000**	**.000**	**.000**
	SAT	**.000**	**.000**	.109	**.000**	**.000**	.128	.999	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.929	.546	**.000**	1.000	**.000**	**.000**
	Kidney	.830	**.045**	.988	.244	**.000**	.968	**.013**	**.000**	**.000**	.949	.913
	Gluteus	.909	.445	**.010**	.997	.959	**.000**	**.003**	**.000**	**.000**	**.000**	.149
	Soleus	.912	.476	**.034**	1.000	.992	**.000**	**.000**	**.000**	**.000**	**.002**	.460
	VAT	.118	.128	1.000	.999	1.000	.199	.106	**.000**	**.000**	**.000**	.352
	SAT	.925	.955	**.000**	.541	.347	.614	.911	**.000**	**.000**	.065	.987
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.002**	.473	**.000**	.088	**.000**	**.000**	**.000**
	Heart	.830	**.045**	.988	.244	**.000**	.968	**.013**	**.000**	**.000**	.949	.913
	Gluteus	1.000	**.000**	.107	.108	**.000**	**.000**	**.000**	**.001**	**.001**	**.000**	.807
	Soleus	1.000	**.001**	.228	.201	**.000**	**.000**	**.000**	.611	.120	**.000**	.982
	VAT	.873	**.000**	.992	.110	**.000**	.790	.968	**.000**	**.001**	**.000**	.971
	SAT	1.000	**.008**	**.000**	1.000	**.000**	.985	**.001**	**.006**	**.036**	**.009**	1.000
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.229	**.000**	**.000**	**.000**	**.000**
	Heart	.909	.445	**.010**	.997	.959	**.000**	**.003**	**.000**	**.000**	**.000**	.149
	Kidney	1.000	**.000**	.107	.108	**.000**	**.000**	**.000**	**.001**	**.001**	**.000**	.807
	Soleus	1.000	1.000	1.000	1.000	1.000	.468	.816	.109	.700	.982	.999
	VAT	.784	.997	**.015**	1.000	.980	**.000**	**.000**	.964	1.000	.993	.998
	SAT	1.000	.977	**.000**	.294	.078	**.000**	.146	.997	.935	.423	.663
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.009**	**.001**	**.000**	**.000**	**.000**
	Heart	.912	.476	**.034**	1.000	.992	**.000**	**.000**	**.000**	**.000**	**.002**	.460
	Kidney	1.000	**.001**	.228	.201	**.000**	**.000**	**.000**	.611	.120	**.000**	.982
	Gluteus	1.000	1.000	1.000	1.000	1.000	.468	.816	.109	.700	.982	.999
	VAT	.834	.998	**.044**	1.000	.997	**.000**	**.000**	**.009**	.745	1.000	1.000
	SAT	1.000	.977	**.000**	.443	.150	**.000**	**.007**	.374	.999	.907	.931
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	**.001**	**.000**	**.000**	**.000**	**.000**
	Heart	.118	.128	1.000	.999	1.000	.199	.106	**.000**	**.000**	**.000**	.352
	Kidney	.873	**.000**	.992	.110	**.000**	.790	.968	**.000**	**.001**	**.000**	.971
	Gluteus	.784	.997	**.015**	1.000	.980	**.000**	**.000**	.964	1.000	.993	.998
	Soleus	.834	.998	**.044**	1.000	.997	**.000**	**.000**	**.009**	.745	1.000	1.000
	SAT	.815	.773	**.000**	.308	.322	.998	**.013**	.744	.957	.791	.902
SAT	Liver	**.000**	**.000**	.109	**.000**	**.000**	.128	.999	**.000**	**.000**	**.000**	**.000**
	Heart	.925	.955	**.000**	.541	.347	.614	.911	**.000**	**.000**	.065	.987
	Kidney	1.000	**.008**	**.000**	1.000	**.000**	.985	**.001**	**.006**	**.036**	**.009**	1.000
	Gluteus	1.000	.977	**.000**	.294	.078	**.000**	.146	.997	.935	.423	.663
	Soleus	1.000	.977	**.000**	.443	.150	**.000**	**.007**	.374	.999	.907	.931
	VAT	.815	.773	**.000**	.308	.322	.998	**.013**	.744	.957	.791	.902

		p value										
		Ceramides										
		Cer(d18:1/24:0) (a)	Cer(d18:1/24:1) (a)	Cer(d18:1/ 26:0)	Cer(d18:1/18:0) (b)	Cer(d18:1/20:0) (b)	Cer(d18:1/22:0) (b)	Cer(d18:1/24:0) (b)	Cer(d18:1/24:1) (b)	Cer(d18:2/ 14:0)	Cer(d18:2/ 16:0)	Cer(d18:2/ 17:0)
Liver	Heart	**.000**	**.000**	**.000**	1.000	1.000	.398	**.000**	**.000**	**.000**	**.000**	.470
	Kidney	**.000**	**.000**	1.000	1.000	1.000	1.000	**.000**	**.000**	.492	**.000**	1.000
	Gluteus	**.000**	**.000**	**.000**	1.000	.999	**.014**	**.000**	**.000**	**.000**	**.000**	.532
	Soleus	**.000**	**.000**	**.000**	.998	.989	.229	**.000**	**.000**	**.000**	**.000**	.661
	VAT	**.000**	**.000**	**.000**	1.000	.579	**.003**	**.000**	**.000**	**.000**	.211	.909
	SAT	**.000**	**.000**	**.000**	1.000	.692	.802	**.000**	**.000**	.300	**.007**	.838
Heart	Liver	**.000**	**.000**	**.000**	1.000	1.000	.398	**.000**	**.000**	**.000**	**.000**	.470
	Kidney	**.000**	**.000**	**.000**	.995	.999	.685	**.000**	.597	**.049**	**.000**	.577
	Gluteus	.650	.951	.921	.999	.983	.657	1.000	.997	.993	.998	1.000
	Soleus	.932	.998	.966	.971	.999	.998	1.000	.981	.997	1.000	1.000
	VAT	.709	.861	.909	.991	.766	.380	.999	.947	1.000	.204	.990
	SAT	.998	.997	1.000	1.000	.846	.999	.681	1.000	.168	**.000**	1.000
Kidney	Liver	**.000**	**.000**	1.000	1.000	1.000	1.000	**.000**	**.000**	.492	**.000**	1.000
	Heart	**.000**	**.000**	**.000**	.995	.999	.685	**.000**	.597	**.049**	**.000**	.577
	Gluteus	**.000**	**.000**	**.000**	1.000	1.000	.054	**.001**	.325	**.015**	**.000**	.626
	Soleus	**.000**	**.000**	**.000**	1.000	.978	.450	**.004**	.244	**.026**	**.000**	.738
	VAT	**.000**	**.000**	**.000**	1.000	.545	**.017**	**.000**	.136	.078	**.000**	.943
	SAT	**.000**	**.000**	**.000**	.999	.651	.944	.103	.864	1.000	**.031**	.886
Gluteus	Liver	**.000**	**.000**	**.000**	1.000	.999	**.014**	**.000**	**.000**	**.000**	**.000**	.532
	Heart	.650	.951	.921	.999	.983	.657	1.000	.997	.993	.998	1.000
	Kidney	**.000**	**.000**	**.000**	1.000	1.000	.054	**.001**	.325	**.015**	**.000**	.626
	Soleus	.999	1.000	1.000	.999	.903	.959	1.000	1.000	1.000	1.000	1.000
	VAT	1.000	1.000	1.000	1.000	.340	1.000	1.000	1.000	.986	.097	.991
	SAT	.958	.765	.990	1.000	.450	.489	.708	.980	.058	**.000**	1.000
Soleus	Liver	**.000**	**.000**	**.000**	.998	.989	.229	**.000**	**.000**	**.000**	**.000**	.661
	Heart	.932	.998	.966	.971	.999	.998	1.000	.981	.997	1.000	1.000
	Kidney	**.000**	**.000**	**.000**	1.000	.978	.450	**.004**	.244	**.026**	**.000**	.738
	Gluteus	.999	1.000	1.000	.999	.903	.959	1.000	1.000	1.000	1.000	1.000
	VAT	1.000	.996	1.000	1.000	.976	.830	.989	1.000	.994	.206	.998
	SAT	.999	.946	.997	.992	.987	.970	.895	.940	.090	**.000**	1.000
VAT	Liver	**.000**	**.000**	**.000**	1.000	.579	**.003**	**.000**	**.000**	**.000**	.211	.909
	Heart	.709	.861	.909	.991	.766	.380	.999	.947	1.000	.204	.990
	Kidney	**.000**	**.000**	**.000**	1.000	.545	**.017**	**.000**	.136	.078	**.000**	.943
	Gluteus	1.000	1.000	1.000	1.000	.340	1.000	1.000	1.000	.986	.097	.991
	Soleus	1.000	.996	1.000	1.000	.976	.830	.989	1.000	.994	.206	.998
	SAT	.977	.609	.988	.999	1.000	.265	.422	.877	.233	**.000**	1.000
SAT	Liver	**.000**	**.000**	**.000**	1.000	.692	.802	**.000**	**.000**	.300	**.007**	.838
	Heart	.998	.997	1.000	1.000	.846	.999	.681	1.000	.168	**.000**	1.000
	Kidney	**.000**	**.000**	**.000**	.999	.651	.944	.103	.864	1.000	**.031**	.886
	Gluteus	.958	.765	.990	1.000	.450	.489	.708	.980	.058	**.000**	1.000
	Soleus	.999	.946	.997	.992	.987	.970	.895	.940	.090	**.000**	1.000
	VAT	.977	.609	.988	.999	1.000	.265	.422	.877	.233	**.000**	1.000

		p value										
		Ceramides										
		Cer(d18:2/18:0)	Cer(d18:2/20:0)	Cer(d18:2/21:0)	Cer(d18:2/22:0)	Cer(d18:2/23:0)	Cer(d18:2/24:0)	Cer(d18:2/24:1)	Cer(d18:2/26:0)	Cer(d19:1/16:0)	Cer(d19:1/18:0)	Cer(d19:1/20:0)
Liver	Heart	**.014**	**.000**	**.000**	.957	.412	**.022**	**.003**	.509	**.000**	.995	.940
	Kidney	.703	.835	.998	**.007**	**.005**	**.000**	**.000**	**.000**	**.000**	.999	.522
	Gluteus	**.000**	.457	.073	**.000**	**.000**	**.000**	**.000**	.113	**.000**	**.015**	.164
	Soleus	**.000**	.927	.278	**.001**	**.000**	**.001**	**.000**	.154	**.000**	.252	.728
	VAT	.840	.974	.863	.346	.927	.846	**.007**	.994	**.000**	.499	.124
	SAT	.997	.159	.622	.322	**.000**	**.016**	.617	.294	**.000**	.986	.533
Heart	Liver	**.014**	**.000**	**.000**	.957	.412	**.022**	**.003**	.509	**.000**	.995	.940
	Kidney	.577	**.000**	**.000**	.077	.390	**.000**	**.000**	**.000**	.606	1.000	.975
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.004**	.595	.243	.955	.995	**.003**	.698
	Soleus	**.000**	**.000**	**.000**	**.000**	**.009**	.713	.477	.968	1.000	.076	.997
	VAT	**.000**	**.000**	**.000**	**.050**	.975	.426	1.000	.907	.998	.866	.637
	SAT	.150	**.000**	**.000**	.841	**.000**	**.000**	**.000**	**.005**	.457	1.000	.971
Kidney	Liver	.703	.835	.998	**.007**	**.005**	**.000**	**.000**	**.000**	**.000**	.999	.522
	Heart	.577	**.000**	**.000**	.077	.390	**.000**	**.000**	**.000**	.606	1.000	.975
	Gluteus	**.000**	**.049**	.290	**.000**	.512	**.000**	**.000**	**.000**	.302	**.007**	.994
	Soleus	**.000**	.296	.642	**.000**	.650	**.000**	**.000**	**.000**	.508	.134	1.000
	VAT	.106	.359	.994	**.000**	.091	**.000**	**.000**	**.000**	.316	.852	.990
	SAT	.976	.878	.372	.807	**.000**	**.000**	**.000**	**.000**	1.000	1.000	1.000
Gluteus	Liver	**.000**	.457	.073	**.000**	**.000**	**.000**	**.000**	.113	**.000**	**.015**	.164
	Heart	**.000**	**.000**	**.000**	**.000**	**.004**	.595	.243	.955	.995	**.003**	.698
	Kidney	**.000**	**.049**	.290	**.000**	.512	**.000**	**.000**	**.000**	.302	**.007**	.994
	Soleus	.876	.990	.999	1.000	1.000	1.000	1.000	1.000	1.000	.952	.975
	VAT	**.000**	.931	.643	.081	**.000**	**.014**	.194	.403	1.000	**.000**	1.000
	SAT	**.000**	**.002**	**.002**	**.000**	**.000**	**.000**	**.000**	**.001**	.210	**.005**	.997
Soleus	Liver	**.000**	.927	.278	**.001**	**.000**	**.001**	**.000**	.154	**.000**	.252	.728
	Heart	**.000**	**.000**	**.000**	**.000**	**.009**	.713	.477	.968	1.000	.076	.997
	Kidney	**.000**	.296	.642	**.000**	.650	**.000**	**.000**	**.000**	.508	.134	1.000
	Gluteus	.876	.990	.999	1.000	1.000	1.000	1.000	1.000	1.000	.952	.975
	VAT	**.000**	1.000	.931	.178	**.001**	**.028**	.399	.472	1.000	**.004**	.965
	SAT	**.000**	**.026**	**.012**	**.000**	**.000**	**.000**	**.000**	**.001**	.378	.090	1.000
VAT	Liver	.840	.974	.863	.346	.927	.846	**.007**	.994	**.000**	.499	.124
	Heart	**.000**	**.000**	**.000**	**.050**	.975	.426	1.000	.907	.998	.866	.637
	Kidney	.106	.359	.994	**.000**	.091	**.000**	**.000**	**.000**	.316	.852	.990
	Gluteus	**.000**	.931	.643	.081	**.000**	**.014**	.194	.403	1.000	**.000**	1.000
	Soleus	**.000**	1.000	.931	.178	**.001**	**.028**	.399	.472	1.000	**.004**	.965
	SAT	.581	**.029**	.099	**.003**	**.000**	**.001**	**.000**	.101	.219	.964	.995
SAT	Liver	.997	.159	.622	.322	**.000**	**.016**	.617	.294	**.000**	.986	.533
	Heart	.150	**.000**	**.000**	.841	**.000**	**.000**	**.000**	**.005**	.457	1.000	.971
	Kidney	.976	.878	.372	.807	**.000**	**.000**	**.000**	**.000**	1.000	1.000	1.000
	Gluteus	**.000**	**.002**	**.002**	**.000**	**.000**	**.000**	**.000**	**.001**	.210	**.005**	.997
	Soleus	**.000**	**.026**	**.012**	**.000**	**.000**	**.000**	**.000**	**.001**	.378	.090	1.000
	VAT	.581	**.029**	.099	**.003**	**.000**	**.001**	**.000**	.101	.219	.964	.995

		p value										
		Ceramides										
		Cer(d19:1/22:0)	Cer(d19:1/23:0)	Cer(d19:1/24:0)	Cer(d19:1/24:1)	Cer(d19:1/26:0)	Cer(d20:1/23:0)	Cer(d20:1/24:0)	Cer(d20:1/24:1)	Cer(d20:1/26:0)	Cer(d18:0/24:1)	Cer1P(d18:1/16:0)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	.378	**.038**	**.000**	**.000**	.403	**.000**	1.000
	Kidney	**.000**	**.000**	**.000**	**.000**	.169	.994	.709	.081	.202	**.000**	.942
	Gluteus	**.000**	**.000**	**.000**	**.000**	.309	**.010**	**.000**	**.000**	.863	**.000**	.904
	Soleus	**.000**	**.000**	**.000**	**.000**	.364	**.001**	**.000**	**.000**	.802	**.000**	.956
	VAT	**.000**	**.000**	**.000**	**.000**	**.042**	**.000**	**.000**	**.000**	**.022**	**.000**	.671
	SAT	**.000**	**.000**	**.000**	**.000**	.801	**.007**	**.000**	**.000**	.194	**.000**	.999
Heart	Liver	**.000**	**.000**	**.000**	**.000**	.378	**.038**	**.000**	**.000**	.403	**.000**	1.000
	Kidney	.990	.999	**.000**	.261	.997	.254	**.040**	**.002**	.998	**.001**	.898
	Gluteus	.917	.561	.521	.559	1.000	.992	.966	.615	.995	.163	.946
	Soleus	.995	.980	.286	.691	1.000	.633	.925	.525	.999	.267	.978
	VAT	.360	.110	.058	.982	.914	.240	.092	**.012**	.787	**.045**	.758
	SAT	.985	.996	.982	**.000**	.999	.961	.957	.728	.995	.693	1.000
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	.169	.994	.709	.081	.202	**.000**	.942
	Heart	.990	.999	**.000**	.261	.997	.254	**.040**	**.002**	.998	**.001**	.898
	Gluteus	.592	.881	**.000**	**.006**	1.000	.086	**.006**	**.000**	.920	**.000**	.384
	Soleus	.864	1.000	**.000**	**.013**	1.000	**.010**	**.005**	**.000**	.971	**.000**	.509
	VAT	.124	.370	**.000**	.060	.999	**.001**	**.000**	**.000**	.983	**.000**	.172
	SAT	.798	1.000	**.000**	.113	.956	.060	**.007**	**.000**	1.000	**.000**	.797
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	.309	**.010**	**.000**	**.000**	.863	**.000**	.904
	Heart	.917	.561	.521	.559	1.000	.992	.966	.615	.995	.163	.946
	Kidney	.592	.881	**.000**	**.006**	1.000	.086	**.006**	**.000**	.920	**.000**	.384
	Soleus	1.000	.980	.999	1.000	1.000	.962	1.000	1.000	1.000	1.000	1.000
	VAT	.972	.980	.943	.955	.983	.727	.587	.599	.451	.999	1.000
	SAT	1.000	.943	.970	**.000**	.993	1.000	1.000	1.000	.893	.982	.997
Soleus	Liver	**.000**	**.000**	**.000**	**.000**	.364	**.001**	**.000**	**.000**	.802	**.000**	.956
	Heart	.995	.980	.286	.691	1.000	.633	.925	.525	.999	.267	.978
	Kidney	.864	1.000	**.000**	**.013**	1.000	**.010**	**.005**	**.000**	.971	**.000**	.509
	Gluteus	1.000	.980	.999	1.000	1.000	.962	1.000	1.000	1.000	1.000	1.000
	VAT	.858	.645	.998	.982	.986	.999	.760	.772	.617	.997	.999
	SAT	1.000	1.000	.841	**.000**	.994	.994	1.000	1.000	.955	.994	.999
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.042**	**.000**	**.000**	**.000**	**.022**	**.000**	.671
	Heart	.360	.110	.058	.982	.914	.240	.092	**.012**	.787	**.045**	.758
	Kidney	.124	.370	**.000**	.060	.999	**.001**	**.000**	**.000**	.983	**.000**	.172
	Gluteus	.972	.980	.943	.955	.983	.727	.587	.599	.451	.999	1.000
	Soleus	.858	.645	.998	.982	.986	.999	.760	.772	.617	.997	.999
	SAT	.913	.512	.476	**.000**	.755	.895	.688	.579	.995	.864	.956
SAT	Liver	**.000**	**.000**	**.000**	**.000**	.801	**.007**	**.000**	**.000**	.194	**.000**	.999
	Heart	.985	.996	.982	**.000**	.999	.961	.957	.728	.995	.693	1.000
	Kidney	.798	1.000	**.000**	.113	.956	.060	**.007**	**.000**	1.000	**.000**	.797
	Gluteus	1.000	.943	.970	**.000**	.993	1.000	1.000	1.000	.893	.982	.997
	Soleus	1.000	1.000	.841	**.000**	.994	.994	1.000	1.000	.955	.994	.999
	VAT	.913	.512	.476	**.000**	.755	.895	.688	.579	.995	.864	.956

