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REVIEW ARTICLE

Clinical advances in analytical profiling of signature lipids: implications for severe non-communicable and neurodegenerative diseases

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Abstract

Background Lipids play key roles in numerous biological processes, including energy storage, cell membrane structure, signaling, immune responses, and homeostasis, making lipidomics a vital branch of metabolomics that analyzes and characterizes a wide range of lipid classes. Addressing the complex etiology, age-related risk, progression, inflammation, and research overlap in conditions like Alzheimer's Disease, Parkinson's Disease, Cardiovascular Diseases, and Cancer poses significant challenges in the quest for effective therapeutic targets, improved diagnostic markers, and advanced treatments. Mass spectrometry is an indispensable tool in clinical lipidomics, delivering quantitative and structural lipid data, and its integration with technologies like Liquid Chromatography (LC), Magnetic Resonance Imaging (MRI), and few emerging Matrix-Assisted Laser Desorption Ionization- Imaging Mass Spectrometry (MALDI-IMS) along with its incorporation into Tissue Microarray (TMA) represents current advances. These innovations enhance lipidomics assessment, bolster accuracy, and offer insights into lipid subcellular localization, dynamics, and functional roles in disease contexts.

Aim of the review The review article summarizes recent advancements in lipidomic methodologies from 2019 to 2023 for diagnosing major neurodegenerative diseases, Alzheimer's and Parkinson's, serious non-communicable cardiovascular diseases and cancer, emphasizing the role of lipid level variations, and highlighting the potential of lipidomics data integration with genomics and proteomics to improve disease understanding and innovative prognostic, diagnostic and therapeutic strategies.

Key scientific concepts of review Clinical lipidomic studies are a promising approach to track and analyze lipid profiles, revealing their crucial roles in various diseases. This lipid-focused research provides insights into disease mechanisms, biomarker identification, and potential therapeutic targets, advancing our understanding and management of conditions such as Alzheimer's Disease, Parkinson's Disease, Cardiovascular Diseases, and specific cancers.

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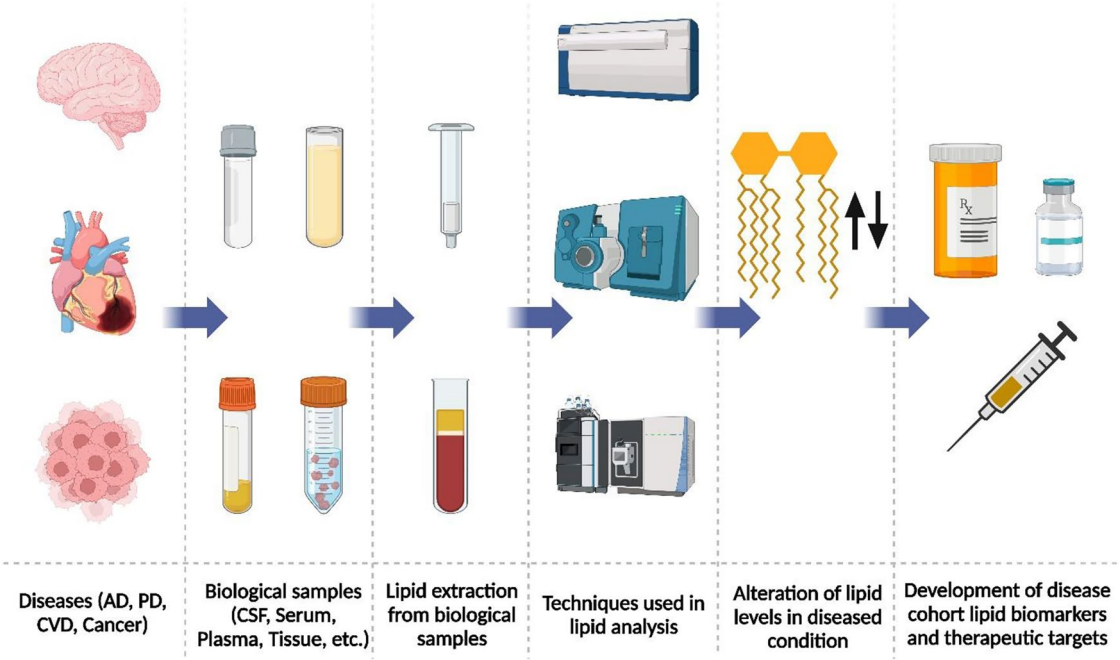
Graphical abstract