		p value										
		Sphingomyelins										
		SM(d17:1/14:0)	SM(d18:0/14:0)	SM(d18:1/14:0)/SM(d16:1/16:0)	SM(d18:2/14:0)	SM(d17:1/16:0)	SM(d18:0/16:0)	SM(d18:1/16:0)	SM(d18:2/16:0)	SM(34:3)	SM(d16:1/19:0)	SM(d18:1/17:0)/SM(d17:1/18:0)
Liver	Heart	.398	**.000**	**.000**	1.000	**.000**	**.000**	**.005**	1.000	.374	**.001**	.823
	Kidney	1.000	**.003**	**.014**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.632	**.008**	**.000**	.746
	Soleus	**.003**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	.857	.132	**.000**	.958
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.975	**.001**	**.000**	**.034**
	SAT	**.000**	**.000**	**.000**	.052	**.000**	**.000**	.052	.889	.940	**.000**	.960
Heart	Liver	.398	**.000**	**.000**	1.000	**.000**	**.000**	**.005**	1.000	.374	**.001**	.823
	Kidney	.593	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.005**	.178	**.000**	**.000**	.081	.605	.462	.845	.557	.407	.107
	Soleus	.277	.682	**.001**	**.002**	.245	.939	.763	.967	.985	.844	.326
	VAT	**.000**	**.029**	**.000**	**.000**	.161	.873	.728	.999	.137	.187	**.001**
	SAT	.053	.988	.079	.081	1.000	.937	.999	.706	.981	.996	.331
Kidney	Liver	1.000	**.003**	**.014**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	.593	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.009**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.632	**.008**	**.000**	.746
	Heart	**.005**	.178	**.000**	**.000**	.081	.605	.462	.845	.557	.407	.107
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	.791	.987	.981	.998	1.000	.997	1.000	1.000	.974	.996	.999
	VAT	.972	.995	.968	.736	1.000	.999	.999	.982	.990	1.000	.690
	SAT	.994	.707	.281	.560	.156	.162	.322	.131	.218	.863	.999
Soleus	Liver	**.003**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	.857	.132	**.000**	.958
	Heart	.277	.682	**.001**	**.002**	.245	.939	.763	.967	.985	.844	.326
	Kidney	**.009**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.791	.987	.981	.998	1.000	.997	1.000	1.000	.974	.996	.999
	VAT	.262	.796	.600	.430	1.000	1.000	1.000	.999	.678	.960	.448
	SAT	.991	.987	.803	.885	.362	.476	.588	.281	.757	.995	1.000
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.975	**.001**	**.000**	**.034**
	Heart	**.000**	**.029**	**.000**	**.000**	.161	.873	.728	.999	.137	.187	**.001**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.972	.995	.968	.736	1.000	.999	.999	.982	.990	1.000	.690
	Soleus	.262	.796	.600	.430	1.000	1.000	1.000	.999	.678	.960	.448
	SAT	.717	.301	**.036**	**.029**	.277	.341	.547	.454	**.039**	.654	.442
SAT	Liver	**.000**	**.000**	**.000**	.052	**.000**	**.000**	.052	.889	.940	**.000**	.960
	Heart	.053	.988	.079	.081	1.000	.937	.999	.706	.981	.996	.331
	Kidney	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.994	.707	.281	.560	.156	.162	.322	.131	.218	.863	.999
	Soleus	.991	.987	.803	.885	.362	.476	.588	.281	.757	.995	1.000
	VAT	.717	.301	**.036**	**.029**	.277	.341	.547	.454	**.039**	.654	.442

		p value										
		Sphingomyelins										
		SM(d18:2/17:0)	SM(35:2)(b)	SM(d18:1/18:0)/SM(d16:1/20:0)	SM(d18:2/18:0)	SM(d18:2/18:1)	SM(37:1)	SM(37:2)	SM(d18:1/20:0)/SM(d16:1/22:0)	SM(d18:2/20:0)	SM(38:3) (a)	SM(38:3) (b)
Liver	Heart	.692	.999	**.004**	**.000**	.057	.916	**.000**	**.000**	**.000**	.966	.662
	Kidney	**.000**	**.000**	.468	**.000**	**.000**	**.000**	**.005**	**.019**	.219	.751	**.000**
	Gluteus	.995	1.000	**.000**	**.024**	**.000**	.995	.648	.238	.990	**.000**	**.000**
	Soleus	1.000	1.000	**.000**	**.013**	**.000**	.999	.250	.923	1.000	**.000**	**.000**
	VAT	.998	.994	**.042**	.821	**.000**	**.000**	.663	.120	.987	**.000**	**.000**
	SAT	.967	.999	.285	1.000	**.000**	**.007**	.999	.679	1.000	**.000**	**.004**
Heart	Liver	.692	.999	**.004**	**.000**	.057	.916	**.000**	**.000**	**.000**	.966	.662
	Kidney	**.000**	**.000**	.527	.460	**.000**	**.000**	**.000**	**.000**	**.000**	.996	**.000**
	Gluteus	.362	1.000	**.039**	**.001**	.250	1.000	**.000**	**.000**	**.000**	**.000**	**.004**
	Soleus	.724	1.000	.130	**.003**	**.045**	.998	**.000**	**.000**	**.000**	**.000**	**.030**
	VAT	.397	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	.999	1.000	**.000**	**.000**	.406	.097	**.000**	**.000**	**.000**	**.000**	.172
Kidney	Liver	**.000**	**.000**	.468	**.000**	**.000**	**.000**	**.005**	**.019**	.219	.751	**.000**
	Heart	**.000**	**.000**	.527	.460	**.000**	**.000**	**.000**	**.000**	**.000**	.996	**.000**
	Gluteus	**.000**	**.000**	**.000**	.168	**.000**	**.000**	.334	**.000**	.068	**.000**	**.000**
	Soleus	**.000**	**.000**	**.002**	.375	**.000**	**.000**	.816	**.002**	.206	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.053	**.000**	**.000**
	SAT	**.000**	**.000**	**.006**	**.000**	**.000**	**.000**	**.045**	**.001**	.369	**.000**	**.000**
Gluteus	Liver	.995	1.000	**.000**	**.024**	**.000**	.995	.648	.238	.990	**.000**	**.000**
	Heart	.362	1.000	**.039**	**.001**	.250	1.000	**.000**	**.000**	**.000**	**.000**	**.004**
	Kidney	**.000**	**.000**	**.000**	.168	**.000**	**.000**	.334	**.000**	.068	**.000**	**.000**
	Soleus	.999	1.000	1.000	1.000	.979	1.000	.991	.928	1.000	.981	.998
	VAT	1.000	1.000	**.000**	**.001**	**.010**	**.000**	**.043**	1.000	1.000	.955	.892
	SAT	.775	1.000	**.000**	**.039**	1.000	.057	.940	.996	.989	.404	.869
Soleus	Liver	1.000	1.000	**.000**	**.013**	**.000**	.999	.250	.923	1.000	**.000**	**.000**
	Heart	.724	1.000	.130	**.003**	**.045**	.998	**.000**	**.000**	**.000**	**.000**	**.030**
	Kidney	**.000**	**.000**	**.002**	.375	**.000**	**.000**	.816	**.002**	.206	**.000**	**.000**
	Gluteus	.999	1.000	1.000	1.000	.979	1.000	.991	.928	1.000	.981	.998
	VAT	1.000	1.000	**.000**	**.000**	.131	**.000**	**.008**	.822	1.000	.560	.619
	SAT	.963	1.000	**.000**	**.022**	.953	.054	.621	.999	1.000	.901	.993
VAT	Liver	.998	.994	**.042**	.821	**.000**	**.000**	.663	.120	.987	**.000**	**.000**
	Heart	.397	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.053	**.000**	**.000**
	Gluteus	1.000	1.000	**.000**	**.001**	**.010**	**.000**	**.043**	1.000	1.000	.955	.892
	Soleus	1.000	1.000	**.000**	**.000**	.131	**.000**	**.008**	.822	1.000	.560	.619
	SAT	.818	1.000	.995	.928	**.009**	.615	.469	.976	.987	.055	.208
SAT	Liver	.967	.999	.285	1.000	**.000**	**.007**	.999	.679	1.000	**.000**	**.004**
	Heart	.999	1.000	**.000**	**.000**	.406	.097	**.000**	**.000**	**.000**	**.000**	.172
	Kidney	**.000**	**.000**	**.006**	**.000**	**.000**	**.000**	**.045**	**.001**	.369	**.000**	**.000**
	Gluteus	.775	1.000	**.000**	**.039**	1.000	.057	.940	.996	.989	.404	.869
	Soleus	.963	1.000	**.000**	**.022**	.953	.054	.621	.999	1.000	.901	.993
	VAT	.818	1.000	.995	.928	**.009**	.615	.469	.976	.987	.055	.208

		p value										
		Sphingomyelins										
		SM(d16:1/23:0)/ SM(d17:1/22:0)	SM(d18:0/22:0)	SM(d18:1/22:0)/ SM(d16:1/24:0)	SM(d16:1/24:1)	SM(d18:2/22:0)	SM(40:3) (a)	SM(40:3) (b)	SM(41:0)	SM(41:1) (a)	SM(d18:1/23:0)/ SM(d17:1/24:0)	SM(d17:1/24:1)
Liver	Heart	**.000**	**.048**	**.027**	**.000**	**.005**	.789	**.004**	**.000**	**.000**	**.000**	**.013**
	Kidney	.452	.972	**.009**	**.000**	**.000**	**.040**	.559	**.000**	**.000**	**.000**	.095
	Gluteus	**.000**	**.002**	**.000**	**.000**	.823	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.007**	.429	**.000**	**.000**	.943	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.001**	**.000**	**.000**	.949	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.008**	.105	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Heart	Liver	**.000**	**.048**	**.027**	**.000**	**.005**	.789	**.004**	**.000**	**.000**	**.000**	**.013**
	Kidney	**.000**	**.007**	**.000**	.836	**.000**	**.001**	.440	**.000**	**.009**	**.001**	.998
	Gluteus	**.000**	.829	**.000**	**.000**	**.000**	**.000**	**.014**	.071	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.001**	**.007**	**.001**	**.001**	**.031**	.976	**.000**	**.014**	**.000**
	VAT	**.000**	.752	**.000**	**.000**	**.000**	**.000**	**.000**	.050	**.000**	**.000**	**.000**
	SAT	**.000**	1.000	**.001**	.066	**.027**	**.000**	**.000**	.927	**.000**	.154	**.000**
Kidney	Liver	.452	.972	**.009**	**.000**	**.000**	**.040**	.559	**.000**	**.000**	**.000**	.095
	Heart	**.000**	**.007**	**.000**	.836	**.000**	**.001**	.440	**.000**	**.009**	**.001**	.998
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.090	**.000**	**.000**
	Soleus	**.000**	.929	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	.309	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.074	**.000**	**.000**
	SAT	**.000**	**.021**	**.000**	**.004**	**.000**	**.000**	**.000**	**.000**	.625	**.000**	**.000**
Gluteus	Liver	**.000**	**.002**	**.000**	**.000**	.823	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.829	**.000**	**.000**	**.000**	**.000**	**.014**	.071	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.090	**.000**	**.000**
	Soleus	.959	**.000**	.841	.975	1.000	.995	1.000	**.018**	.999	.966	.878
	VAT	1.000	1.000	1.000	1.000	1.000	.566	**.015**	1.000	1.000	1.000	1.000
	SAT	.943	.882	.849	.647	.804	1.000	.281	.666	.943	.521	.419
Soleus	Liver	**.007**	.429	**.000**	**.000**	.943	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	**.000**	**.001**	**.007**	**.001**	**.001**	**.031**	.976	**.000**	**.014**	**.000**
	Kidney	**.000**	.929	**.000**	**.000**	**.000**	**.000**	**.000**	**.001**	.309	**.000**	**.000**
	Gluteus	.959	**.000**	.841	.975	1.000	.995	1.000	**.018**	.999	.966	.878
	VAT	.853	**.000**	.858	.973	1.000	.233	**.015**	**.012**	.998	.981	.772
	SAT	1.000	**.001**	1.000	.988	.924	.983	.259	.562	.999	.972	.988
VAT	Liver	**.000**	**.001**	**.000**	**.000**	.949	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	.752	**.000**	**.000**	**.000**	**.000**	**.000**	.050	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.074	**.000**	**.000**
	Gluteus	1.000	1.000	1.000	1.000	1.000	.566	**.015**	1.000	1.000	1.000	1.000
	Soleus	.853	**.000**	.858	.973	1.000	.233	**.015**	**.012**	.998	.981	.772
	SAT	.819	.828	.865	.621	.932	.737	.934	.616	.937	.569	.286
SAT	Liver	**.008**	.105	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Heart	**.000**	1.000	**.001**	.066	**.027**	**.000**	**.000**	.927	**.000**	.154	**.000**
	Kidney	**.000**	**.021**	**.000**	**.004**	**.000**	**.000**	**.000**	**.000**	.625	**.000**	**.000**
	Gluteus	.943	.882	.849	.647	.804	1.000	.281	.666	.943	.521	.419
	Soleus	1.000	**.001**	1.000	.988	.924	.983	.259	.562	.999	.972	.988
	VAT	.819	.828	.865	.621	.932	.737	.934	.616	.937	.569	.286

		p value										
		Sphingomyelins										
		SM(d18:2/23:0)	SM(d18:1/24:0)	SM(d18:1/24:1)	SM(d18:2/24:0)	SM(43:1)	SM(d19:1/24:1)	SM(43:2) (b)	SM(43:2) (c)	SM(44:1)	SM(44:2)	SM(44:3)
Liver	Heart	**.030**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	.164	.121	**.000**	1.000
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	.841	.460	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.025**	**.000**	**.000**	.859	**.000**	**.000**	**.000**	**.000**	**.003**	**.000**	**.000**
	Soleus	.095	**.000**	**.000**	.926	**.000**	**.000**	**.000**	**.000**	**.013**	**.000**	**.004**
	VAT	.352	**.000**	**.000**	.933	**.000**	**.000**	**.000**	**.001**	**.002**	**.000**	**.000**
	SAT	.916	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	.588	**.008**	**.000**	.061
Heart	Liver	**.030**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	.164	.121	**.000**	1.000
	Kidney	.084	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	.618	**.031**	.939	.373	.628	**.000**	.074	.709	.168	**.000**
	Soleus	**.000**	.937	.921	.974	.679	1.000	**.019**	.220	.896	.589	**.004**
	VAT	**.000**	.530	**.008**	.979	.248	**.046**	**.002**	.454	.621	.125	**.000**
	SAT	.548	.915	.710	1.000	.684	1.000	.985	.998	.833	.564	.061
Kidney	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.841	.460	**.000**	**.000**	**.000**	**.000**
	Heart	.084	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	SAT	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
Gluteus	Liver	**.025**	**.000**	**.000**	.859	**.000**	**.000**	**.000**	**.000**	**.003**	**.000**	**.000**
	Heart	**.000**	.618	**.031**	.939	.373	.628	**.000**	.074	.709	.168	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Soleus	1.000	.998	.482	1.000	1.000	.891	.918	1.000	1.000	.995	.832
	VAT	.863	1.000	1.000	1.000	1.000	.853	.993	.950	1.000	1.000	1.000
	SAT	**.003**	.999	.748	.975	1.000	.769	**.011**	**.042**	1.000	.996	.266
Soleus	Liver	.095	**.000**	**.000**	.926	**.000**	**.000**	**.000**	**.000**	**.013**	**.000**	**.004**
	Heart	**.000**	.937	.921	.974	.679	1.000	**.019**	.220	.896	.589	**.004**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	1.000	.998	.482	1.000	1.000	.891	.918	1.000	1.000	.995	.832
	VAT	.981	.996	.265	1.000	.998	.195	.999	.997	1.000	.991	.907
	SAT	**.013**	1.000	1.000	.990	1.000	1.000	.204	.124	1.000	1.000	.965
VAT	Liver	.352	**.000**	**.000**	.933	**.000**	**.000**	**.000**	**.001**	**.002**	**.000**	**.000**
	Heart	**.000**	.530	**.008**	.979	.248	**.046**	**.002**	.454	.621	.125	**.000**
	Kidney	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	.863	1.000	1.000	1.000	1.000	.853	.993	.950	1.000	1.000	1.000
	Soleus	.981	.996	.265	1.000	.998	.195	.999	.997	1.000	.991	.907
	SAT	.059	.998	.510	.994	.998	.113	**.045**	.272	1.000	.993	.341
SAT	Liver	.916	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	.588	**.008**	**.000**	.061
	Heart	.548	.915	.710	1.000	.684	1.000	.985	.998	.833	.564	.061
	Kidney	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**
	Gluteus	**.003**	.999	.748	.975	1.000	.769	**.011**	**.042**	1.000	.996	.266
	Soleus	**.013**	1.000	1.000	.990	1.000	1.000	.204	.124	1.000	1.000	.965
	VAT	.059	.998	.510	.994	.998	.113	**.045**	.272	1.000	.993	.341

		p value													
		Monohexosylceramides													
		Hex1Cer (d16:1/18:0)	Hex1Cer (d16:1/20:0)	Hex1Cer(d 16:1/22:0)	Hex1Cer(d 16:1/24:0)	Hex1Cer(d 18:1/16:0)	Hex1Cer(d 18:1/18:0)	Hex1Cer(d 18:1/20:0)	Hex1Cer(d 18:1/22:0)	Hex1Cer(d 18:1/24:0)	Hex1Cer(d 18:1/24:1)	Hex1Cer(d 18:2/18:0)	Hex1Cer(d 18:2/20:0)	Hex1Cer(d 18:2/22:0)	Hex1Cer(d 18:2/24:0)
Liver	Heart	.970	1.000	1.000	**.003**	**.000**	.482	.978	**.013**	**.000**	.565	1.000	.898	.999	.916
	Kidney	1.000	1.000	1.000	**.004**	.349	1.000	1.000	.168	.204	1.000	.621	**.000**	**.000**	**.000**
	Gluteus	.993	.258	1.000	.103	**.000**	.087	.206	**.011**	**.000**	.584	1.000	.991	.978	.911
	Soleus	1.000	1.000	.940	**.036**	**.000**	**.000**	**.000**	**.049**	.393	**.000**	**.025**	**.000**	**.000**	**.000**
	VAT	1.000	.975	.985	**.010**	**.000**	**.000**	.095	**.005**	**.000**	.418	.998	.993	.976	.909
	SAT	.966	1.000	1.000	.115	**.000**	.442	1.000	.346	**.035**	1.000	.999	1.000	.970	.981
Heart	Liver	.970	1.000	1.000	**.003**	**.000**	.482	.978	**.013**	**.000**	.565	1.000	.898	.999	.916
	Kidney	.992	1.000	.999	1.000	**.000**	.681	.898	.982	.363	.599	.755	**.000**	**.000**	**.000**
	Gluteus	1.000	.149	1.000	.940	.963	.935	.656	1.000	1.000	1.000	1.000	.541	1.000	1.000
	Soleus	.996	1.000	.988	.999	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.043**	**.000**	**.000**	**.000**
	VAT	.973	.902	.999	1.000	.989	.092	.437	.999	1.000	1.000	.989	.535	1.000	1.000
	SAT	.596	1.000	1.000	.966	.662	1.000	.997	.932	.916	.557	.992	.993	.843	.532
Kidney	Liver	1.000	1.000	1.000	**.004**	.349	1.000	1.000	.168	.204	1.000	.621	**.000**	**.000**	**.000**
	Heart	.992	1.000	.999	1.000	**.000**	.681	.898	.982	.363	.599	.755	**.000**	**.000**	**.000**
	Gluteus	.999	.225	1.000	.912	**.000**	.179	.132	.936	.291	.611	.573	**.000**	**.000**	**.000**
	Soleus	1.000	1.000	.902	.998	**.000**	**.000**	**.001**	**.000**	**.002**	**.000**	.657	.969	**.016**	.439
	VAT	1.000	.942	.965	1.000	**.000**	**.002**	.059	.885	.218	.456	.347	**.000**	**.000**	**.000**
	SAT	.949	1.000	1.000	.946	**.000**	.616	.998	1.000	.979	1.000	.428	**.000**	**.007**	**.000**
Gluteus	Liver	.993	.258	1.000	.103	**.000**	.087	.206	**.011**	**.000**	.584	1.000	.991	.978	.911
	Heart	1.000	.149	1.000	.940	.963	.935	.656	1.000	1.000	1.000	1.000	.541	1.000	1.000
	Kidney	.999	.225	1.000	.912	**.000**	.179	.132	.936	.291	.611	.573	**.000**	**.000**	**.000**
	Soleus	.999	.339	.950	.998	.949	**.000**	**.000**	**.000**	**.000**	**.000**	**.026**	**.000**	**.000**	**.000**
	VAT	.994	.779	.988	.988	1.000	.672	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	SAT	.749	.438	1.000	1.000	.221	.991	.406	.851	.840	.568	1.000	.951	.667	.543
Soleus	Liver	1.000	1.000	.940	**.036**	**.000**	**.000**	**.000**	**.049**	.393	**.000**	**.025**	**.000**	**.000**	**.000**
	Heart	.996	1.000	.988	.999	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.043**	**.000**	**.000**	**.000**
	Kidney	1.000	1.000	.902	.998	**.000**	**.000**	**.001**	**.000**	**.002**	**.000**	.657	.969	**.016**	.439
	Gluteus	.999	.339	.950	.998	.949	**.000**	**.000**	**.000**	**.000**	**.000**	**.026**	**.000**	**.000**	**.000**
	VAT	1.000	.979	1.000	1.000	.980	**.000**	**.000**	**.000**	**.000**	**.000**	**.009**	**.000**	**.000**	**.000**
	SAT	.949	1.000	.970	.999	.828	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	**.000**	**.000**	**.000**
VAT	Liver	1.000	.975	.985	**.010**	**.000**	**.000**	.095	**.005**	**.000**	.418	.998	.993	.976	.909
	Heart	.973	.902	.999	1.000	.989	.092	.437	.999	1.000	1.000	.989	.535	1.000	1.000
	Kidney	1.000	.942	.965	1.000	**.000**	**.002**	.059	.885	.218	.456	.347	**.000**	**.000**	**.000**
	Gluteus	.994	.779	.988	.988	1.000	.672	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	Soleus	1.000	.979	1.000	1.000	.980	**.000**	**.000**	**.000**	**.000**	**.000**	**.009**	**.000**	**.000**	**.000**
	SAT	.971	.994	.994	.995	.282	.275	.242	.773	.777	.422	1.000	.956	.644	.529
SAT	Liver	.966	1.000	1.000	.115	**.000**	.442	1.000	.346	**.035**	1.000	.999	1.000	.970	.981
	Heart	.596	1.000	1.000	.966	.662	1.000	.997	.932	.916	.557	.992	.993	.843	.532
	Kidney	.949	1.000	1.000	.946	**.000**	.616	.998	1.000	.979	1.000	.428	**.000**	**.007**	**.000**
	Gluteus	.749	.438	1.000	1.000	.221	.991	.406	.851	.840	.568	1.000	.951	.667	.543
	Soleus	.949	1.000	.970	.999	.828	**.000**	**.000**	**.000**	**.000**	**.000**	**.017**	**.000**	**.000**	**.000**
	VAT	.971	.994	.994	.995	.282	.275	.242	.773	.777	.422	1.000	.956	.644	.529

		p value															
		Dihexosylceramides										*Trihexosylceramides*					
		Hex2Cer(d 16:1/16:0)	Hex2Cer(d 16:1/24:1)	Hex2Cer(d 18:1/16:0)	Hex2Cer(d 18:1/18:0)	Hex2Cer(d 18:1/20:0)	Hex2Cer(d 18:1/22:0)	Hex2Cer(d 18:1/24:0)	Hex2Cer(d 18:1/24:1)	Hex2Cer(d 18:2/16:0)	Hex2Cer(d 18:2/24:1)	Hex3Cer(d 18:1/16:0)	Hex3Cer(d 18:1/18:0)	Hex3Cer(d 18:1/20:0)	Hex3Cer(d 18:1/22:0)	Hex3Cer(d 18:1/24:0)	Hex3Cer(d 18:1/24:1)
Liver	Heart	.801	.998	**.006**	1.000	**.000**	**.000**	**.009**	**.024**	.999	**.000**	1.000	.963	1.000	.993	1.000	1.000
	Kidney	.855	.974	.650	.984	1.000	.055	**.006**	**.006**	.989	.166	.986	.903	.993	.919	1.000	.874
	Gluteus	.696	.982	**.000**	1.000	1.000	**.004**	**.000**	**.000**	.907	1.000	.998	1.000	.995	1.000	.883	1.000
	Soleus	.904	.864	**.000**	**.000**	.687	.074	**.000**	**.043**	.980	.898	.999	.941	.992	.967	.325	.999
	VAT	.997	.965	**.000**	1.000	.832	**.000**	**.000**	**.000**	1.000	.999	.859	.999	.996	.998	.857	1.000
	SAT	1.000	.954	**.000**	.831	.958	**.000**	**.000**	**.000**	.991	.920	.923	.125	.957	.985	.536	.381
Heart	Liver	.801	.998	**.006**	1.000	**.000**	**.000**	**.009**	**.024**	.999	**.000**	1.000	.963	1.000	.993	1.000	1.000
	Kidney	1.000	1.000	.448	.986	**.000**	**.000**	1.000	.990	.882	**.000**	.922	1.000	.991	.999	1.000	.902
	Gluteus	.081	1.000	.660	1.000	**.000**	**.000**	**.005**	.522	.665	**.000**	1.000	.957	.997	.999	.799	1.000
	Soleus	1.000	.985	.800	**.000**	**.000**	**.000**	.175	1.000	1.000	**.000**	1.000	.501	.994	.727	.241	.998
	VAT	.468	1.000	**.020**	1.000	**.000**	**.000**	**.000**	**.001**	.984	**.000**	.965	.999	.994	1.000	.762	.999
	SAT	.657	.763	.410	.840	**.000**	**.000**	**.000**	**.020**	.903	**.000**	.789	.527	.950	1.000	.648	.422
Kidney	Liver	.855	.974	.650	.984	1.000	.055	**.006**	**.006**	.989	.166	.986	.903	.993	.919	1.000	.874
	Heart	1.000	1.000	.448	.986	**.000**	**.000**	1.000	.990	.882	**.000**	.922	1.000	.991	.999	1.000	.902
	Gluteus	.122	1.000	**.022**	.996	1.000	.966	**.025**	.936	1.000	.268	.877	.897	.875	.971	.935	.907
	Soleus	1.000	1.000	**.047**	**.000**	.731	1.000	.391	.998	.764	.893	.920	.404	.859	.498	.437	.688
	VAT	.557	1.000	**.000**	.979	.874	.101	**.000**	**.013**	.999	.401	.454	.991	1.000	.997	.920	.714
	SAT	.722	.598	**.010**	.998	.970	.317	**.000**	.151	1.000	.868	1.000	.749	1.000	1.000	.546	.978
Gluteus	Liver	.696	.982	**.000**	1.000	1.000	**.004**	**.000**	**.000**	.907	1.000	.998	1.000	.995	1.000	.883	1.000
	Heart	.081	1.000	.660	1.000	**.000**	**.000**	**.005**	.522	.665	**.000**	1.000	.957	.997	.999	.799	1.000
	Kidney	.122	1.000	**.022**	.996	1.000	.966	**.025**	.936	1.000	.268	.877	.897	.875	.971	.935	.907
	Soleus	.172	.999	1.000	**.000**	.775	.973	.904	.713	.534	.948	1.000	.970	1.000	.945	.959	.999
	VAT	.953	1.000	.662	1.000	.837	.536	.087	.179	.980	1.000	.993	.999	.890	1.000	1.000	1.000
	SAT	.937	.633	.999	.914	.955	.845	.401	.697	1.000	.962	.729	.142	.748	.997	.090	.456
Soleus	Liver	.904	.864	**.000**	**.000**	.687	.074	**.000**	**.043**	.980	.898	.999	.941	.992	.967	.325	.999
	Heart	1.000	.985	.800	**.000**	**.000**	**.000**	.175	1.000	1.000	**.000**	1.000	.501	.994	.727	.241	.998
	Kidney	1.000	1.000	**.047**	**.000**	.731	1.000	.391	.998	.764	.893	.920	.404	.859	.498	.437	.688
	Gluteus	.172	.999	1.000	**.000**	.775	.973	.904	.713	.534	.948	1.000	.970	1.000	.945	.959	.999
	VAT	.646	1.000	.600	**.000**	.108	.132	**.005**	**.004**	.929	.990	.990	.786	.874	.813	.956	1.000
	SAT	.787	.394	.997	**.000**	.248	.364	**.049**	.059	.795	1.000	.798	**.022**	.731	.706	**.011**	.244
VAT	Liver	.997	.965	**.000**	1.000	.832	**.000**	**.000**	**.000**	1.000	.999	.859	.999	.996	.998	.857	1.000
	Heart	.468	1.000	**.020**	1.000	**.000**	**.000**	**.000**	**.001**	.984	**.000**	.965	.999	.994	1.000	.762	.999
	Kidney	.557	1.000	**.000**	.979	.874	.101	**.000**	**.013**	.999	.401	.454	.991	1.000	.997	.920	.714
	Gluteus	.953	1.000	.662	1.000	.837	.536	.087	.179	.980	1.000	.993	.999	.890	1.000	1.000	1.000
	Soleus	.646	1.000	.600	**.000**	.108	.132	**.005**	**.004**	.929	.990	.990	.786	.874	.813	.956	1.000
	SAT	1.000	.553	.922	.814	1.000	1.000	.996	.985	1.000	.994	.302	.309	1.000	1.000	.071	.241
SAT	Liver	1.000	.954	**.000**	.831	.958	**.000**	**.000**	**.000**	.991	.920	.923	.125	.957	.985	.536	.381
	Heart	.657	.763	.410	.840	**.000**	**.000**	**.000**	**.020**	.903	**.000**	.789	.527	.950	1.000	.648	.422
	Kidney	.722	.598	**.010**	.998	.970	.317	**.000**	.151	1.000	.868	1.000	.749	1.000	1.000	.546	.978
	Gluteus	.937	.633	.999	.914	.955	.845	.401	.697	1.000	.962	.729	.142	.748	.997	.090	.456
	Soleus	.787	.394	.997	**.000**	.248	.364	**.049**	.059	.795	1.000	.798	**.022**	.731	.706	**.011**	.244
	VAT	1.000	.553	.922	.814	1.000	1.000	.996	.985	1.000	.994	.302	.309	1.000	1.000	.071	.241

		p value													
		Gangliosides								*Sulfatides*					
		GM1(d 18:1/16:0)	GM3(d 18:1/16:0)	GM3(d 18:1/18:0)	GM3(d 18:1/20:0)	GM3(d 18:1/22:0)	GM3(d 18:1/24:0)	GM3(d 18:1/24:1)	GM3(d 18:2/24:1)	(d18:1:/16:0 (OH))	(d18:1:/16:0)	(d18:1:/24:0 (OH))	(d18:1:/24:0)	(d18:1:/24:1 (OH))	(d18:1:/24:1)
Liver	Heart	.248	**.001**	**.042**	**.000**	**.000**	.139	.309	**.000**	.211	1.000	1.000	1.000	.999	1.000
	Kidney	.695	**.006**	1.000	.997	.758	.185	.146	**.010**	.935	**.000**	**.000**	.902	**.000**	.999
	Gluteus	.547	**.000**	**.001**	.694	**.000**	**.000**	**.000**	1.000	.746	.998	1.000	1.000	.984	1.000
	Soleus	.483	**.000**	**.000**	.999	**.003**	**.000**	**.000**	.999	.153	.607	.063	**.000**	**.002**	**.000**
	VAT	.445	**.000**	.303	.459	**.000**	**.000**	**.000**	1.000	**.040**	.944	1.000	1.000	.654	1.000
	SAT	1.000	**.001**	.543	.817	**.031**	**.000**	**.000**	**.004**	.540	1.000	1.000	.777	.998	1.000
Heart	Liver	.248	**.001**	**.042**	**.000**	**.000**	.139	.309	**.000**	.211	1.000	1.000	1.000	.999	1.000
	Kidney	.996	**.000**	**.031**	**.000**	**.000**	1.000	.998	**.025**	**.026**	**.000**	**.000**	.863	**.000**	.995
	Gluteus	1.000	**.000**	.684	**.000**	**.000**	**.000**	**.000**	**.000**	.986	1.000	1.000	1.000	1.000	1.000
	Soleus	1.000	**.013**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.402	.085	**.000**	**.000**	**.000**
	VAT	1.000	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.981	.993	1.000	1.000	.904	1.000
	SAT	.404	.986	**.001**	**.000**	**.000**	**.000**	**.000**	.114	1.000	1.000	1.000	.722	1.000	.998
Kidney	Liver	.695	**.006**	1.000	.997	.758	.185	.146	**.010**	.935	**.000**	**.000**	.902	**.000**	.999
	Heart	.996	**.000**	**.031**	**.000**	**.000**	1.000	.998	**.025**	**.026**	**.000**	**.000**	.863	**.000**	.995
	Gluteus	1.000	**.000**	**.001**	.412	**.006**	**.000**	**.000**	**.007**	.216	**.000**	**.000**	.916	**.000**	.996
	Soleus	1.000	**.000**	**.000**	1.000	.172	**.000**	**.001**	.078	**.021**	**.025**	**.005**	**.000**	**.031**	**.000**
	VAT	1.000	**.000**	.571	.228	**.007**	**.000**	**.000**	**.023**	**.004**	**.000**	**.000**	.800	**.000**	.984
	SAT	.808	**.000**	.782	.549	.573	**.000**	**.000**	.999	.124	**.000**	**.000**	1.000	**.000**	1.000
Gluteus	Liver	.547	**.000**	**.001**	.694	**.000**	**.000**	**.000**	1.000	.746	.998	1.000	1.000	.984	1.000
	Heart	1.000	**.000**	.684	**.000**	**.000**	**.000**	**.000**	**.000**	.986	1.000	1.000	1.000	1.000	1.000
	Kidney	1.000	**.000**	**.001**	.412	**.006**	**.000**	**.000**	**.007**	.216	**.000**	**.000**	.916	**.000**	.996
	Soleus	1.000	.972	**.000**	.522	.898	.457	.274	.988	.925	.352	.103	**.000**	**.000**	**.000**
	VAT	1.000	.997	**.000**	1.000	1.000	1.000	1.000	.998	.728	.999	1.000	1.000	.987	1.000
	SAT	.687	**.014**	**.000**	1.000	.466	.198	.413	**.003**	1.000	1.000	1.000	.804	1.000	.998
Soleus	Liver	.483	**.000**	**.000**	.999	**.003**	**.000**	**.000**	.999	.153	.607	.063	**.000**	**.002**	**.000**
	Heart	1.000	**.013**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.402	.085	**.000**	**.000**	**.000**
	Kidney	1.000	**.000**	**.000**	1.000	.172	**.000**	**.001**	.078	**.021**	**.025**	**.005**	**.000**	**.031**	**.000**
	Gluteus	1.000	.972	**.000**	.522	.898	.457	.274	.988	.925	.352	.103	**.000**	**.000**	**.000**
	VAT	1.000	1.000	**.000**	.323	.945	.302	.107	1.000	1.000	.149	.062	**.000**	**.000**	**.000**
	SAT	.620	.154	**.000**	.652	.990	.999	1.000	**.035**	.992	.634	.227	**.000**	**.001**	**.000**
VAT	Liver	.445	**.000**	.303	.459	**.000**	**.000**	**.000**	1.000	**.040**	.944	1.000	1.000	.654	1.000
	Heart	1.000	**.002**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.981	.993	1.000	1.000	.904	1.000
	Kidney	1.000	**.000**	.571	.228	**.007**	**.000**	**.000**	**.023**	**.004**	**.000**	**.000**	.800	**.000**	.984
	Gluteus	1.000	.997	**.000**	1.000	1.000	1.000	1.000	.998	.728	.999	1.000	1.000	.987	1.000
	Soleus	1.000	1.000	**.000**	.323	.945	.302	.107	1.000	1.000	.149	.062	**.000**	**.000**	**.000**
	SAT	.603	**.044**	1.000	1.000	.547	.109	.186	**.009**	.931	.983	.999	.649	.959	.992
SAT	Liver	1.000	**.001**	.543	.817	**.031**	**.000**	**.000**	**.004**	.540	1.000	1.000	.777	.998	1.000
	Heart	.404	.986	**.001**	**.000**	**.000**	**.000**	**.000**	.114	1.000	1.000	1.000	.722	1.000	.998
	Kidney	.808	**.000**	.782	.549	.573	**.000**	**.000**	.999	.124	**.000**	**.000**	1.000	**.000**	1.000
	Gluteus	.687	**.014**	**.000**	1.000	.466	.198	.413	**.003**	1.000	1.000	1.000	.804	1.000	.998
	Soleus	.620	.154	**.000**	.652	.990	.999	1.000	**.035**	.992	.634	.227	**.000**	**.001**	**.000**
	VAT	.603	**.044**	1.000	1.000	.547	.109	.186	**.009**	.931	.983	.999	.649	.959	.992

p values < 0.05 are represented in bold numbers.

8.3.5. Sterol lipids

Table S20. Sterol lipid species concentration detected by targeted lipidomic analysis in all the studied tissues. Lipid species detected were cholesterol, 6 desmosterol, 10 hydroxycholesterol, 27 cholesteryl esters and 2 oxidized CE.

Lipid species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Cholesterol							
COH	5,912±297.3	3,481±349.4	8,819±542.6	1,172±69.38	1,818±230.4	808.0±169.1	2,540±325.9
Desmosterol							
Desmosterol(16:0)	1.05±0.07	0.63±0.04	0.69±0.05	0.53±0.06	0.60±0.03	0.43±0.08	0.41±0.06
Desmosterol(18:1)	3.96±0.27	0.47±0.04	0.57±0.03	0.36±0.03	0.35±0.03	0.24±0.02	0.38±0.03
Desmosterol(18:2)	3.03±0.30	0.62±0.07	0.68±0.12	0.32±0.04	0.20±0.03	0.13±0.02	0.18±0.03
Desmosterol(20:4)	2.46±0.27	1.65±0.23	2.22±0.46	0.23±0.03	0.19±0.02	0.10±0.02	0.16±0.02
Desmosterol(20:5)	8.09±0.25	8.41±0.27	8.84±0.47	7.76±0.15	7.74±0.14	11.34±1.55	9.95±0.93
Desmosterol(22:6)	0.26±0.05	0.22±0.03	0.44±0.10	0.16±0.03	0.13±0.01	0.11±0.02	0.17±0.02
Hydroxycholesterol							
OH-Cholesterol18:0	1.08±0.13	2.06±0.12	2.20±0.19	1.87±0.19	1.39±0.12	0.19±0.05	0.21±0.03
OH-Cholesterol18:1(a)	1.51±0.21	0.26±0.02	0.34±0.03	0.26±0.04	0.21±0.02	0.24±0.03	0.33±0.06
OH-Cholesterol18:1(b)	1.42±0.12	1.31±0.10	1.47±0.07	1.21±0.13	0.81±0.04	0.16±0.03	0.18±0.03
OH-Cholesterol18:2(a)	0.35±0.06	0.26±0.04	0.33±0.07	0.23±0.04	0.16±0.02	0.38±0.09	0.68±0.04
OH-Cholesterol18:2(b)	0.84±0.12	0.25±0.05	0.22±0.01	0.25±0.07	0.18±0.05	0.51±0.17	0.62±0.15
OH-Cholesterol18:2(c)	1.23±0.15	0.28±0.04	0.36±0.04	0.22±0.02	0.23±0.03	0.43±0.12	0.41±0.06
OH-Cholesterol18:2(d)	1.10±0.13	0.26±0.03	0.40±0.03	0.24±0.03	0.19±0.02	0.17±0.02	0.22±0.02
OH-Cholesterol18:2(e)	0.78±0.10	2.80±0.30	2.56±0.23	2.16±0.52	1.29±0.17	0.13±0.05	0.04±0.02
OH-Cholesterol20:4(a)	0.74±0.08	0.26±0.05	0.46±0.05	0.18±0.01	0.17±0.06	0.14±0.03	0.27±0.06
OH-Cholesterol20:4(b)	6.91±0.59	1.98±0.10	2.00±0.11	1.58±0.09	1.47±0.10	2.16±0.38	1.21±0.19
Cholesterylesters							
CE(14:0)	8.14±0.66	12.29±1.03	19.45±1.51	10.29±0.88	7.06±0.95	0.65±0.07	0.73±0.10
CE(15:0)	20.02±1.30	13.63±0.88	16.76±0.97	14.06±0.69	12.70±2.28	2.44±0.38	1.84±0.23
CE(16:0)	374.09±28.03	33.61±3.16	59.99±14.07	14.19±0.80	17.13±1.56	20.19±2.18	40.44±5.75
CE(16:1)	146.02±14.42	20.14±1.47	26.06±2.55	12.67±1.23	9.90±2.10	0.73±0.12	1.08±0.09
CE(16:2)	0.42±0.03	0.44±0.07	0.65±0.08	0.32±0.04	0.18±0.03	0.08±0.01	0.10±0.01
CE(17:0)	41.90±4.60	2.91±0.12	4.29±0.55	2.43±0.13	2.53±0.25	1.68±0.09	2.06±0.22
CE(17:1)	24.39±2.33	2.43±0.21	2.78±0.27	2.26±0.24	2.40±0.63	0.31±0.10	0.40±0.09
CE(18:0)	29.49±4.57	2.13±0.18	5.30±1.21	1.18±0.12	1.41±0.17	5.15±0.85	6.39±0.89
CE(18:1)	1,212±95.92	27.27±2.56	59.65±12.42	13.89±1.22	16.05±1.82	22.60±2.57	45.87±5.86

CE(18:2)	1,250±78.06	90.79±11.06	133.15±27.35	28.95±4.16	29.23±4.44	4.19±0.52	6.19±0.69
CE(18:3)	31.09±1.88	6.28±0.68	9.47±1.86	1.49±0.25	0.96±0.13	0.08±0.01	0.10±0.02
CE(20:1)	7.83±1.17	0.89±0.08	3.63±0.90	0.66±0.05	0.81±0.16	3.64±0.84	4.22±0.63
CE(20:2)	7.21±0.83	0.49±0.04	3.69±1.02	0.41±0.04	0.47±0.12	0.72±0.09	1.06±0.14
CE(20:3)	28.52±2.99	3.54±0.42	21.76±7.44	1.38±0.13	1.59±0.22	0.76±0.13	1.01±0.13
CE(20:4)	699.5±38.06	267.4±31.70	337.5±61.39	13.95±1.89	17.81±1.25	0.41±0.08	0.60±0.11
CE(20:5)	7.79±0.38	2.61±0.20	6.21±1.35	1.05±0.17	0.70±0.11	0.06±0.01	0.06±0.01
CE(22:0)	1.01±0.24	0.60±0.03	0.91±0.07	0.59±0.03	0.67±0.06	0.95±0.10	0.74±0.06
CE(22:1)	1.52±0.35	0.43±0.04	1.24±0.28	0.40±0.03	0.46±0.09	0.70±0.09	0.61±0.07
CE(22:4)	8.10±1.44	1.03±0.17	15.47±4.73	0.28±0.04	0.43±0.08	0.82±0.14	1.81±0.41
CE(22:5)(n3)	1.90±0.20	0.49±0.06	4.16±1.21	0.10±0.01	0.11±0.01	0.05±0.01	0.05±0.01
CE(22:5)(n6)	3.32±0.54	0.88±0.15	16.55±5.71	0.17±0.02	0.16±0.01	0.06±0.01	0.09±0.01
CE(22:6)	10.58±1.37	6.34±0.98	46.02±16.60	0.96±0.19	0.66±0.07	0.05±0.01	0.05±0.01
CE(24:0)	1.95±0.50	1.05±0.06	1.62±0.10	1.03±0.07	1.10±0.12	1.73±0.20	1.23±0.11
CE(24:1)	1.60±0.46	0.66±0.05	1.65±0.29	0.58±0.05	0.66±0.12	1.10±0.14	0.82±0.09
CE(24:4)	4.88±0.72	0.29±0.04	9.27±2.79	0.21±0.02	0.29±0.09	0.19±0.02	0.28±0.08
CE(24:5)	2.83±0.50	0.14±0.03	8.31±2.92	0.04±0.01	0.04±0.01	0.03±0.01	0.04±0.01
CE(24:6)	0.17±0.03	0.04±0.01	2.71±0.80	0.01±0.002	0.02±0.004	0.01±0.002	0.01±0.002
Oxidizedcholesterylesters							
oxCE(18:2)[+2O]	26.09±1.48	20.68±0.73	29.30±2.38	27.76±0.72	26.35±0.89	37.89±5.99	35.97±3.41
oxCE(18:2)[+O]	45.25±5.23	3.46±0.16	4.22±0.29	3.34±0.27	3.05±0.21	4.26±0.89	3.65±0.21