Lipidome analysis methodology in major diseases and discovery of therapeutics and biomarkers

Keywords Alzheimer's · Cardiovascular · Cancer · Lipidomics · Mass-Spectrometry · Parkinson's

Abbreviations

2HG	2-Hydroxyglutarate
AA	Arachidonic acid
ACC1	Acetyl-Coenzyme A carboxylase 1
ACLY	ATP citrate lyase
AD	Alzheimer's Disease
AdA	Adrenic acid
AHA	American Heart Association
AKT YapS127A	Protein Kinase B/Yes-associated protein 1 (mutated)
AMPK	AMP-activated protein kinase
apoA-I	Apolipoprotein A-I
APP	Amyloid Precursor Protein
ASCVD	Atherosclerotic cardiovascular disease
ATP	Adenosine triphosphate
AUC	Area Under the ROC Curve
Bax	Bcl-2-associated X protein
BCFA	Branched-chain Fatty Acid
BCL2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
CD274	Cluster of differentiation 274
CE	Cholesterol ester
Cer	Ceramide
CLRD	Chronic Lower Respiratory Disease
CRC	Colorectal Cancer
CSC	Cancer Stem Cell
CSF	Cerebrospinal Fluid
CTLA4	Cytotoxic T-lymphocyte–associated antigen 4
CVD	Cardiovascular Disease
DDA	Data-Dependent Acquisition
DHA	Docosahexaenoic acid
DIA	Data-Independent Acquisition
ECM	Extracellular matrix
ELOVL6	Long-chain fatty acids family member 6
EPA	Eicosapentaenoic acid
FA	Fatty acid
FABP5	Fatty acid-binding protein 5
FADS1	Fatty acid desaturases 1
FADS2	Fatty acid desaturases 2
FASN	Fatty Acid Synthase
FIA-MS/MS	Flow Injection Analysis Tandem Mass Spectrometry
FTICR	Fourier-transform ion cyclotron resonance
GC	Gas Chromatography