Table S21. Statistic multiple comparison post hoc Tuckey of the sterol lipid species between all the studied tissues.

		p value						
		Cholesterol	*Desmosterol*					
		COH	Desmosterol(16:0)	Desmosterol(18:1)	Desmosterol(18:2)	Desmosterol(20:4)	Desmosterol(20:5)	Desmosterol(22:6)
Liver	Heart	**.000**	**.000**	**.000**	**.000**	.216	1.000	.998
	Kidney	**.000**	**.006**	**.000**	**.000**	.994	.994	.167
	Gluteus	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.778
	Soleus	**.000**	**.001**	**.000**	**.000**	**.000**	1.000	.584
	VAT	**.000**	**.000**	**.000**	**.000**	**.000**	.076	.314
	SAT	**.000**	**.000**	**.000**	**.000**	**.000**	.720	.912
Heart	Liver	**.000**	**.000**	**.000**	**.000**	.216	1.000	.998
	Kidney	**.000**	.994	.998	1.000	.688	1.000	.053
	Gluteus	**.001**	.921	.998	.811	**.004**	.998	.967
	Soleus	**.041**	1.000	.997	.533	**.005**	.998	.864
	VAT	**.000**	.282	.863	.251	**.001**	.144	.638
	SAT	.561	.290	.999	.483	**.004**	.861	.995
Kidney	Liver	**.000**	**.006**	**.000**	**.000**	.994	.994	.167
	Heart	**.000**	.994	.998	1.000	.688	1.000	.053
	Gluteus	**.000**	.638	.942	.716	**.000**	.973	**.008**
	Soleus	**.000**	.970	.942	.444	**.000**	.976	**.004**
	VAT	**.000**	.104	.609	.204	**.000**	.373	**.001**
	SAT	**.000**	.114	.972	.399	**.000**	.976	**.023**
Gluteus	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	1.000	.778
	Heart	**.001**	.921	.998	.811	**.004**	.998	.967
	Kidney	**.000**	.638	.942	.716	**.000**	.973	**.008**
	Soleus	.903	.992	1.000	.999	1.000	1.000	1.000
	VAT	.992	.940	.995	.978	1.000	.060	.994
	SAT	.196	.917	1.000	.998	1.000	.609	1.000
Soleus	Liver	**.000**	**.001**	**.000**	**.000**	**.000**	1.000	.584
	Heart	**.041**	1.000	.997	.533	**.005**	.998	.864
	Kidney	**.000**	.970	.942	.444	**.000**	.976	**.004**
	Gluteus	.903	.992	1.000	.999	1.000	1.000	1.000
	VAT	.506	.605	.997	1.000	1.000	.078	1.000
	SAT	.869	.583	1.000	1.000	1.000	.638	.998
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.076	.314
	Heart	**.000**	.282	.863	.251	**.001**	.144	.638
	Kidney	**.000**	.104	.609	.204	**.000**	.373	**.001**
	Gluteus	.992	.940	.995	.978	1.000	.060	.994
	Soleus	.506	.605	.997	1.000	1.000	.078	1.000
	SAT	**.036**	1.000	.990	1.000	1.000	.920	.975
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.000**	.720	.912
	Heart	.561	.290	.999	.483	**.004**	.861	.995
	Kidney	**.000**	.114	.972	.399	**.000**	.976	**.023**
	Gluteus	.196	.917	1.000	.998	1.000	.609	1.000
	Soleus	.869	.583	1.000	1.000	1.000	.638	.998
	VAT	**.036**	1.000	.990	1.000	1.000	.920	.975

		p value									
		Hydroxycholesterol									
		OH-COH 18:0	OH-COH 18:1 (a)	OH-COH 18:1 (b)	OH-COH 18:2 (a)	OH-COH 18:2 (b)	OH-COH 18:2 (c)	OH-COH 18:2 (d)	OH-COH 18:2 (e)	OH-COH 20:4 (a)	OH-COH 20:4 (b)
Liver	Heart	**.000**	**.000**	.980	.946	**.006**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	**.000**	**.000**	1.000	1.000	**.008**	**.000**	**.000**	**.001**	**.022**	**.000**
	Gluteus	**.007**	**.000**	.764	.846	**.013**	**.000**	**.000**	**.021**	**.000**	**.000**
	Soleus	.791	**.000**	**.002**	.458	**.006**	**.000**	**.000**	.889	**.000**	**.000**
	VAT	**.001**	**.000**	**.000**	1.000	.378	**.000**	**.000**	.631	**.000**	**.000**
	SAT	**.004**	**.000**	**.000**	**.026**	.867	**.000**	**.000**	.587	**.000**	**.000**
Heart	Liver	**.000**	**.000**	.980	.946	**.006**	**.000**	**.000**	**.000**	**.000**	**.000**
	Kidney	.991	.999	.891	.992	1.000	.997	.782	.997	.183	1.000
	Gluteus	.974	1.000	.993	1.000	1.000	1.000	1.000	.702	.971	.981
	Soleus	**.049**	1.000	**.020**	.942	1.000	1.000	.990	**.014**	.962	.950
	VAT	**.000**	1.000	**.000**	.820	.640	.914	.950	**.000**	.777	1.000
	SAT	**.000**	.999	**.000**	**.002**	.314	.960	1.000	**.000**	1.000	.733
Kidney	Liver	**.000**	**.000**	1.000	1.000	**.008**	**.000**	**.000**	**.001**	**.022**	**.000**
	Heart	.991	.999	.891	.992	1.000	.997	.782	.997	.183	1.000
	Gluteus	.741	.999	.573	.955	1.000	.969	.727	.968	**.037**	.982
	Soleus	**.014**	.987	**.001**	.675	1.000	.982	.438	.090	**.041**	.954
	VAT	**.000**	.995	**.000**	.996	.606	.999	.249	**.000**	**.008**	1.000
	SAT	**.000**	1.000	**.000**	**.022**	.299	1.000	.652	**.000**	.352	.759
Gluteus	Liver	**.007**	**.000**	.764	.846	**.013**	**.000**	**.000**	**.021**	**.000**	**.000**
	Heart	.974	1.000	.993	1.000	1.000	1.000	1.000	.702	.971	.981
	Kidney	.741	.999	.573	.955	1.000	.969	.727	.968	**.037**	.982
	Soleus	.351	1.000	.140	.994	1.000	1.000	.998	.456	1.000	1.000
	VAT	**.000**	1.000	**.000**	.673	.724	.780	.987	**.000**	.999	.905
	SAT	**.000**	.999	**.000**	**.001**	.396	.868	1.000	**.000**	.962	.993
Soleus	Liver	.791	**.000**	**.002**	.458	**.006**	**.000**	**.000**	.889	**.000**	**.000**
	Heart	**.049**	1.000	**.020**	.942	1.000	1.000	.990	**.014**	.962	.950
	Kidney	**.014**	.987	**.001**	.675	1.000	.982	.438	.090	**.041**	.954
	Gluteus	.351	1.000	.140	.994	1.000	1.000	.998	.456	1.000	1.000
	VAT	**.000**	1.000	**.001**	.297	.507	.842	1.000	.125	1.000	.836
	SAT	**.000**	.989	**.004**	**.000**	.239	.908	1.000	.123	.953	.999
VAT	Liver	**.001**	**.000**	**.000**	1.000	.378	**.000**	**.000**	.631	**.000**	**.000**
	Heart	**.000**	1.000	**.000**	.820	.640	.914	.950	**.000**	.777	1.000
	Kidney	**.000**	.995	**.000**	.996	.606	.999	.249	**.000**	**.008**	1.000
	Gluteus	**.000**	1.000	**.000**	.673	.724	.780	.987	**.000**	.999	.905
	Soleus	**.000**	1.000	**.001**	.297	.507	.842	1.000	.125	1.000	.836
	SAT	1.000	.996	1.000	.072	.995	1.000	.998	1.000	.781	.540
SAT	Liver	**.004**	**.000**	**.000**	**.026**	.867	**.000**	**.000**	.587	**.000**	**.000**
	Heart	**.000**	.999	**.000**	**.002**	.314	.960	1.000	**.000**	1.000	.733
	Kidney	**.000**	1.000	**.000**	**.022**	.299	1.000	.652	**.000**	.352	.759
	Gluteus	**.000**	.999	**.000**	**.001**	.396	.868	1.000	**.000**	.962	.993
	Soleus	**.000**	.989	**.004**	**.000**	.239	.908	1.000	.123	.953	.999
	VAT	1.000	.996	1.000	.072	.995	1.000	.998	1.000	.781	.540

		p value																	
		Cholesteryl ester																	
		CE(14:0)	CE(15:0)	CE(16:0)	CE(16:1)	CE(16:2)	CE(17:0)	CE(17:1)	CE(18:0)	CE(18:1)	CE(18:2)	CE(18:3)	CE(20:1)	CE(20:2)	CE(20:3)	CE(20:4)	CE(20:5)	CE(22:0)	CE(22:1)
Liver	Heart	**.041**	**.006**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.230	**.005**
	Kidney	**.000**	.530	**.000**	**.000**	.063	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.010**	**.002**	.793	**.000**	.506	.997	.960
	Gluteus	.723	**.025**	**.000**	**.000**	.867	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.259	**.009**
	Soleus	.990	**.005**	**.000**	**.000**	.079	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.572	**.022**
	VAT	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**	1.000	.089
	SAT	**.000**	**.000**	**.000**	**.000**	**.006**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.058	**.000**	**.000**	**.000**	**.000**	.798	.074
Heart	Liver	**.041**	**.006**	**.000**	**.000**	1.000	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.230	**.005**
	Kidney	**.000**	.577	.866	.997	.115	.999	1.000	.956	.999	.987	.531	.217	**.006**	**.007**	.780	**.002**	.647	.118
	Gluteus	.785	1.000	.966	.988	.729	1.000	1.000	1.000	1.000	.920	.108	1.000	1.000	.999	**.000**	.525	1.000	1.000
	Soleus	**.014**	.999	.988	.955	**.043**	1.000	1.000	1.000	1.000	.936	.073	1.000	1.000	1.000	**.000**	.331	1.000	1.000
	VAT	**.000**	**.000**	.994	.414	**.000**	1.000	.824	.958	1.000	.670	**.010**	.181	1.000	.996	**.000**	**.044**	.456	.959
	SAT	**.000**	**.000**	1.000	.533	**.003**	1.000	.894	.867	1.000	.766	**.022**	.098	.994	.999	**.000**	.079	.990	.997
Kidney	Liver	**.000**	.530	**.000**	**.000**	.063	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.010**	**.002**	.793	**.000**	.506	.997	.960
	Heart	**.000**	.577	.866	.997	.115	.999	1.000	.956	.999	.987	.531	.217	**.006**	**.007**	.780	**.002**	.647	.118
	Gluteus	**.000**	.779	.392	.862	**.004**	.998	1.000	.890	.994	.573	**.001**	.197	**.008**	**.004**	**.000**	**.000**	.654	.142
	Soleus	**.000**	.382	.520	.759	**.000**	.999	1.000	.927	.996	.621	**.001**	.291	**.015**	**.007**	**.000**	**.000**	.904	.237
	VAT	**.000**	**.000**	.522	.190	**.000**	.982	.756	1.000	.998	.283	**.000**	1.000	**.016**	**.002**	**.000**	**.000**	1.000	.596
	SAT	**.000**	**.000**	.978	.277	**.000**	.995	.838	1.000	1.000	.385	**.000**	.999	.078	**.005**	**.000**	**.000**	.982	.490
Gluteus	Liver	.723	**.025**	**.000**	**.000**	.867	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.259	**.009**
	Heart	.785	1.000	.966	.988	.729	1.000	1.000	1.000	1.000	.920	.108	1.000	1.000	.999	**.000**	.525	1.000	1.000
	Kidney	**.000**	.779	.392	.862	**.004**	.998	1.000	.890	.994	.573	**.001**	.197	**.008**	**.004**	**.000**	**.000**	.654	.142
	Soleus	.380	.992	1.000	1.000	.683	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	**.000**	**.000**	1.000	.902	.067	1.000	.902	.893	1.000	.999	.985	.166	1.000	1.000	1.000	.909	.476	.956
	SAT	**.000**	**.000**	.914	.937	.172	1.000	.943	.767	.999	1.000	.990	.091	.991	1.000	1.000	.934	.987	.996
Soleus	Liver	.990	**.005**	**.000**	**.000**	.079	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.572	**.022**
	Heart	**.014**	.999	.988	.955	**.043**	1.000	1.000	1.000	1.000	.936	.073	1.000	1.000	1.000	**.000**	.331	1.000	1.000
	Kidney	**.000**	.382	.520	.759	**.000**	.999	1.000	.927	.996	.621	**.001**	.291	**.015**	**.007**	**.000**	**.000**	.904	.237
	Gluteus	.380	.992	1.000	1.000	.683	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	**.002**	**.000**	1.000	.976	.893	1.000	.891	.931	1.000	1.000	.999	.256	1.000	1.000	1.000	.992	.792	.987
	SAT	**.005**	**.000**	.958	.986	.971	1.000	.933	.827	1.000	1.000	.999	.145	.995	1.000	1.000	.994	1.000	.999
VAT	Liver	**.000**	**.000**	**.000**	**.000**	**.001**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	**.007**	**.000**	**.000**	**.000**	**.000**	1.000	.089
	Heart	**.000**	**.000**	.994	.414	**.000**	1.000	.824	.958	1.000	.670	**.010**	.181	1.000	.996	**.000**	**.044**	.456	.959
	Kidney	**.000**	**.000**	.522	.190	**.000**	.982	.756	1.000	.998	.283	**.000**	1.000	**.016**	**.002**	**.000**	**.000**	1.000	.596
	Gluteus	**.000**	**.000**	1.000	.902	.067	1.000	.902	.893	1.000	.999	.985	.166	1.000	1.000	1.000	.909	.476	.956
	Soleus	**.002**	**.000**	1.000	.976	.893	1.000	.891	.931	1.000	1.000	.999	.256	1.000	1.000	1.000	.992	.792	.987
	SAT	1.000	1.000	.970	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000	.939	1.000
SAT	Liver	**.000**	**.000**	**.000**	**.000**	**.006**	**.000**	**.000**	**.000**	**.000**	**.000**	**.000**	.058	**.000**	**.000**	**.000**	**.000**	.798	.074
	Heart	**.000**	**.000**	1.000	.533	**.003**	1.000	.894	.867	1.000	.766	**.022**	.098	.994	.999	**.000**	.079	.990	.997
	Kidney	**.000**	**.000**	.978	.277	**.000**	.995	.838	1.000	1.000	.385	**.000**	.999	.078	**.005**	**.000**	**.000**	.982	.490
	Gluteus	**.000**	**.000**	.914	.937	.172	1.000	.943	.767	.999	1.000	.990	.091	.991	1.000	1.000	.934	.987	.996
	Soleus	**.005**	**.000**	.958	.986	.971	1.000	.933	.827	1.000	1.000	.999	.145	.995	1.000	1.000	.994	1.000	.999
	VAT	1.000	1.000	.970	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.999	1.000	1.000	1.000	1.000	.939	1.000

		p value										
		Cholesteryl esters									*Oxidized CE*	
		CE(22:4)	CE(22:5) (n3)	CE(22:5) (n6)	CE(22:6)	CE(24:0)	CE(24:1)	CE(24:4)	CE(24:5)	CE(24:6)	oxCE (18:2) [+2O]	oxCE (18:2) [+O]
Liver	Heart	.155	.370	.986	.999	.175	.117	.078	.645	1.000	.864	**.000**
	Kidney	.178	**.043**	**.005**	**.012**	.977	1.000	.153	**.042**	**.000**	.992	**.000**
	Gluteus	.129	.183	.963	.954	.218	.114	.107	.676	1.000	1.000	**.000**
	Soleus	.181	.228	.970	.957	.349	.215	.152	.722	1.000	1.000	**.000**
	VAT	.156	.130	.949	.918	.997	.800	.083	.634	1.000	.130	**.000**
	SAT	.396	.198	.966	.943	.558	.429	.150	.722	1.000	.392	**.000**
Heart	Liver	.155	.370	.986	.999	.175	.117	.078	.645	1.000	.864	**.000**
	Kidney	**.000**	**.000**	**.000**	**.003**	.739	.127	**.000**	**.000**	**.000**	.502	1.000
	Gluteus	1.000	.998	1.000	.998	1.000	1.000	1.000	1.000	1.000	.716	1.000
	Soleus	1.000	.999	1.000	.998	1.000	1.000	1.000	1.000	1.000	.897	1.000
	VAT	1.000	.995	1.000	.994	.522	.875	1.000	1.000	1.000	**.006**	1.000
	SAT	1.000	.997	1.000	.996	.999	.999	1.000	1.000	1.000	**.038**	1.000
Kidney	Liver	.178	**.043**	**.005**	**.012**	.977	1.000	.153	**.042**	**.000**	.992	**.000**
	Heart	**.000**	**.000**	**.000**	**.003**	.739	.127	**.000**	**.000**	**.000**	.502	1.000
	Gluteus	**.000**	**.000**	**.001**	**.001**	.762	.120	**.000**	**.001**	**.000**	1.000	1.000
	Soleus	**.001**	**.000**	**.001**	**.002**	.870	.216	**.000**	**.002**	**.000**	.997	1.000
	VAT	**.000**	**.000**	**.000**	**.001**	1.000	.773	**.000**	**.001**	**.000**	.539	1.000
	SAT	**.002**	**.000**	**.001**	**.002**	.966	.417	**.000**	**.002**	**.000**	.840	1.000
Gluteus	Liver	.129	.183	.963	.954	.218	.114	.107	.676	1.000	1.000	**.000**
	Heart	1.000	.998	1.000	.998	1.000	1.000	1.000	1.000	1.000	.716	1.000
	Kidney	**.000**	**.000**	**.001**	**.001**	.762	.120	**.000**	**.001**	**.000**	1.000	1.000
	Soleus	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	1.000	1.000	1.000	1.000	.564	.826	1.000	1.000	1.000	.341	1.000
	SAT	.999	1.000	1.000	1.000	.999	.997	1.000	1.000	1.000	.668	1.000
Soleus	Liver	.181	.228	.970	.957	.349	.215	.152	.722	1.000	1.000	**.000**
	Heart	1.000	.999	1.000	.998	1.000	1.000	1.000	1.000	1.000	.897	1.000
	Kidney	**.001**	**.000**	**.001**	**.002**	.870	.216	**.000**	**.002**	**.000**	.997	1.000
	Gluteus	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000
	VAT	1.000	1.000	1.000	1.000	.715	.924	1.000	1.000	1.000	.244	1.000
	SAT	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.534	1.000
VAT	Liver	.156	.130	.949	.918	.997	.800	.083	.634	1.000	.130	**.000**
	Heart	1.000	.995	1.000	.994	.522	.875	1.000	1.000	1.000	**.006**	1.000
	Kidney	**.000**	**.000**	**.000**	**.001**	1.000	.773	**.000**	**.001**	**.000**	.539	1.000
	Gluteus	1.000	1.000	1.000	1.000	.564	.826	1.000	1.000	1.000	.341	1.000
	Soleus	1.000	1.000	1.000	1.000	.715	.924	1.000	1.000	1.000	.244	1.000
	SAT	1.000	1.000	1.000	1.000	.886	.992	1.000	1.000	1.000	1.000	1.000
SAT	Liver	.396	.198	.966	.943	.558	.429	.150	.722	1.000	.392	**.000**
	Heart	1.000	.997	1.000	.996	.999	.999	1.000	1.000	1.000	**.038**	1.000
	Kidney	**.002**	**.000**	**.001**	**.002**	.966	.417	**.000**	**.002**	**.000**	.840	1.000
	Gluteus	.999	1.000	1.000	1.000	.999	.997	1.000	1.000	1.000	.668	1.000
	Soleus	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	1.000	.534	1.000
	VAT	1.000	1.000	1.000	1.000	.886	.992	1.000	1.000	1.000	1.000	1.000

8.3.6. Prenol lipids

Table S22. Ubiquinone concentration detected by targeted lipidomic analysis in all the studied tissues.

Lipid Species	Liver	Heart	Kidney	Gluteus	Soleus	VAT	SAT
Quinones							
Ubiquinone	238.4 ± 25.87	1,165 ± 67.35	621.8 ± 36.66	55.49 ± 5.78	103.4 ± 15.10	5.82 ± 0.37	6.13 ± 0.40

Table S23. Statistic multiple comparison post hoc Tuckey of the sterol lipid species between all the studied tissues.

		p value
		Quinones
		Ubiquinone
Liver	Heart	.155
	Kidney	.178
	Gluteus	.129
	Soleus	.181
	VAT	.156
	SAT	.396
Heart	Liver	.155
	Kidney	**.000**
	Gluteus	1.000
	Soleus	1.000
	VAT	1.000
	SAT	1.000
Kidney	Liver	.178
	Heart	**.000**
	Gluteus	**.000**
	Soleus	**.001**
	VAT	**.000**
	SAT	**.002**
Gluteus	Liver	.129
	Heart	1.000
	Kidney	**.000**
	Soleus	1.000
	VAT	1.000
	SAT	.999
Soleus	Liver	.181
	Heart	1.000
	Kidney	**.001**
	Gluteus	1.000
	VAT	1.000
	SAT	1.000
VAT	Liver	.156
	Heart	1.000
	Kidney	**.000**
	Gluteus	1.000
	Soleus	1.000
	SAT	1.000
SAT	Liver	.396
	Heart	1.000
	Kidney	**.002**
	Gluteus	.999
	Soleus	1.000
	VAT	1.000

p values < 0.05 are represented in bold numbers.

8.4 Annex 4

This section contains all the information of the unidentified compounds statistically different between old animals and adult animals by a non-parametric t-test of the data obtained in the untargeted lipidomic and metabolomic analysis.

8.4.1. Skeletal muscle

Table S24. Skeletal muscle unidentified lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
183,1609@1,04	184,1609	1,04	-9,57	1,61E-03	down
258,3037@2,85	259,3037	2,85	-6,76	1,52E-03	down
491,4261@6,01	492,4261	6,01	7,01	6,90E-03	up
563,4776@7,42	564,4776	7,42	-6,43	2,07E-02	down
567,6989@7,10	568,6989	7,10	-0,24	3,79E-02	down
580,2376@3,26	581,2376	3,26	5,12	3,41E-02	up
632,8737@0,86	633,8737	0,86	-5,30	3,93E-02	down
641,2933@3,26	642,2933	3,26	7,84	4,42E-04	up
789,2344@6,75	790,2344	6,75	-5,02	3,22E-02	down
831,2318@8,75	832,2318	8,75	-4,74	1,72E-02	down
863,2592@7,20	864,2592	7,20	-6,81	1,64E-03	down
939,5556@6,09	940,5556	6,09	-7,57	5,32E-03	down
996,3211@9,39	997,3211	9,39	-5,74	4,27E-02	down
997,8709@9,93	998,8709	9,93	8,32	6,99E-03	up
1111,367@9,53	1112,367	9,53	-6,76	1,09E-02	down
1408,4012@8,47	1409,4012	8,47	-3,65	4,36E-02	down
1502,397@10,10	1503,397	10,10	5,16	4,87E-02	up
1543,4218@10,10	1544,4218	10,10	-5,47	3,74E-02	down
1589,425@8,95	1590,425	8,95	-4,83	4,77E-02	down

Table S25. Skeletal muscle unidentified metabolites statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
313,2136@7,88	314,2136	7,88	-5,98	3,49E-02	down
393,7182@7,32	394,7182	7,32	5,69	2,27E-02	up
409,3125@12,09	410,3125	12,09	-4,91	3,94E-02	down
415,3579@12,61	416,3579	12,61	-6,02	7,12E-03	down
428,3662@12,72	429,3662	12,72	-7,99	1,62E-02	down
452,1628@8,31	453,1628	8,31	-7,49	1,01E-02	down
460,3646@12,58	461,3646	12,58	-5,95	4,67E-02	down
466,3174@4,92	467,3174	4,92	-3,57	1,88E-02	down
475,834@11,00	476,834	11,00	6,83	1,06E-02	up
497,8481@11,03	498,8481	11,03	-4,41	3,08E-02	down
504,8895@12,40	505,8895	12,40	-7,43	2,97E-03	down
507,5798@12,07	508,5798	12,07	5,76	1,49E-02	up
512,7749@8,18	513,7749	8,18	-6,35	1,81E-02	down
534,558@13,97	535,558	13,97	4,46	2,66E-02	up
578,2897@9,42	579,2897	9,42	6,70	9,56E-03	up
611,5484@13,31	612,5484	13,31	-5,90	4,26E-02	down
613,5633@13,45	614,5633	13,45	-5,20	2,13E-02	down
615,17@8,77	616,17	8,77	5,04	4,85E-02	up
626,4283@7,88	627,4283	7,88	5,14	4,08E-02	up
627,5489@13,46	628,5489	13,46	-5,93	2,49E-02	down
631,6274@13,57	632,6274	13,57	-5,53	2,46E-02	down
657,5014@11,22	658,5014	11,22	5,12	4,03E-02	up
657,5309@13,05	658,5309	13,05	-4,77	4,13E-02	down
668,175@8,77	669,175	8,77	4,72	2,97E-02	up
679,5709@13,51	680,5709	13,51	-6,44	2,61E-02	down
733,563@13,56	734,563	13,56	-6,50	3,23E-02	down
742,5249@11,84	743,5249	11,84	-5,77	2,73E-02	down
755,5475@13,25	756,5475	13,25	-5,88	4,95E-02	down
759,5304@11,05	760,5304	11,05	-4,16	3,87E-02	down
761,6385@13,81	762,6385	13,81	-7,32	9,44E-03	down
783,5773@13,45	784,5773	13,45	-10,46	2,06E-03	down
787,9725@0,80	788,9725	0,80	7,44	2,20E-03	up

815,6989@13,99	816,6989	13,99	-6,52	2,19E-02	down
820,6579@13,99	821,6579	13,99	-4,53	4,44E-02	down
821,4698@12,97	822,4698	12,97	-4,24	4,00E-02	down
821,7952@14,47	822,7952	14,47	7,49	5,39E-03	up
833,6052@11,30	834,6052	11,30	-6,05	3,73E-02	down
851,7934@15,08	852,7934	15,08	-6,79	2,68E-02	down
861,4077@12,89	862,4077	12,89	-6,09	3,32E-02	down
867,731@14,09	868,731	14,09	-9,48	1,46E-03	down
874,7081@14,20	875,7081	14,20	-6,02	4,54E-02	down
902,2889@7,32	903,2889	7,32	-5,97	1,11E-02	down
905,2526@13,64	906,2526	13,64	-6,11	3,14E-02	down
917,7536@14,10	918,7536	14,10	-5,40	2,22E-02	down
947,7046@12,39	948,7046	12,39	-5,90	6,16E-03	down
961,6874@12,18	962,6874	12,18	4,93	2,18E-02	up
971,3284@12,90	972,3284	12,90	5,05	1,25E-02	up
1132,3005@14,12	1133,3005	14,12	-4,11	4,11E-02	down
1169,8306@13,31	1170,8306	13,31	-3,95	1,88E-02	down
1197,8003@13,38	1198,8003	13,38	-5,11	1,53E-02	down
1207,3138@13,31	1208,3138	13,31	-5,41	2,16E-02	down

8.4.2. Adipose tissue

Table S26. Adipose tissue unidentified lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
562.5334@10.34	563.5334	10.34	12.41	4.29E-08	up
833.7834@10.25	834.7834	10.25	9.3	1.35E-03	up
487.4254@6.99	488.4254	6.99	7.58	3.43E-03	up
606.0338@5.04	607.0338	5.04	7.18	5.27E-03	up
429.3731@6.99	430.3731	6.99	4.99	9.78E-03	up
807.7693@10.23	808.7693	10.23	5.93	1.14E-02	up
321.1808@0.81	322.1808	0.81	4.14	1.29E-02	up
804.6664@8.48	804.6664	8.48	-4.08	2.25E-02	down
1159.3853@7.09	1160.3853	7.09	-5.94	2.39E-02	down
1162.2117@7.13	1163.2117	7.13	-5.82	2.63E-02	down
338.2809@7.78	339.2809	7.78	-5.33	2.73E-02	down
709.6694@9.17	710.6694	9.17	-5.93	2.89E-02	down
854.2082@6.29	855.2082	6.29	4.13	2.91E-02	up
683.1965@8.06	684.1965	8.06	4.32	3.41E-02	up
1760.4867@10.31	1761.4867	10.31	-3.72	3.64E-02	down
1373.3467@8.46	1374.3467	8.46	2.88	3.68E-02	up

8.4.3. Kidney

Table S27. Kidney unidentified lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
108.088@0.83	109.088	0.83	8.56	2.40E-02	up
126.0983@0.83	127.0983	0.83	-7.48	3.05E-02	down
271.1728@0.80	272.1728	0.8	10.15	2.64E-03	up
343.2165@0.79	344.2165	0.79	8.65	2.84E-02	up
395.3869@5.26	396.3869	5.26	9.06	3.37E-02	up
431.23@0.80	432.23	0.8	-6.81	4.79E-02	down
626.5172@0.84	627.5172	0.84	-8.87	9.29E-03	down
686.1922@8.07	687.1922	8.07	-7.61	2.61E-02	down
701.2069@5.12	702.2069	5.12	-10.06	4.35E-03	down
702.5582@0.88	703.5582	0.88	-7.2	3.13E-02	down
716.2407@3.26	717.2407	3.26	7.43	2.97E-02	up
833.4248@1.01	834.4248	1.01	10.1	4.95E-03	up
914.81@9.91	915.81	9.91	-9	2.58E-02	down
947.8471@10.05	948.8471	10.05	7.92	2.32E-02	up
960.3313@9.21	961.3313	9.21	7.97	2.80E-02	up
1091.8438@7.18	1092.8438	7.18	7.87	1.03E-02	up
1111.3708@9.53	1112.3708	9.53	-7.92	2.12E-02	down
1135.923@7.71	1136.923	7.71	-8.83	8.98E-03	down
1218.3806@9.78	1219.3806	9.78	-7.89	2.23E-02	down
1428.3749@10.01	1429.3749	10.01	7.07	2.81E-02	up
1612.4502@10.18	1613.4502	10.18	-7.88	1.30E-02	down
1704.4688@9.07	1705.4688	9.07	-8.02	2.87E-02	down

Table S28. Kidney unidentified metabolites statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	LogFC	p value	Old vs Adult
301.291@8.57	302.291	8.57	-16.75	5.79E-04	down
1233.3395@13.27	1234.3395	13.27	-9.27	1.37E-03	down
809.6256@13.48	810.6256	13.48	-17.77	2.02E-03	down
909.5038@14.07	910.5038	14.07	-11.56	4.13E-03	down
590.4992@13.34	591.4992	13.34	-10.13	6.27E-03	down
399.2837@6.21	400.2837	6.21	-11.32	7.08E-03	down
734.5935@13.47	734.5935	13.47	-14.8	9.10E-03	down
751.5833@13.20	752.5833	13.2	-13.71	1.13E-02	down
950.5492@13.25	951.5492	13.25	-9.96	1.15E-02	down
472.078@6.02	473.078	6.02	6.11	1.15E-02	up
751.6068@13.20	752.6068	13.2	11.22	1.52E-02	up
777.0916@10.56	778.0916	10.56	-9.35	1.59E-02	down
276.1407@7.96	277.1407	7.96	6.15	1.97E-02	up
753.5714@13.07	754.5714	13.07	-8.25	2.00E-02	down
736.1945@11.50	737.1945	11.5	7.04	2.11E-02	up
459.2482@7.44	460.2482	7.44	-7.41	2.60E-02	down
381.7217@7.33	382.7217	7.33	-10.65	2.79E-02	down
501.4028@0.55	502.4028	0.55	-5.58	3.22E-02	down
605.3785@11.58	606.3785	11.58	-10.28	3.42E-02	down
809.6344@13.48	810.6344	13.48	12.05	3.47E-02	up
716.5595@12.94	716.5595	12.94	-8.83	3.69E-02	down
297.2689@8.66	298.2689	8.66	-9.61	4.22E-02	down
306.0749@0.46	307.0749	0.46	-9.62	4.43E-02	down
157.1466@7.11	158.1466	7.11	-7.05	4.81E-02	down
850.7687@14.45	851.7687	14.45	-6.98	4.82E-02	down

8.4.4. Heart

Table S29 Heart unidentified lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
926.258@6.76	927.258	6.75	6.03	3.40E-02	up
581.5709@8.78	582.5709	8.77	0.32	3.87E-02	up
1377.449@9.71	1378.449	9.70	0.31	3.14E-02	up
287.1753@0.82	288.1753	0.82	8.16	1.86E-02	up
852.2357@6.29	853.2357	6.28	-7.29	2.54E-02	down
733.7558@6.84	734.7558	6.84	-9.02	1.81E-02	down
946.2794@9.00	947.2794	8.99	-5.87	4.15E-02	down
1130.3109@9.55	1131.3109	9.55	-8.15	1.82E-02	down

Table S30. Heart unidentified metabolites statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
1010.1688@0.65	1011.1688	0.65	9.17	1.01E-02	up
408.7557@10.63	409.7557	10.63	8.05	2.98E-02	up
767.5876@13.13	768.5876	13.13	13.46	2.28E-02	up
775.567@10.91	776.567	10.91	-7.67	1.61E-02	down
791.6091@13.11	792.6091	13.11	10.62	4.43E-02	up
819.5918@10.94	820.5918	10.94	-7.75	2.69E-02	down
832.6721@13.82	833.6721	13.82	9.88	2.03E-02	up
850.7761@14.45	851.7761	14.45	12.9	1.08E-02	up
988.5961@11.49	989.5961	11.49	8.24	2.02E-02	up
247.1432@0.57	248.1432	0.57	-7.47	3.75E-02	down
428.3145@10.49	429.3145	10.49	11.28	1.86E-02	up
442.2286@8.63	443.2286	8.63	-9.05	4.44E-02	down
353.2806@9.05	354.2806	9.05	13.18	2.78E-02	up
445.2418@8.36	446.2418	8.36	9.21	4.05E-02	up
383.27@7.24	384.27	7.24	11.27	2.65E-02	up
615.1426@0.67	616.1426	0.67	11.51	5.65E-03	up
428.4027@12.58	429.4027	12.58	12.58	5.83E-03	up
408.3555@12.11	409.3555	12.11	8.3	2.09E-02	up
646.4276@10.49	647.4276	10.49	9.08	4.04E-02	up
731.5395@10.88	732.5395	10.88	-9.91	9.53E-03	down
515.3669@7.94	516.3669	7.94	-9.72	6.31E-03	down
596.5318@12.87	597.5318	12.87	10.34	9.76E-03	up
608.5417@13.06	609.5417	13.06	8.56	1.89E-02	up

695.4236@11.50	696.4236	11.5	7.3	4.20E-02	up
748.6029@13.82	749.6029	13.82	7.25	4.95E-02	up
693.6841@12.26	694.6841	12.26	-8.42	1.50E-02	down
694.1232@0.65	695.1232	0.65	17.02	1.50E-03	up
218.1757@9.88	219.1757	9.88	9.45	8.96E-03	up
327.9979@7.70	328.9979	7.7	13.38	9.49E-03	up
122.0469@0.94	123.0469	0.94	11.16	4.86E-02	up
548.5126@13.18	549.5126	13.18	11.86	1.45E-02	up

8.4.5. Liver

Table S31. Liver unidentified metabolites statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
262.1598@0.43	263.1598	0.43	-14.51	2.01E-03	down
529.3038@8.30	530.3038	8.3	10.93	2.09E-03	up
848.6875@14.15	849.6875	14.15	13.4	4.25E-03	up
421.7582@13.21	422.7582	13.21	-10.6	9.46E-03	down
709.4009@12.81	710.4009	12.81	-10.67	1.02E-02	down
816.6015@13.85	817.6015	13.85	13.15	1.04E-02	up
415.3583@12.60	416.3583	12.6	11.78	1.14E-02	up
856.7518@14.56	857.7518	14.56	-11.89	1.18E-02	down
452.3658@12.51	453.3658	12.51	11.93	1.22E-02	up
569.4099@10.58	570.4099	10.58	10.84	1.55E-02	up
611.549@13.32	612.549	13.32	9.46	1.58E-02	up
338.2816@13.29	339.2816	13.29	8.93	1.62E-02	up
862.6837@14.34	863.6837	14.34	11.44	2.01E-02	up
706.1887@11.52	707.1887	11.52	8.5	2.41E-02	up
627.4597@10.94	628.4597	10.94	8.05	2.73E-02	up
858.5319@10.94	859.5319	10.94	-10.88	3.25E-02	down
506.8173@11.03	507.8173	11.03	-9.31	3.57E-02	down
666.4002@10.98	667.4002	10.98	-8.19	4.16E-02	down
702.1586@10.58	703.1586	10.58	-8.19	4.29E-02	down
685.7721@11.44	686.7721	11.44	-7.09	4.33E-02	down
364.2419@11.70	365.2419	11.7	-10.07	4.84E-02	up

Table S32. Liver unidentified lipid species statistically different in adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	Log FC	p value	Old vs Adult
1370.3636@8.47	1371.3636	8.47	10.95	9.66E-04	up
865.5448@0.86	866.5448	0.86	-10.1	3.63E-03	down
785.5448@0.88	786.5448	0.88	-9.79	3.80E-03	down
1589.4352@8.94	1590.4352	8.94	8.75	5.51E-03	up
1486.4432@9.31	1487.4432	9.31	8.18	5.86E-03	up
1164.0159@10.95	1165.0159	10.95	10.5	6.60E-03	up
1275.3508@9.81	1276.3508	9.81	-9.33	8.30E-03	down
1363.4149@9.98	1364.4149	9.98	-8.72	8.88E-03	down
766.3055@0.80	767.3055	0.8	12.24	9.05E-03	up
803.5393@0.87	804.5393	0.87	9.07	1.08E-02	up
782.2801@0.81	783.2801	0.81	10.05	1.41E-02	up
1761.4991@9.92	1762.4991	9.92	-8.41	1.56E-02	down
306.1088@0.67	307.1088	0.67	-8.78	3.47E-02	up
1731.4668@9.75	1732.4668	9.75	-8.01	3.73E-02	down
1316.374@9.81	1317.374	9.81	-6.67	3.77E-02	down
598.5027@9.74	599.5027	9.74	-8.74	3.96E-02	down
1216.0583@8.08	1217.0583	8.08	6.79	4.22E-02	up
738.2673@0.76	739.2673	0.76	8.3	4.34E-02	up
403.197@0.82	404.197	0.82	0.18	4.53E-02	up
859.6314@0.84	860.6314	0.84	6.7	4.66E-02	up
1437.4398@10.06	1438.4398	10.06	-7.78	4.80E-02	down
1390.3969@9.92	1391.3969	9.92	-7.53	4.81E-02	down
1335.4022@9.04	1336.4022	9.04	6.74	4.94E-02	up

8.5 Annex 5

This section contains all the information of the unidentified compounds statistically different between the experimental groups (RMet old animals and control animals, old and adult) by a one-way ANOVA of the data obtained in the untargeted lipidomic and metabolomic analysis.

8.5.1. Skeletal muscle

8.5.1.1. Gluteus

Table S33. Gluteus unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	Log FC RMet vs Old	RMet vs Old	Log FC RMet vs Adult	RMet vs Adult
259.3038@2.85	259.3038	2.85	8.48E-03	-0.76	down	-9.75	down
633.8802@0.86	633.8802	0.86	3.95E-02	-3.83	down	-7.75	down
654.7979@3.26	654.7979	3.26	4.47E-02	-7.69	down	-9.9	down
683.5967@9.63	683.5967	9.63	2.02E-02	-2.10	down	-8.47	down
782.5616@0.89	782.5616	0.89	4.35E-02	-6.67	down	-8.81	down
887.5587@6.02	887.5587	6.02	3.88E-02	-3.88	down	-7.92	down
910.7254@9.18	910.7254	9.18	8.84E-04	-0.56	down	-12.12	down
1006.7565@6.89	1006.7565	6.89	2.15E-02	-2.21	down	-8.59	down
1465.4154@10.02	1465.4154	10.02	6.39E-03	-7.80	down	-8.18	down
1705.469@9.07	1705.469	9.07	2.98E-03	-4.86	down	-11.32	down
290.1849@0.79	290.1849	0.79	1.03E-02	-7.17	down	2.24	up
434.7723@0.85	434.7723	0.85	9.54E-03	-12.59	down	-4.89	down
599.3824@1.24	599.3824	1.24	5.31E-03	-10.70	down	-8.27	down
642.298@3.26	642.298	3.26	8.87E-04	-9.00	down	2.19	up
670.3346@0.84	670.3346	0.84	9.46E-03	-11.70	down	-5.29	down
686.4057@0.85	686.4057	0.85	3.26E-02	-8.55	down	-3.14	down
718.4624@0.86	718.4624	0.86	8.93E-04	-8.38	down	0.19	up
855.5078@0.85	855.5078	0.85	4.47E-02	-8.07	down	-6.22	down
974.8684@10.06	974.8684	10.06	1.82E-02	-10.24	down	1.05	up
996.8612@9.76	996.8612	9.76	1.70E-02	-8.41	down	2.54	up
998.8775@9.93	998.8775	9.93	4.22E-02	-9.11	down	0.67	up
1000.8882@10.07	1000.8882	10.07	4.45E-02	-9.11	down	0.85	up
1684.5182@9.89	1684.5182	9.89	1.01E-02	-6.66	down	2.09	up
105.0583@0.83	105.0583	0.83	1.86E-03	0.36	up	0.37	up
429.2431@0.84	429.2431	0.84	4.03E-03	8.02	up	8.15	up
452.4328@8.50	452.4328	8.5	1.24E-02	0.10	up	0.21	up
468.4336@6.55	468.4336	6.55	4.22E-02	0.16	up	0.17	up
480.5413@9.53	480.5413	9.53	5.61E-03	0.14	up	0.31	up
572.4433@7.92	572.4433	7.92	5.60E-03	0.18	up	0.37	up
601.4077@0.84	601.4077	0.84	1.75E-02	2.32	up	9.05	up
680.4739@7.72	680.4739	7.72	2.68E-02	0.20	up	0.22	up
699.5889@8.91	699.5889	8.91	2.89E-03	0.11	up	0.34	up
736.5376@7.72	736.5376	7.72	2.87E-02	0.04	up	0.22	up
928.828@10.08	928.828	10.08	1.44E-02	2.41	up	11.03	up
1040.3112@7.17	1040.3112	7.17	4.22E-02	1.29	up	8.47	up
1043.3036@7.16	1043.3036	7.16	4.13E-02	1.12	up	7.21	up
338.3342@5.27	338.3342	5.27	4.83E-02	10.54	up	8.16	up
819.4713@3.23	819.4713	3.23	5.00E-02	5.41	up	-3.98	down
864.2605@7.20	864.2605	7.2	1.38E-02	3.77	up	-5.71	down
914.7194@7.29	914.7194	7.29	3.60E-02	5.06	up	-3.73	down
940.5551@6.09	940.5551	6.09	3.21E-02	3.89	up	-6.62	down
1094.8627@9.16	1094.8627	9.16	2.11E-02	5.64	up	-4.22	down
1197.415@9.33	1197.415	9.33	3.86E-02	8.99	up	1.42	up
1443.4283@10.04	1443.4283	10.04	2.63E-02	8.15	up	6.72	up
1451.4354@9.18	1451.4354	9.18	2.17E-02	1.93	up	-6.21	down

Table S34. Gluteus unidentified metabolites statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	Log FC RMet vs Old	RMet vs Old	Log FC RMet vs Adult	RMet vs Adult
761.6385@13.80	762.6385	13.8	4.24E-06	4.51	up	-0.33	down
768.6236@13.90	769.6236	13.9	5.92E-06	3.60	up	0.12	up
299.2879@9.19	300.2879	9.19	6.42E-06	-3.50	down	4.49	up
963.7058@12.07	964.7058	12.07	1.87E-05	-2.92	down	3.99	up
867.7296@14.09	868.7296	14.09	3.20E-05	1.65	up	3.49	up
947.7034@12.39	948.7034	12.39	8.60E-05	0.00	down	3.28	up
833.5989@13.52	834.5989	13.52	1.54E-04	-3.14	down	4.19	up
701.4889@10.74	702.4889	10.74	2.01E-04	0.08	up	3.68	up
785.5946@13.66	786.5946	13.66	2.03E-04	0.78	up	4.25	up
1207.3325@13.31	1208.3325	13.31	2.20E-04	4.08	up	-0.88	down
917.7403@14.11	918.7403	14.11	2.46E-04	2.84	up	0.68	up
789.6819@13.94	790.6819	13.94	4.35E-04	0.51	up	3.07	up
1169.8306@13.31	1170.8306	13.31	4.36E-04	2.71	up	0.12	up
796.6463@14.06	797.6463	14.06	4.57E-04	3.18	up	0.12	up
751.5487@13.17	752.5487	13.17	4.81E-04	3.67	up	1.66	up
594.9197@12.43	595.9197	12.43	6.84E-04	-0.64	down	3.40	up
727.5912@12.86	728.5912	12.86	7.44E-04	-3.17	down	3.46	up
787.6035@12.02	788.6035	12.02	7.66E-04	-1.83	down	3.70	up
1028.3434@13.69	1029.3434	13.69	8.18E-04	-3.18	down	2.97	up
776.4254@7.31	777.4254	7.31	1.01E-03	0.11	up	2.57	up
791.5828@13.47	792.5828	13.47	1.13E-03	1.57	up	3.20	up
602.916@12.12	603.916	12.12	1.42E-03	-1.85	down	3.41	up
635.5493@13.22	636.5493	13.22	1.44E-03	0.15	up	3.36	up
781.5632@13.30	782.5632	13.3	1.76E-03	0.25	up	4.08	up
787.5158@12.80	788.5158	12.8	1.97E-03	0.14	up	3.15	up
741.5693@13.49	742.5693	13.49	2.02E-03	0.85	up	3.05	up
717.5698@13.63	718.5698	13.63	2.06E-03	-0.65	down	3.72	up
874.7067@14.20	875.7067	14.2	2.06E-03	2.11	up	2.26	up
653.5621@13.49	654.5621	13.49	2.15E-03	3.94	up	-0.34	down
763.6659@13.91	764.6659	13.91	2.17E-03	0.46	up	2.53	up
817.722@14.11	818.722	14.11	2.28E-03	1.89	up	2.57	up
709.6316@13.73	710.6316	13.73	3.42E-03	3.11	up	0.22	up
679.0546@7.32	680.0546	7.32	3.49E-03	-1.25	down	-2.68	down
537.5198@12.87	538.5198	12.87	3.63E-03	-0.03	down	3.47	up
490.8764@12.07	491.8764	12.07	3.78E-03	-2.52	down	2.37	up
452.1626@8.31	453.1626	8.31	3.82E-03	1.20	up	2.83	up
797.536@13.16	798.536	13.16	3.98E-03	1.42	up	2.95	up
512.7747@8.18	513.7747	8.18	4.10E-03	1.23	up	2.57	up
1192.3083@13.33	1193.3083	13.33	4.25E-03	2.91	up	0.19	up
822.6724@14.11	823.6724	14.11	4.26E-03	1.72	up	2.26	up
586.4624@13.00	587.4624	13	4.30E-03	3.08	up	0.19	up
811.6913@14.07	812.6913	14.07	4.56E-03	0.16	up	-3.07	down
717.5992@13.64	718.5992	13.64	4.75E-03	0.16	up	-2.91	down
631.5637@13.02	632.5637	13.02	4.76E-03	0.16	up	-2.90	down
867.7826@14.09	868.7826	14.09	4.82E-03	0.16	up	-2.87	down
848.6893@14.15	849.6893	14.15	4.83E-03	1.62	up	2.35	up
787.9718@0.80	788.9718	0.8	4.97E-03	0.77	up	-2.74	down
739.701@13.99	740.701	13.99	5.02E-03	0.16	up	-2.74	down
820.6579@13.99	821.6579	13.99	5.03E-03	2.40	up	0.73	up
1049.2373@12.87	1050.2373	12.87	5.19E-03	2.26	up	0.71	up
777.7154@13.98	778.7154	13.98	5.38E-03	0.16	up	-2.53	down
630.7975@1.16	631.7975	1.16	5.38E-03	0.16	up	-2.54	down
339.2535@7.31	340.2535	7.31	5.50E-03	0.22	up	0.57	up
920.2667@7.32	921.2667	7.32	5.91E-03	0.16	up	-2.30	down
446.9093@8.61	447.9093	8.61	6.28E-03	2.49	up	-2.94	down
745.5095@12.98	746.5095	12.98	6.61E-03	1.02	up	3.25	up
1203.804@13.30	1204.804	13.3	6.63E-03	1.78	up	1.91	up
919.4258@13.61	920.4258	13.61	6.65E-03	2.97	up	-0.41	down
507.5794@12.07	508.5794	12.07	6.81E-03	-0.42	down	-2.36	down
715.5169@12.92	716.5169	12.92	6.83E-03	1.54	up	2.48	up
702.5668@13.11	703.5668	13.11	6.83E-03	1.60	up	2.66	up
1218.8069@13.33	1219.8069	13.33	6.84E-03	2.18	up	0.12	up
893.7477@14.15	894.7477	14.15	6.88E-03	3.47	up	0.38	up
699.5245@13.00	700.5245	13	6.92E-03	1.44	up	2.38	up
900.7209@14.26	901.7209	14.26	6.98E-03	-0.09	down	3.40	up
508.8551@11.22	509.8551	11.22	7.64E-03	-0.95	down	-2.30	down
627.5508@13.46	628.5508	13.46	7.73E-03	3.11	up	0.25	up
749.5358@13.03	750.5358	13.03	8.07E-03	1.76	up	2.73	up
1197.7882@13.38	1198.7882	13.38	8.18E-03	2.76	up	0.20	up
758.2095@13.36	759.2095	13.36	8.43E-03	0.04	up	3.24	up
767.5477@13.10	768.5477	13.1	8.46E-03	1.79	up	2.70	up
565.5439@13.07	566.5439	13.07	8.59E-03	1.66	up	2.79	up
726.9978@12.45	727.9978	12.45	8.63E-03	-0.76	down	2.96	up
743.5472@13.12	744.5472	13.12	8.70E-03	1.60	up	2.53	up

504.892@12.40	505.892	12.4	8.86E-03	-0.74	down	2.98	up
791.5469@13.08	792.5469	13.08	9.07E-03	1.69	up	2.64	up
845.4168@12.97	846.4168	12.97	9.18E-03	1.46	up	2.33	up
578.428@12.11	579.428	12.11	9.56E-03	-2.70	down	3.28	up
858.3775@8.31	859.3775	8.31	9.66E-03	0.41	up	2.16	up
889.4192@12.91	890.4192	12.91	9.67E-03	2.20	up	0.70	up
872.1614@11.45	873.1614	11.45	9.82E-03	0.15	up	2.20	up
526.4048@12.41	527.4048	12.41	9.92E-03	-1.55	down	3.22	up
646.9427@12.13	647.9427	12.13	1.00E-02	-1.33	down	2.85	up
850.7038@14.32	851.7038	14.32	1.02E-02	2.37	up	1.74	up
903.6797@12.39	904.6797	12.39	1.06E-02	-1.32	down	3.26	up
783.59@13.45	784.59	13.45	1.10E-02	0.78	up	3.54	up
421.3211@9.37	422.3211	9.37	1.11E-02	2.06	up	1.41	up
479.1218@0.52	480.1218	0.52	1.12E-02	-0.74	down	3.21	up
659.5487@13.19	660.5487	13.19	1.15E-02	0.49	up	2.76	up
876.7212@14.38	877.7212	14.38	1.16E-02	2.26	up	1.77	up
861.4038@12.89	862.4038	12.89	1.16E-02	2.11	up	1.57	up
835.5397@14.07	836.5397	14.07	1.19E-02	1.98	up	1.75	up
638.9462@12.44	639.9462	12.44	1.20E-02	-2.08	down	3.21	up
1007.724@12.08	1008.724	12.08	1.21E-02	-1.26	down	2.84	up
759.5795@13.58	760.5795	13.58	1.24E-02	0.94	up	3.05	up
733.563@13.56	734.563	13.56	1.26E-02	0.82	up	2.77	up
798.6709@14.22	799.6709	14.22	1.29E-02	1.97	up	1.54	up
985.9909@11.44	986.9909	11.44	1.31E-02	2.58	up	-0.35	down
428.3662@12.72	429.3662	12.72	1.37E-02	2.08	up	1.52	up
807.5773@13.37	808.5773	13.37	1.42E-02	0.96	up	2.86	up
675.5201@13.09	676.5201	13.09	1.43E-02	1.67	up	1.33	up
757.5631@13.39	758.5631	13.39	1.45E-02	0.98	up	3.24	up
440.3679@12.74	441.3679	12.74	1.45E-02	1.86	up	1.44	up
865.714@14.00	866.714	14	1.47E-02	2.58	up	0.70	up
843.7325@14.16	844.7325	14.16	1.47E-02	1.86	up	2.08	up
841.7162@14.03	842.7162	14.03	1.53E-02	1.72	up	1.82	up
903.8248@15.19	904.8248	15.19	1.53E-02	-1.62	down	3.90	up
612.475@13.06	613.475	13.06	1.57E-02	2.68	up	0.95	up
905.2522@13.64	906.2522	13.64	1.62E-02	0.86	up	2.53	up
129.1534@1.93	130.1534	1.93	1.71E-02	-1.65	down	3.74	up
835.4383@12.91	836.4383	12.91	1.72E-02	1.28	up	2.11	up
613.5635@13.45	614.5635	13.45	1.75E-02	0.83	up	2.37	up
791.7004@14.07	792.7004	14.07	1.78E-02	1.89	up	1.80	up
728.5732@13.17	729.5732	13.17	1.79E-02	2.04	up	1.60	up
657.9133@11.03	658.9133	11.03	1.81E-02	1.10	up	1.85	up
588.1667@0.53	589.1667	0.53	1.85E-02	-1.80	down	3.00	up
869.7478@14.21	870.7478	14.21	1.89E-02	1.71	up	2.09	up
824.6852@14.26	825.6852	14.26	1.89E-02	1.70	up	1.76	up
459.2652@8.02	460.2652	8.02	1.96E-02	0.58	up	2.54	up
548.4173@12.41	549.4173	12.41	1.98E-02	-1.70	down	2.70	up
611.5483@13.31	612.5483	13.31	2.00E-02	0.86	up	2.32	up
1170.316@13.38	1171.316	13.38	2.06E-02	2.19	up	0.76	up
570.4253@12.42	571.4253	12.42	2.10E-02	-0.13	down	2.88	up
636.9697@12.44	637.9697	12.44	2.11E-02	-1.30	down	2.94	up
749.5875@13.07	750.5875	13.07	2.15E-02	-1.39	down	-2.38	down
737.6522@13.86	738.6522	13.86	2.18E-02	2.83	up	0.37	up
1215.8202@13.30	1216.8202	13.3	2.30E-02	1.04	up	1.76	up
1170.8231@13.38	1171.8231	13.38	2.31E-02	1.70	up	1.42	up
514.8407@11.06	515.8407	11.06	2.31E-02	0.34	up	0.36	up
871.7633@14.38	872.7633	14.38	2.39E-02	1.76	up	2.16	up
742.5249@11.84	743.5249	11.84	2.47E-02	1.17	up	1.96	up
1086.2115@12.87	1087.2115	12.87	2.50E-02	2.07	up	0.17	up
115.0554@0.42	116.0554	0.42	2.50E-02	2.30	up	0.20	up
697.4965@12.72	698.4965	12.72	2.54E-02	0.15	up	0.28	up
895.7622@14.27	896.7622	14.27	2.74E-02	1.52	up	2.01	up
819.7864@14.26	820.7864	14.26	2.78E-02	-0.59	down	-2.61	down
303.2938@8.58	304.2938	8.58	2.79E-02	-0.22	down	0.68	up
96.0943@11.64	97.0943	11.64	2.82E-02	2.58	up	0.42	up
897.7775@14.44	898.7775	14.44	2.83E-02	1.58	up	2.08	up
246.2127@9.72	247.2127	9.72	2.85E-02	1.67	up	1.31	up
845.748@14.33	846.748	14.33	2.86E-02	2.64	up	1.33	up
581.5092@13.01	582.5092	13.01	2.88E-02	1.58	up	1.74	up
859.66@12.38	860.66	12.38	2.89E-02	-0.26	down	2.61	up
497.396@5.87	498.396	5.87	2.91E-02	0.26	up	1.45	up
678.5092@7.32	679.5092	7.32	2.95E-02	-0.76	down	-3.01	down
428.2217@8.81	429.2217	8.81	2.96E-02	0.21	up	0.25	up
1132.3005@14.11	1133.3005	14.11	3.00E-02	1.65	up	1.32	up
711.6349@13.83	712.6349	13.83	3.04E-02	1.42	up	1.59	up
905.281@13.64	906.281	13.64	3.05E-02	-0.56	down	-2.42	down
724.5192@12.45	725.5192	12.45	3.06E-02	-1.65	down	2.64	up
733.0189@12.17	734.0189	12.17	3.07E-02	-1.44	down	2.35	up
756.4628@10.55	757.4628	10.55	3.07E-02	0.17	up	1.88	up
805.7215@14.16	806.7215	14.16	3.10E-02	1.41	up	1.55	up
408.3756@12.63	409.3756	12.63	3.11E-02	0.82	up	1.78	up
879.4554@13.29	880.4554	13.29	3.12E-02	1.62	up	1.76	up
583.5177@13.14	584.5177	13.14	3.14E-02	1.60	up	1.78	up

609.5346@13.19	610.5346	13.19	3.14E-02	1.72	up	1.94	up
492.8274@11.04	493.8274	11.04	3.15E-02	0.26	up	0.44	up
817.767@14.11	818.767	14.11	3.16E-02	-0.61	down	-2.50	down
656.3042@10.47	657.3042	10.47	3.19E-02	0.26	up	-2.57	down
831.7285@14.21	832.7285	14.21	3.22E-02	2.05	up	0.99	up
682.9703@11.22	683.9703	11.22	3.22E-02	0.16	up	-1.83	down
112.1261@11.84	113.1261	11.84	3.23E-02	1.54	up	1.79	up
761.5873@13.05	762.5873	13.05	3.26E-02	-0.52	down	-2.24	down
300.1514@9.42	301.1514	9.42	3.27E-02	-0.51	down	-2.22	down
1221.3093@13.34	1222.3093	13.34	3.27E-02	2.20	up	-0.40	down
908.2879@13.65	909.2879	13.65	3.28E-02	-0.49	down	-2.16	down
789.2902@12.92	790.2902	12.92	3.29E-02	-0.50	down	-2.18	down
607.5524@13.06	608.5524	13.06	3.30E-02	-0.57	down	-2.35	down
633.5545@13.13	634.5545	13.13	3.33E-02	-0.61	down	-2.46	down
843.7743@14.16	844.7743	14.16	3.33E-02	-0.63	down	-2.50	down
833.7429@14.39	834.7429	14.39	3.36E-02	1.37	up	1.62	up
374.3136@10.65	375.3136	10.65	3.38E-02	0.11	up	1.97	up
354.0633@12.94	355.0633	12.94	3.42E-02	1.32	up	1.55	up
822.7242@14.11	823.7242	14.11	3.44E-02	-0.48	down	-2.10	down
56.0652@9.39	57.0652	9.39	3.46E-02	1.46	up	1.78	up
1127.3047@14.12	1128.3047	14.12	3.46E-02	1.49	up	1.76	up
569.4538@11.14	570.4538	11.14	3.47E-02	-0.56	down	-2.28	down
789.2408@12.92	790.2408	12.92	3.47E-02	1.45	up	1.69	up
494.4338@12.88	495.4338	12.88	3.52E-02	1.55	up	1.75	up
520.4767@12.94	521.4767	12.94	3.52E-02	-0.53	down	-2.19	down
662.4482@13.21	663.4482	13.21	3.52E-02	1.75	up	1.98	up
777.6865@13.98	778.6865	13.98	3.53E-02	0.69	up	2.10	up
572.5112@13.06	573.5112	13.06	3.55E-02	-0.52	down	-2.15	down
699.5988@13.18	700.5988	13.18	3.56E-02	-0.52	down	-2.16	down
851.7934@15.08	852.7934	15.08	3.58E-02	-0.01	down	2.86	up
861.8374@14.67	862.8374	14.67	3.60E-02	-0.47	down	-2.02	down
686.1945@13.15	687.1945	13.15	3.64E-02	1.49	up	1.70	up
609.1781@12.94	610.1781	12.94	3.66E-02	1.75	up	2.04	up
148.02@9.43	149.02	9.43	3.68E-02	3.43	up	0.48	up
550.887@12.41	551.887	12.41	3.69E-02	-2.17	down	2.62	up
746.5327@12.46	747.5327	12.46	3.71E-02	-2.18	down	2.62	up
893.7914@14.15	894.7914	14.15	3.74E-02	-0.53	down	-2.14	down
751.6@13.17	752.6	13.17	3.74E-02	-0.62	down	-2.35	down
534.4933@13.03	535.4933	13.03	3.74E-02	-0.47	down	-1.99	down
729.2366@13.06	730.2366	13.06	3.75E-02	1.39	up	1.56	up
683.1963@13.15	684.1963	13.15	3.75E-02	1.68	up	1.92	up
805.7565@14.16	806.7565	14.16	3.79E-02	-0.48	down	-2.00	down
650.5681@13.08	651.5681	13.08	3.81E-02	-0.48	down	-2.00	down
557.5013@13.10	558.5013	13.1	3.88E-02	1.51	up	1.68	up
761.5006@12.90	762.5006	12.9	3.90E-02	0.73	up	2.34	up
368.3779@10.27	369.3779	10.27	3.93E-02	-2.01	down	0.14	up
821.7467@14.47	822.7467	14.47	3.94E-02	1.48	up	1.81	up
809.5874@13.56	810.5874	13.56	3.99E-02	1.73	up	2.02	up
831.7745@14.21	832.7745	14.21	3.99E-02	-0.48	down	-1.95	down
552.2485@8.31	553.2485	8.31	4.00E-02	0.20	up	0.26	up
1168.3102@13.38	1169.3102	13.38	4.02E-02	-1.97	down	2.40	up
522.466@13.09	523.466	13.09	4.05E-02	1.64	up	1.83	up
737.5016@12.90	738.5016	12.9	4.06E-02	0.81	up	2.56	up
481.4006@11.16	482.4006	11.16	4.07E-02	1.89	up	0.81	up
551.4457@7.32	552.4457	7.32	4.11E-02	-0.39	down	-1.73	down
869.1683@11.45	870.1683	11.45	4.11E-02	-0.47	down	-2.22	down
296.2696@12.06	297.2696	12.06	4.14E-02	2.06	up	1.02	up
428.1044@13.15	429.1044	13.15	4.21E-02	-0.40	down	-1.72	down
875.6533@12.05	876.6533	12.05	4.30E-02	-0.70	down	2.60	up
415.3641@12.61	416.3641	12.61	4.30E-02	0.90	up	1.67	up
763.5692@13.57	764.5692	13.57	4.53E-02	0.06	up	2.46	up
962.555@11.01	963.555	11.01	4.65E-02	-0.09	down	2.27	up
723.5207@12.99	724.5207	12.99	4.74E-02	0.72	up	2.62	up
852.1135@11.44	853.1135	11.44	4.75E-02	2.68	up	-0.76	down
831.6247@12.03	832.6247	12.03	4.76E-02	-0.75	down	2.58	up
548.4919@13.15	549.4919	13.15	4.81E-02	2.23	up	1.11	up
845.4356@8.31	846.4356	8.31	4.90E-02	1.75	up	1.10	up
118.0793@8.31	119.0793	8.31	4.97E-02	0.18	up	0.23	up
152.1216@8.61	153.1216	8.61	4.99E-02	0.52	up	1.98	up
904.7504@14.65	905.7504	14.65	4.99E-02	0.66	up	2.37	up

8.5.1.2. Soleus

Table S35. Soleus unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
150.0888@0.72	151.0888	0.72	6.36E-03	10.28	up	-2.98	down
514.4089@7.52	515.4089	7.52	1.99E-02	9.85	up	-0.15	down
627.6231@9.17	628.6231	9.17	1.63E-02	11.02	up	3.62	up
656.7902@3.25	657.7902	3.25	1.90E-03	9.34	up	11.45	up
658.7726@3.25	659.7726	3.25	4.92E-02	6.68	up	-2.79	down
740.288@3.25	741.288	3.25	1.27E-02	2.23	up	-6.99	down
831.2329@8.75	832.2329	8.75	2.12E-02	6.90	up	-0.19	down
833.4234@1.01	834.4234	1.01	1.12E-02	7.01	up	-4.96	down
872.2617@8.75	873.2617	8.75	2.09E-02	7.02	up	-0.19	down
875.6356@0.84	876.6356	0.84	2.85E-02	8.60	up	-0.52	down
993.3236@9.39	994.3236	9.39	8.36E-03	4.55	up	-7.55	down
996.3153@9.39	997.3153	9.39	5.14E-03	2.27	up	-9.16	down
1096.2965@8.32	1097.2965	8.32	1.01E-02	2.25	up	-7.22	down
1185.3856@9.66	1186.3856	9.66	1.47E-02	10.88	up	5.16	up
1245.3527@9.68	1246.3527	9.68	9.42E-03	4.63	up	-6.93	down
365.3641@5.72	366.3641	5.72	3.37E-02	-8.50	down	0.71	up
375.1644@0.80	376.1644	0.8	3.08E-02	-11.31	down	-8.04	down
523.4443@3.98	524.4443	3.98	4.98E-02	-0.07	down	-0.21	down
538.0666@5.15	539.0666	5.15	2.91E-02	-2.52	down	-10.5	down
567.45@5.52	568.45	5.52	4.58E-02	-0.22	down	-0.11	down
665.0965@5.04	666.0965	5.04	3.53E-02	-10.17	down	-5.56	down
689.4315@0.85	690.4315	0.85	3.98E-02	-2.07	down	-9.26	down
794.3344@0.83	795.3344	0.83	1.49E-02	-8.45	down	-8.35	down
852.2401@6.30	853.2401	6.3	3.97E-02	-0.19	down	5.52	up
886.552@0.84	887.552	0.84	2.61E-02	-0.03	down	-8.86	down
994.3259@9.39	995.3259	9.39	1.04E-02	-5.12	down	7.06	up
997.3242@9.39	998.3242	9.39	7.87E-03	-6.64	down	4.2	up
1034.3502@9.38	1035.3502	9.38	4.64E-02	-9.75	down	-3.49	down
1068.676@4.20	1069.676	4.2	3.40E-02	-6.03	down	2.75	up
1337.3815@8.27	1338.3815	8.27	2.36E-03	-11.02	down	-11.88	down
1561.433@8.80	1562.433	8.8	4.91E-02	-1.86	down	-7.04	down

Table S36. Soleus unidentified metabolites statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
611.4109@10.95	612.4109	10.95	2.89E-04	-3.12	down	3.4	up
737.4995@12.90	738.4995	12.9	8.26E-04	5.33	up	1.63	up
1204.324@14.33	1205.324	14.33	1.20E-03	2.93	up	0.65	up
751.5558@13.17	752.5558	13.17	1.55E-03	4.44	up	0.83	up
1158.8268@13.38	1159.8268	13.38	1.57E-03	3.47	up	0.04	up
926.5225@13.39	927.5225	13.39	2.21E-03	3.8	up	2.82	up
1127.3046@14.12	1128.3046	14.12	2.31E-03	4.11	up	3.06	up
435.3368@11.84	436.3368	11.84	2.32E-03	4.41	up	3.35	up
963.4079@13.23	964.4079	13.23	3.56E-03	3.45	up	2.64	up
1053.7355@11.41	1054.7355	11.41	3.96E-03	-2.72	down	2.96	up
833.5988@13.52	834.5988	13.52	5.01E-03	-0.49	down	-3.72	down
569.4124@10.59	570.4124	10.59	5.63E-03	-2.47	down	2.75	up
552.8798@11.27	553.8798	11.27	5.85E-03	-2.31	down	2.6	up
971.3284@12.89	972.3284	12.89	5.94E-03	0.29	up	-2.3	down
685.3228@10.84	686.3228	10.84	7.03E-03	-2.49	down	3.44	up
769.0476@12.47	770.0476	12.47	7.09E-03	1.46	up	2.1	up
399.152@0.68	400.152	0.68	7.25E-03	3.11	up	0.65	up
787.6248@13.88	788.6248	13.88	7.44E-03	4.18	up	0.78	up
730.6008@13.25	731.6008	13.25	9.13E-03	4.65	up	2.55	up
748.4982@10.87	749.4982	10.87	9.27E-03	0.88	up	0.49	up
103.0853@0.39	104.0853	0.39	1.09E-02	1.87	up	-2.03	down
793.5628@13.16	794.5628	13.16	1.11E-02	4.3	up	1.6	up
1201.3236@14.33	1202.3236	14.33	1.19E-02	3.82	up	1.49	up
1012.2997@13.42	1013.2997	13.42	1.24E-02	2.9	up	0	up
659.5548@13.19	660.5548	13.19	1.25E-02	2.44	up	1.49	up
798.67@14.22	799.67	14.22	1.31E-02	3	up	2.73	up
795.7194@14.43	796.7194	14.43	1.40E-02	3.81	up	2.13	up
1021.2668@12.87	1022.2668	12.87	1.47E-02	1.69	up	2.13	up

769.5043@12.97	770.5043	12.97	1.49E-02	2.85	up	1.63	up
583.4661@11.47	584.4661	11.47	1.65E-02	3.35	up	2.33	up
641.256@10.25	642.256	10.25	1.66E-02	-1.55	down	3.02	up
534.4739@13.00	535.4739	13	1.67E-02	-1.08	down	3.36	up
181.1468@5.88	182.1468	5.88	1.76E-02	1.66	up	-1.72	down
640.5052@13.22	641.5052	13.22	1.77E-02	3.32	up	3.02	up
504.8846@12.40	505.8846	12.4	1.82E-02	-1.61	down	3.21	up
821.747@14.47	822.747	14.47	1.84E-02	3.46	up	2.4	up
622.4541@12.13	623.4541	12.13	1.95E-02	-1.08	down	3.48	up
629.6079@13.45	630.6079	13.45	1.96E-02	2.98	up	0.06	up
627.5547@13.46	628.5547	13.46	2.02E-02	-3.16	down	-2.38	down
711.6346@13.83	712.6346	13.83	2.05E-02	2.31	up	2.07	up
558.8666@11.11	559.8666	11.11	2.11E-02	0.54	up	0.14	up
726.4538@10.84	727.4538	10.84	2.13E-02	-1.43	down	4.32	up
393.7205@7.32	394.7205	7.32	2.15E-02	2.79	up	2.53	up
979.2713@13.78	980.2713	13.78	2.19E-02	3.52	up	2.42	up
675.5203@13.09	676.5203	13.09	2.33E-02	3.06	up	0.68	up
889.4401@13.08	890.4401	13.08	2.39E-02	3.09	up	2.26	up
704.4944@13.58	705.4944	13.58	2.41E-02	3.32	up	3	up
494.434@12.88	495.434	12.88	2.50E-02	2.55	up	2.25	up
763.6734@13.90	764.6734	13.9	2.70E-02	2.32	up	2.23	up
467.7854@10.97	468.7854	10.97	2.72E-02	2.19	up	-0.48	down
126.1407@12.18	127.1407	12.18	2.87E-02	3.09	up	0.7	up
539.4283@12.31	540.4283	12.31	2.91E-02	-3.34	down	-1.86	down
1158.3242@13.38	1159.3242	13.38	3.13E-02	3.05	up	0.61	up
854.7201@14.75	855.7201	14.75	3.16E-02	3.15	up	2.93	up
889.631@11.80	890.631	11.8	3.23E-02	-2.89	down	-1	down
497.3962@5.87	498.3962	5.87	3.28E-02	1.78	up	1.65	up
458.2749@4.89	459.2749	4.89	3.29E-02	1.47	up	1.17	up
747.5232@12.97	748.5232	12.97	3.42E-02	0.28	up	-3.47	down
442.8017@10.94	443.8017	10.94	3.78E-02	0.37	up	0.1	up
508.84@11.02	509.84	11.02	3.86E-02	0.37	up	0.09	up
866.323@7.31	867.323	7.31	3.92E-02	2.56	up	1.73	up
492.8272@11.04	493.8272	11.04	4.04E-02	0.66	up	0.21	up
236.2105@10.67	237.2105	10.67	4.19E-02	-1.72	down	2	up
770.4811@10.88	771.4811	10.88	4.34E-02	-3.19	down	-0.58	down
419.7835@10.63	420.7835	10.63	4.39E-02	-1.56	down	1.85	up
965.6841@11.34	966.6841	11.34	4.41E-02	2.19	up	0.62	up
514.8401@11.06	515.8401	11.06	4.48E-02	0.57	up	0.17	up
387.2485@4.04	388.2485	4.04	4.53E-02	0.32	up	0.03	up
665.6315@12.46	666.6315	12.46	4.55E-02	-2.68	down	-0.45	down
681.3567@11.45	682.3567	11.45	4.59E-02	0.35	up	0.11	up
500.4932@10.06	501.4932	10.06	4.59E-02	-1.42	down	1.7	up
787.9725@0.80	788.9725	0.8	4.62E-02	0.25	up	-2.26	down
343.2228@3.52	344.2228	3.52	4.64E-02	0.32	up	0.03	up
481.8068@11.01	482.8068	11.01	4.69E-02	0.35	up	0.11	up
464.8284@11.17	465.8284	11.17	4.71E-02	-2.44	down	-0.39	down
1117.7301@11.12	1118.7301	11.12	4.89E-02	-2.44	down	-0.4	down
431.2746@4.49	432.2746	4.49	4.94E-02	0.31	up	0.03	up
1039.7216@11.06	1040.7216	11.06	4.97E-02	-2.5	down	-0.42	down
656.2993@10.47	657.2993	10.47	4.99E-02	1.62	up	1.44	up

8.5.2. Adipose tissue

8.5.2.1. Visceral adipose tissue

Table S37. Visceral adipose tissue unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
343.2175@0.80	344.2175	0.8	2.19E-02	-9.51	down	0.8	up
408.1532@0.84	409.1532	0.84	1.48E-02	-7.75	down	6.56	up
414.2029@0.81	415.2029	0.81	3.21E-02	7.34	up	-2.19	down
429.3733@6.99	430.3733	6.99	4.06E-02	-1.64	down	6.75	up
487.4259@6.99	488.4259	6.99	2.31E-02	1.21	up	9.49	up
531.3576@0.84	532.3576	0.84	3.89E-02	7.4	up	-2.71	down
550.0983@3.26	551.0983	3.26	4.25E-02	-3.92	down	3.4	up
562.5363@10.34	563.5363	10.34	1.36E-06	2.87	up	14.88	up
605.5472@10.27	606.5472	10.27	4.85E-02	-3.93	down	3.93	up
606.0345@5.04	607.0345	5.04	1.53E-03	-9.09	down	2.01	up
663.454@0.84	664.454	0.84	4.77E-02	-6.45	down	2.52	up
743.5689@0.84	744.5689	0.84	2.29E-02	9.68	up	6.64	up

791.433@3.25	792.433	3.25	1.39E-02	6.02	up	9.39	up
807.7761@10.25	808.7761	10.25	1.19E-03	6.45	up	12.94	up
816.4513@2.85	817.4513	2.85	4.72E-02	-2.54	down	-7.1	down
833.7834@10.25	834.7834	10.25	7.33E-03	-1.65	down	10.29	up
980.2802@9.21	981.2802	9.21	2.20E-02	-11.11	down	-6.6	down
1007.3601@8.98	1008.3601	8.98	3.92E-02	7.32	up	-2.76	down
1044.9774@10.88	1045.9774	10.88	4.92E-03	7.53	up	7.55	up
1053.2878@9.38	1054.2878	9.38	2.96E-02	-9.74	down	-0.13	down
1071.0015@10.92	1072.0015	10.92	5.35E-03	7.67	up	7.69	up
1128.0249@10.40	1129.0249	10.4	1.60E-02	-5.52	down	-10.05	down
1159.3853@7.09	1160.3853	7.09	1.09E-02	1.9	up	-7.41	down
1276.9446@7.72	1277.9446	7.72	4.99E-02	7.46	up	-1.48	down
1278.3477@9.80	1279.3477	9.8	4.42E-02	1.72	up	-5.4	down
1497.4043@10.10	1498.4043	10.1	1.16E-02	1.9	up	-7.42	down
1762.5082@9.94	1763.5082	9.94	2.47E-02	-5.94	down	1.94	up

8.5.2.2. Subcutaneous adipose tissue

Table S38. Subcutaneous adipose tissue unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
221.1361@0.84	222.1361	0.84	2.88E-02	1.77	up	-6.31	down
380.1253@0.77	381.1253	0.77	4.15E-02	3.1	up	9.85	up
414.2069@1.16	415.2069	1.16	4.66E-02	-7.62	down	0.40	up
429.3731@6.99	430.3731	6.99	8.25E-06	0.27	up	1.80	up
487.4258@6.99	488.4258	6.99	4.52E-02	2.66	up	8.18	up
558.518@6.99	559.518	6.99	5.20E-03	0.93	up	9.51	up
562.532@10.34	563.532	10.34	4.53E-03	2.57	up	11.03	up
576.5101@6.02	577.5101	6.02	3.10E-02	-0.09	down	-0.17	down
605.5447@10.25	606.5447	10.25	3.31E-02	7.64	up	6.14	up
606.0338@5.04	607.0338	5.04	1.22E-02	-2.43	down	8.14	up
627.193@4.39	628.193	4.39	2.86E-02	7.34	up	5.93	up
658.7716@3.25	659.7716	3.25	2.88E-02	5.23	up	-4.43	down
678.4094@0.84	679.4094	0.84	3.38E-02	-9.11	down	-3.30	down
759.1958@6.88	760.1958	6.88	1.08E-02	6.6	up	0.03	up
765.4533@0.91	766.4533	0.91	2.49E-02	4.18	up	-5.96	down
859.7985@10.23	860.7985	10.23	2.24E-02	6.8	up	9.41	up
980.274@9.20	981.274	9.2	3.90E-02	10.35	up	3.73	up
995.8631@9.36	996.8631	9.36	2.61E-02	5.02	up	-6.88	down
1009.9123@10.42	1010.9123	10.42	4.01E-02	0.43	up	8.23	up
1074.297@7.49	1075.297	7.49	3.35E-02	-9.06	down	-6.48	down
1094.0035@10.81	1095.0035	10.81	4.53E-02	2.89	up	7.05	up
1096.013@10.89	1097.013	10.89	3.07E-06	11	up	13.21	up
1130.0321@10.47	1131.0321	10.47	3.79E-03	7.64	up	7.69	up
1158.9993@10.42	1159.9993	10.42	3.22E-02	7.27	up	5.83	up
1178.0284@10.32	1179.0284	10.32	2.48E-02	5.14	up	7.26	up
1180.0446@10.41	1181.0446	10.41	2.09E-04	9.3	up	11.43	up
1181.1779@7.12	1182.1779	7.12	4.44E-02	9.31	up	7.45	up
1206.998@7.71	1207.998	7.71	2.69E-02	7.27	up	7.78	up
1233.0122@7.75	1234.0122	7.75	9.36E-03	10.85	up	7.12	up
1352.3635@9.91	1353.3635	9.91	2.79E-02	-0.58	down	-8.06	down
1485.4178@8.63	1486.4178	8.63	3.31E-03	7.56	up	7.61	up

8.5.3. Kidney

Table S39. Kidney unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
431.228@0.80	432.228	0.8	2.42E-02	7.21	up	-2.04	down
126.0983@0.83	127.0983	0.83	4.90E-02	3.75	up	-5.67	down
148.016@4.77	149.016	4.77	2.73E-03	-9.27	down	-0.07	down
206.1373@0.80	207.1373	0.8	3.58E-02	3.05	up	-6.95	down
343.2175@0.80	344.2175	0.8	5.40E-03	-5.5	down	7.19	up

395.3869@5.27	396.3869	5.27	5.01E-04	-14.47	down	-4.05	down
440.78@2.04	441.78	2.04	4.59E-02	-6.16	down	-6.14	down
488.3866@8.15	489.3866	8.15	2.42E-02	11.15	up	5.6	up
523.4444@3.98	524.4444	3.98	9.90E-03	-7.5	down	-11.5	down
527.5512@9.70	528.5512	9.7	2.92E-02	-5.36	down	1.47	up
620.3254@0.87	621.3254	0.87	8.73E-03	-6.95	down	-11	down
655.7951@3.25	656.7951	3.25	2.77E-02	-9.49	down	-9.6	down
686.1934@8.07	687.1934	8.07	4.53E-03	10.26	up	1.41	up
701.2069@5.11	702.2069	5.11	1.23E-02	5.31	up	-5.26	down
716.2407@3.26	717.2407	3.26	5.48E-03	-10.16	down	-1.61	down
723.5178@0.86	724.5178	0.86	6.75E-03	-3.71	down	-11.21	down
724.4988@0.86	725.4988	0.86	1.42E-02	6.15	up	10.45	up
766.3056@0.80	767.3056	0.8	2.26E-02	9.72	up	2.3	up
909.7228@9.17	910.7228	9.17	4.15E-02	-0.35	down	-0.71	down
928.2308@6.76	929.2308	6.76	3.19E-03	8.91	up	9.6	up
980.2714@9.21	981.2714	9.21	3.22E-02	-5.9	down	1.7	up
1039.331@8.24	1040.331	8.24	1.50E-02	-4.85	down	4.83	up
1086.2039@3.25	1087.2039	3.25	1.91E-02	-8.38	down	-7.02	down
1141.9706@7.54	1142.9706	7.54	2.17E-02	7.71	up	6.04	up
1218.3806@9.78	1219.3806	9.78	1.61E-02	0.87	up	-8.06	down
1245.352@9.68	1246.352	9.68	4.80E-02	-2.51	down	-8.79	down
1303.4269@9.60	1304.4269	9.6	2.46E-02	5.45	up	-0.07	down
1428.3749@10.01	1429.3749	10.01	2.06E-02	-7.68	down	-0.11	down
1483.446@9.31	1484.446	9.31	4.89E-02	-7.31	down	1.63	up
1612.456@10.18	1613.456	10.18	7.74E-03	6.89	up	-3.63	down
1686.4612@10.25	1687.4612	10.25	1.20E-02	-10.82	down	-3.36	down

Table S40. Kidney unidentified metabolites statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
465.3105@8.93	466.3105	8.93	1.76E-04	2.89	up	2.85	up
736.1996@11.50	737.1996	11.5	1.37E-03	1.24	up	3.87	up
1203.8696@13.27	1204.8696	13.27	1.53E-03	3.36	up	2.4	up
301.291@8.56	302.291	8.56	1.78E-03	1.53	up	-3	down
401.6842@7.33	402.6842	7.33	2.07E-03	3.16	up	0.63	up
803.3805@7.33	804.3805	7.33	2.70E-03	-3.52	down	-1.45	down
494.4399@12.93	495.4399	12.93	2.81E-03	2.36	up	2.32	up
660.4925@7.34	661.4925	7.34	2.98E-03	-1.94	down	0.42	up
693.0938@5.89	694.0938	5.89	3.04E-03	3.03	up	1.14	up
541.0597@0.58	542.0597	0.58	3.60E-03	-0.02	down	-2.36	down
257.2745@9.11	258.2745	9.11	4.61E-03	0.01	up	2.69	up
276.1407@7.97	277.1407	7.97	4.66E-03	0.03	up	2.39	up
809.6256@13.48	810.6256	13.48	5.36E-03	2.53	up	-2.31	down
789.0799@13.34	790.0799	13.34	8.78E-03	1.79	up	2.9	up
751.6019@13.20	752.6019	13.2	8.82E-03	-0.81	down	3.08	up
956.6196@11.05	957.6196	11.05	9.62E-03	3.02	up	0.89	up
892.8324@14.91	893.8324	14.91	1.03E-02	2.1	up	2.69	up
256.1574@7.17	257.1574	7.17	1.16E-02	-1.23	down	-3.04	down
555.8421@11.12	556.8421	11.12	1.18E-02	1.19	up	3.13	up
745.5965@13.32	746.5965	13.32	1.18E-02	3.08	up	2.71	up
642.4017@8.26	643.4017	8.26	1.20E-02	2.5	up	1.64	up
809.6336@13.49	810.6336	13.49	1.30E-02	-1.66	down	2.47	up
866.807@14.85	867.807	14.85	1.34E-02	2.77	up	2.62	up
754.4539@11.13	755.4539	11.13	1.37E-02	1.18	up	2.87	up
366.2129@7.33	367.2129	7.33	1.43E-02	-0.11	down	0	down
171.1246@10.59	172.1246	10.59	1.46E-02	1.92	up	3.29	up
687.102@5.90	688.102	5.9	1.64E-02	2.02	up	0	down
612.1499@0.46	613.1499	0.46	1.69E-02	-2.46	down	-0.51	down
512.2719@8.22	513.2719	8.22	1.72E-02	3.03	up	0.56	up
985.6554@11.09	986.6554	11.09	1.82E-02	-3.45	down	-2.84	down
398.2466@10.04	399.2466	10.04	1.83E-02	2.62	up	0.48	up
368.2334@6.89	369.2334	6.89	1.92E-02	-2.37	down	-0.51	down
122.0605@7.44	123.0605	7.44	2.00E-02	-2.65	down	0.04	up
689.5674@12.89	690.5674	12.89	2.00E-02	-3.17	down	-1.58	down
747.5708@12.97	748.5708	12.97	2.10E-02	-2.15	down	0.63	up
777.0916@10.56	778.0916	10.56	2.15E-02	0.55	up	-1.75	down
257.0986@0.48	258.0986	0.48	2.24E-02	-2.27	down	0.69	up
256.105@1.00	257.105	1	2.27E-02	-1.79	down	0.55	up
535.2048@12.72	536.2048	12.72	2.36E-02	-3.01	down	0.09	up
362.2511@11.47	363.2511	11.47	2.36E-02	2.35	up	0.05	up
426.3541@13.89	427.3541	13.89	2.42E-02	-0.07	down	1.98	up
814.0889@13.30	815.0889	13.3	2.52E-02	1.67	up	2.21	up
629.6276@13.51	630.6276	13.51	2.69E-02	2.98	up	2.24	up
234.1639@9.19	235.1639	9.19	2.78E-02	0	up	2.36	up
710.465@7.33	711.465	7.33	2.84E-02	-2.79	down	-1.3	down

268.0814@0.67	269.0814	0.67	2.91E-02	0.01	up	-0.12	down
733.5959@13.47	734.5959	13.47	2.91E-02	3.39	up	-0.56	down
705.4679@7.33	706.4679	7.33	2.96E-02	-0.74	down	1.46	up
976.9137@11.49	977.9137	11.49	3.01E-02	2.99	up	2.26	up
714.0951@13.01	715.0951	13.01	3.05E-02	2.61	up	0.81	up
324.9894@0.81	325.9894	0.81	3.08E-02	-0.04	down	2.25	up
649.4105@11.02	650.4105	11.02	3.12E-02	-1.27	down	-3.1	down
827.7032@13.82	828.7032	13.82	3.13E-02	-1.15	down	-2.79	down
590.4992@13.34	591.4992	13.34	3.18E-02	-0.05	down	-2.59	down
909.5038@14.08	910.5038	14.08	3.19E-02	2.53	up	-0.44	down
614.5288@13.21	615.5288	13.21	3.32E-02	1.35	up	3.06	up
611.7945@11.49	612.7945	11.49	3.44E-02	2.25	up	2.41	up
494.4621@12.92	495.4621	12.92	3.71E-02	-2.33	down	0.19	up
936.4213@11.50	937.4213	11.5	3.75E-02	2.29	up	2.58	up
464.8149@11.01	465.8149	11.01	3.89E-02	3.4	up	2.01	up
1064.4882@10.28	1065.4882	10.28	4.28E-02	-1.63	down	-2.52	down
911.2679@13.69	912.2679	13.69	4.35E-02	-1.18	down	1.03	up
666.4007@11.04	667.4007	11.04	4.47E-02	1.19	up	2.32	up
292.9928@0.50	293.9928	0.5	4.50E-02	1.15	up	2.22	up
757.6093@13.36	758.6093	13.36	4.58E-02	-0.83	down	2.53	up
779.0876@10.51	780.0876	10.51	4.62E-02	1.64	up	2.22	up
751.5926@13.20	752.5926	13.2	4.74E-02	1.59	up	-2.02	down
843.7998@14.28	844.7998	14.28	4.78E-02	1.82	up	2.75	up
704.1738@10.44	705.1738	10.44	4.78E-02	-1.16	down	-2.3	down
718.4498@12.25	719.4498	12.25	4.84E-02	0.62	up	2.68	up
605.3785@11.58	606.3785	11.58	4.86E-02	1.22	up	-1.37	down

8.5.4. Heart

Table S41. Heart unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
287.1753@0.82	288.1753	0.82	2.33E-02	-8.88	down	-2.19	down
431.4262@7.24	432.4262	7.24	2.44E-03	1.87	up	-8.72	down
566.6933@7.10	567.6933	7.1	7.65E-03	0.13	up	0.27	up
776.5149@0.84	777.5149	0.84	3.61E-02	6.85	up	9.02	up
787.5819@0.85	788.5819	0.85	8.50E-03	10.79	up	4.32	up
881.5647@0.85	882.5647	0.85	2.14E-02	7.17	up	0.11	up
926.258@6.76	927.258	6.76	1.33E-03	-0.2	down	8.34	up
1023.2978@9.19	1024.2978	9.19	1.07E-02	-11.42	down	-6.85	down
1034.3502@9.38	1035.3502	9.38	2.47E-03	-1.75	down	9.43	up
1035.3552@9.38	1036.3552	9.38	2.33E-03	1.92	up	-8.88	down
1130.3081@9.55	1131.3081	9.55	2.72E-02	5.46	up	-5.08	down
1145.3162@7.79	1146.3162	7.79	4.45E-02	-5.93	down	-5.78	down

Table S42. Heart unidentified metabolites statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
327.9979@7.70	328.9979	7.7	5.72E-04	-3.19	down	-0.1	down
229.2433@8.07	230.2433	8.07	2.99E-02	-2.63	down	-2.25	down
247.1437@0.57	248.1437	0.57	6.73E-03	-0.5	down	-3.69	down
313.1406@0.68	314.1406	0.68	2.71E-02	2.21	up	-0.28	down
358.3324@11.68	359.3324	11.68	1.58E-02	3.32	up	0.55	up
385.2817@7.81	386.2817	7.81	3.98E-02	-2.38	down	-0.63	down
395.3051@8.96	396.3051	8.96	4.30E-02	-1.82	down	0.53	up
420.7898@10.94	421.7898	10.94	3.04E-02	0.74	up	-2.13	down
468.3914@12.57	469.3914	12.57	3.30E-03	0.84	up	3.95	up
489.8039@11.04	490.8039	11.04	1.90E-02	-1.04	down	-2.69	down
516.3618@10.63	517.3618	10.63	1.38E-02	2.17	up	-0.15	down
570.3497@4.11	571.3497	4.11	4.14E-03	2.78	up	-0.22	down
590.3504@5.85	591.3504	5.85	2.41E-02	0.69	up	-1.77	down
615.144@0.67	616.144	0.67	4.14E-02	-1.36	down	1.17	up
616.9826@12.47	617.9826	12.47	2.66E-02	2.98	up	1.33	up
626.0567@0.89	627.0567	0.89	2.13E-02	0.61	up	-1.39	down
627.2623@11.97	628.2623	11.97	1.42E-02	3.17	up	0.32	up
650.5637@13.11	651.5637	13.11	3.15E-02	1.37	up	3.06	up

656.2979@10.44	657.2979	10.44	3.99E-02	-1.56	down	-2.57	down
693.6837@12.26	694.6837	12.26	2.25E-03	1.35	up	-2.11	down
694.1278@0.64	695.1278	0.64	1.33E-04	-2.35	down	1.84	up
695.1156@0.65	696.1156	0.65	2.60E-02	0.68	up	-1.45	down
731.5419@10.87	732.5419	10.87	1.01E-02	3.06	up	-0.85	down
780.5223@10.91	781.5223	10.91	4.60E-02	-0.51	down	-2.92	down
785.6171@13.54	786.6171	13.54	3.48E-02	-0.6	down	-3.37	down
792.674@13.99	793.674	13.99	4.64E-02	2.73	up	2.01	up
795.5354@10.64	796.5354	10.64	1.43E-02	2.25	up	-0.11	down
800.4925@10.64	801.4925	10.64	3.88E-02	1.45	up	-1.4	down
819.5925@10.94	820.5925	10.94	4.09E-02	0.85	up	-2.41	down
850.779@14.45	851.779	14.45	2.48E-02	-1.15	down	1.8	up
853.5911@10.99	854.5911	10.99	1.77E-02	1.69	up	-1.98	down
863.6186@10.98	864.6186	10.98	1.98E-02	2.19	up	-1.15	down
868.5721@10.98	869.5721	10.98	1.56E-02	1.43	up	-1.66	down
956.6304@11.04	957.6304	11.04	6.42E-03	0.13	up	-2.63	down
1010.1647@0.64	1011.1647	0.64	2.92E-02	-1.31	down	0.99	up
1060.6007@8.70	1061.6007	8.7	3.73E-02	0.77	up	-2.35	down

8.5.5. Liver

Table S43. Liver unidentified lipid species statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted lipidomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
255.1667@0.74	256.1667	0.74	4.22E-02	-9.54	down	-7.04	down
306.1088@0.67	307.1088	0.67	9.71E-04	-14.19	down	-6.95	down
337.3342@5.26	338.3342	5.26	4.41E-02	-7.99	down	-10.32	down
454.2735@0.81	455.2735	0.81	4.44E-02	-8.69	down	-4.29	down
582.8687@3.03	583.8687	3.03	3.47E-02	-3.16	down	-9.82	down
724.4801@0.86	725.4801	0.86	3.61E-02	-7.30	down	-9.37	down
744.5865@8.70	744.5865	8.7	3.47E-02	-6.62	down	-6.49	down
785.5381@0.88	786.5381	0.88	4.27E-03	-2.98	down	-12.26	down
809.0272@4.06	810.0272	4.06	6.40E-03	-2.46	down	-10.96	down
859.6499@0.84	860.6499	0.84	1.63E-02	-5.69	down	5.15	up
865.5448@0.87	866.5448	0.87	2.13E-02	1.84	up	-6.8	down
866.0417@4.50	867.0417	4.5	6.07E-03	-11.09	down	-8.94	down
886.56@0.84	887.56	0.84	4.92E-02	-5.88	down	-6.03	down
909.7279@9.17	910.7279	9.17	1.44E-02	-0.77	down	-0.5	down
953.5439@6.40	954.5439	6.4	9.06E-03	-0.14	down	-0.29	down
1127.1879@7.15	1128.1879	7.15	3.10E-02	-4.76	down	-9.04	down
1164.0159@10.95	1165.0159	10.95	1.34E-02	0.47	up	10.01	up
1187.368@8.70	1188.368	8.7	1.27E-02	-9.50	down	-7.14	down
1275.3508@9.81	1276.3508	9.81	3.45E-03	9.31	up	-0.05	down
1335.4022@9.04	1336.4022	9.04	2.45E-02	0.10	up	6.55	up
1349.3678@9.92	1350.3678	9.92	2.91E-02	9.28	up	2.26	up
1370.3636@8.47	1371.3636	8.47	1.93E-02	-7.03	down	3.47	up
1390.403@9.92	1391.403	9.92	1.86E-02	9.30	up	2.19	up
1589.4264@8.93	1590.4264	8.93	4.93E-02	-0.82	down	7.94	up
1686.4716@10.25	1687.4716	10.25	2.35E-03	-11.02	down	-10.96	down
1709.4788@9.88	1710.4788	9.88	2.39E-02	-9.07	down	-8.86	down

Table S44. Liver unidentified metabolites statistically different in RMet animals versus adult and old animals. Results were obtained by a non-parametric t-test of an untargeted metabolomic analysis with positive ESI polarity.

Compound	m/z	RT	p value	LogFC RMet vs Old	RMet vs Old	LogFC RMet vs Adult	RMet vs Adult
262.1598@0.43	263.1598	0.43	3.25E-08	-0.03	down	-4.43	down
575.1915@8.47	576.1915	8.47	9.44E-06	-4.41	down	-3.63	down
461.2779@7.99	462.2779	7.99	1.25E-05	4.39	up	3.92	up
1206.3185@13.28	1207.3185	13.28	1.84E-05	3.54	up	3.62	up
636.1875@0.54	637.1875	0.54	2.35E-05	3.47	up	3.54	up
152.0597@1.40	153.0597	1.4	2.41E-05	-5.03	down	-3.24	down
553.1789@10.54	554.1789	10.54	7.53E-05	-1.61	down	-4.18	down
709.4009@12.81	710.4009	12.81	9.97E-05	-1.17	down	-4.41	down
1182.2765@13.09	1183.2765	13.09	4.33E-04	2.42	up	3.17	up
594.2443@0.54	595.2443	0.54	4.62E-04	2.9	up	2.97	up
632.1781@0.54	633.1781	0.54	5.62E-04	2.76	up	2.83	up
289.1222@0.52	290.1222	0.52	5.90E-04	4.23	up	4.3	up

452.3658@12.51	453.3658	12.51	1.17E-03	-3.45	down	0.11	up
753.5335@13.08	754.5335	13.08	1.53E-03	-0.25	down	-0.4	down
465.31@8.88	466.31	8.88	2.11E-03	0.64	up	0.88	up
447.2988@8.01	448.2988	8.01	2.14E-03	2.75	up	3.94	up
529.3038@8.30	530.3038	8.3	2.26E-03	-2.62	down	0.64	up
321.0993@0.60	322.0993	0.6	2.57E-03	-3.27	down	-0.5	down
973.9573@11.43	974.9573	11.43	2.69E-03	4.19	up	2.13	up
862.6838@14.36	863.6838	14.36	2.84E-03	-3.25	down	0.17	up
599.1788@10.32	600.1788	10.32	3.77E-03	-1.81	down	-3.62	down
637.5638@13.30	638.5638	13.3	4.06E-03	-2.6	down	0.04	up
759.4927@12.73	760.4927	12.73	4.83E-03	-3.28	down	-3.44	down
816.6015@13.85	817.6015	13.85	4.88E-03	-3.12	down	0.81	up
782.9934@12.88	783.9934	12.88	5.40E-03	2.25	up	2.32	up
217.13@0.74	218.13	0.74	5.52E-03	0.25	up	0.37	up
848.6861@14.15	849.6861	14.15	6.62E-03	-2.03	down	1.97	up
517.232@8.06	518.232	8.06	6.85E-03	2.63	up	2.95	up
525.2079@8.05	526.2079	8.05	7.90E-03	1.31	up	3.31	up
494.3715@8.86	495.3715	8.86	8.30E-03	2.89	up	2.48	up
369.0722@6.14	370.0722	6.14	8.64E-03	3.24	up	1.85	up
612.2808@9.42	613.2808	9.42	9.14E-03	2.66	up	2.28	up
904.2786@7.31	905.2786	7.31	9.19E-03	-2.83	down	-0.89	down
376.1246@9.42	377.1246	9.42	9.40E-03	-0.55	down	-3.09	down
258.1987@12.81	259.1987	12.81	9.95E-03	0.6	up	2.84	up
724.5426@13.64	725.5426	13.64	1.08E-02	0.52	up	3	up
103.0912@0.39	104.0912	0.39	1.10E-02	-2.1	down	-4.21	down
939.5602@7.73	940.5602	7.73	1.12E-02	-3.19	down	-2.53	down
622.2176@9.45	623.2176	9.45	1.18E-02	-3.21	down	-2.32	down
561.2188@8.05	562.2188	8.05	1.19E-02	1.9	up	2.85	up
569.4091@10.58	570.4091	10.58	1.24E-02	-1.21	down	2.02	up
115.0582@0.42	116.0582	0.42	1.29E-02	-3.62	down	-3.01	down
635.5508@13.19	636.5508	13.19	1.29E-02	-2.26	down	1.44	up
1056.288@13.93	1057.288	13.93	1.31E-02	3.22	up	2.74	up
745.561@13.26	746.561	13.26	1.38E-02	-3.6	down	-0.92	down
856.7518@14.56	857.7518	14.56	1.38E-02	1.58	up	-2.03	down
558.8663@11.10	559.8663	11.1	1.41E-02	3.17	up	2.51	up
421.7584@13.22	422.7584	13.22	1.64E-02	1.33	up	-1.89	down
901.2867@7.31	902.2867	7.31	1.74E-02	-2.92	down	-1.42	down
415.3574@12.60	416.3574	12.6	1.89E-02	-2.05	down	1.46	up
635.5492@12.79	636.5492	12.79	1.94E-02	1.81	up	3.22	up
429.2892@8.88	430.2892	8.88	1.95E-02	2.11	up	3.42	up
234.1567@0.43	235.1567	0.43	1.99E-02	-1.22	down	-3.64	down
1059.2611@13.93	1060.2611	13.93	2.32E-02	3.11	up	1.95	up
627.4617@10.94	628.4617	10.94	2.37E-02	-1.77	down	0.62	up
877.8082@15.10	878.8082	15.1	2.38E-02	-1.27	down	-3.19	down
777.0544@10.86	778.0544	10.86	2.42E-02	0.53	up	-1.91	down
327.0805@0.47	328.0805	0.47	2.63E-02	2.85	up	2.46	up
1236.8684@13.50	1237.8684	13.5	2.64E-02	-2.85	down	-2.46	down
611.549@13.32	612.549	13.32	2.74E-02	-0.27	down	2.55	up
616.4925@12.77	617.4925	12.77	2.82E-02	-1.92	down	-3.24	down
997.6083@12.91	998.6083	12.91	2.83E-02	-0.82	down	-2.58	down
463.8039@10.70	464.8039	10.7	2.84E-02	-2.43	down	-0.49	down
393.749@12.95	394.749	12.95	2.84E-02	-3.23	down	-1.41	down
837.6263@13.78	838.6263	13.78	2.86E-02	0.59	up	-2.16	down
310.246@11.01	311.246	11.01	2.86E-02	-0.91	down	-2.71	down
700.5518@12.91	701.5518	12.91	2.96E-02	-2.06	down	-2.03	down
685.7721@11.44	686.7721	11.44	3.03E-02	-0.05	down	-2.21	down
484.0743@5.95	485.0743	5.95	3.09E-02	0.52	up	-1.77	down
611.1696@8.47	612.1696	8.47	3.12E-02	-2.23	down	-0.44	down
729.5304@13.01	730.5304	13.01	3.16E-02	-2.93	down	-2.66	down
702.1669@10.46	703.1669	10.46	3.19E-02	-1.46	down	0.04	up
506.8219@11.03	507.8219	11.03	3.33E-02	0.62	up	-2.21	down
1204.312@13.28	1205.312	13.28	3.44E-02	-2.86	down	-2.58	down
306.0749@0.45	307.0749	0.45	3.53E-02	-1.84	down	-3.16	down
678.1536@10.82	679.1536	10.82	3.56E-02	3.04	up	-0.16	down
1534.9807@12.89	1535.9807	12.89	3.65E-02	1.36	up	2.14	up
753.1061@10.55	754.1061	10.55	3.70E-02	-0.18	down	-2.41	down
537.2758@9.45	538.2758	9.45	3.88E-02	-2.98	down	-0.43	down
1140.7448@12.90	1141.7448	12.9	3.95E-02	2.1	up	2.39	up
537.5119@12.86	538.5119	12.86	4.01E-02	-2.83	down	-2.09	down
108.0934@10.66	109.0934	10.66	4.03E-02	2.66	up	2.74	up
874.7044@14.21	875.7044	14.21	4.11E-02	-2.1	down	-1.97	down
1055.6434@8.67	1056.6434	8.67	4.13E-02	-1.74	down	-2.51	down
640.5042@13.19	641.5042	13.19	4.16E-02	-0.01	down	1.98	up
787.6197@13.83	788.6197	13.83	4.46E-02	-1.48	down	1.81	up
802.5606@10.88	803.5606	10.88	4.51E-02	2.05	up	2.39	up
529.2104@8.06	530.2104	8.06	4.53E-02	2.23	up	1.82	up
490.1472@0.44	491.1472	0.44	4.58E-02	-1.45	down	-2.46	down
614.482@12.79	615.482	12.79	4.63E-02	2.28	up	2.67	up
616.4197@10.74	617.4197	10.74	4.65E-02	-0.48	down	-0.38	down
583.4293@10.89	584.4293	10.89	4.75E-02	1.58	up	0.02	up
460.3736@12.56	461.3736	12.56	4.77E-02	-2.78	down	-2.68	down
325.0694@2.45	326.0694	2.45	4.81E-02	-1.2	down	1.16	up

489.8041@10.99	490.8041	10.99	4.95E-02	-3.16	down	-0.87	down
399.2835@6.16	400.2835	6.16	4.99E-02	-0.96	down	-2.62	down