GC	Gastric cancer
GL	Glycerolipid
GP	Glycerophospholipid
GPX4	Glutathione peroxidase 4
HAVCR2	Hepatitis A virus cellular receptor 2
HDL-C	High-density lipoprotein Cholesterol
HER2	Human epidermal growth factor receptor 2
HETE	Hydroxyeicosatetraenoic acid
HexCer	Hexosylceramides
HILIC	Hydrophilic interaction liquid chromatography
HRMS	High Resolution Mass Spectrometry
HR-MS	Shotgun high-resolution mass spectrometry
HSL	Hormone-sensitive lipase
ICC	Intrahepatic cholangiocarcinoma
IDL	Intermediate-Density Lipoproteins
IS	Internal Standard
KAROLA	Langzeiterfolge der KARdiOLogischen Anschlussheilbehandlung
KRAS	Ki-ras2 Kirsten rat sarcoma virus
LAG3	Lymphocyte activating 3 gene
LC	Liquid Chromatography
LC-ESI MS	Liquid Chromatography – Electrospray Ionization Mass Spectrometry
LC–MS/MS	Liquid Chromatography – Tandem Mass Spectrometry
LDL	Low-density lipoprotein
LDL-C	Low-density lipoprotein Cholesterol
LDLR	Low-density Lipoprotein Receptor
LIPID	Long-Term Intervention with Pravastatin in Ischaemic Disease
LM	Lipid Mediator
LMN	LipidMatch Normalization
LPC/LysoPC	Lysophosphatidylcholine
LPE	Lysophosphatidylethanolamine
LPI	Lysophosphatidylinositol
LR-MS	Shotgun low-resolution mass spectrometry
LSI	Lipidomics Standard Initiative
MALDI-IMS	Matrix Assisted Laser Desorption Ionization – Imaging Mass Spectrometry
MAPK	Mitogen-activated protein kinase/
MCI	Mild Cognitive Impairment
MHC	Monohexosylceramide
mIDH1	Cytosolic isocitrate dehydrogenase 1
MPTP	1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic Resonance Imaging
MRI-MS	Magnetic Resonance Imaging – Mass Spectrometry
MRM	Multiple Reaction Monitor
MRS	Magnetic Resonance Spectrometry
MS-DIAL	Mass Spectrometry – Data Independent Analysis
MSI	Mass Spectrometry Imaging
MTBE	Methyl tert-butyl ether
mTORC2	Mammalian target of rapamycin complex 2
MUFA	Monounsaturated fatty acids
NFT	Neurofibrillary tangles
NMR	Nuclear Magnetic Resonance
OCFA	Odd-chain Fatty Acid
PA	Phosphatidic acid
PAG	Phenylacetylglutamine
PC	Phosphatidylcholine
PCA	Principal Component Analysis
PD	Parkinson's Disease
PDCD1	Programmed cell death 1
PE	Phosphatidylethanolamine
PI	Phosphatidylinositol
PL	Phospholipid
PPARα	Peroxisome proliferator-activated receptor alpha
PPARγ-ACLY/ACC	Peroxisome proliferator-activated receptor gamma ATP-citratelyase/ acetyl-CoA carboxylase
PQN	Probabilistic Quotient Normalization
PRM	Parallel Reaction Monitor
PS	Phosphatidylserine
PUFA	Polyunsaturated fatty acids
QQQ	Triple Quadrupole
Q-TOF	Quadrupole Time-of-Flight
ROC	Receiver operating curve
ROS	Reactive Oxygen Species
RPLC	Reverse Phase Liquid Chromatography
RP-UHPLC/MS	Reversed-phase Ultra-high Performance Liquid Chromatography/ Mass Spectrometry
SCD1	Syndecan-1
SFA	Saturated fatty acids
SILL	Strategy Inventory of Language Learning
SIM	Single Ion Monitoring
SM	Sphingomyelin

SREBP-1c	Sterol regulatory element-binding protein 1
STAT	Signal Transducer and Activator of Transcription
SWATH	Sequence Window of All Theoretical Fragment Ion Spectra
TG	Triacylglycerol
TIGIT	T cell immunoreceptor with immunoglobulin and ITIM domain
TIL	Tumor Infiltrating Lymphocytes
TIMS	Trapped Ion Mobility Spectrometry
TLC	Thin layer Chromatography
TMA	Tissue Microarray
TNBC	Triple Negative Breast Cancer
TVB-2640	Denifanstat
UHPLC	Ultra High-Performance Liquid Chromatography
UHPSFC-MS	Ultra-High Performance supercritical fluid chromatography/mass spectrometry
UPLC-MS/MS	Ultra-High Performance Liquid Chromatography – Tandem Mass Spectrometry
USP22	Ubiquitin specific peptidase 22
VLDL	Very low-density lipoprotein
WECAC	The Western Norway Coronary Angiography Cohort
Zeb1	Zinc-finger E-box-binding homeobox 1
Zeb2	Zinc-finger E-box-binding homeobox 2
αS	Alpha-synuclein

1 Introduction

Lipids play an indispensable role in biological systems, including cell signaling, storage of energy, and they also form a major component of cell membrane, lipoproteins, and exosomes. Lipids comprise of 13% of total dry weight of a mammalian cell (Feijó Delgado et al., 2013). An organism naturally maintains lipid levels to keep homeostasis (Berná et al., 2023), but in cases of altered physiological conditions, concentration of cellular lipids is impacted, sometimes very significantly, thereby making them potential biomarkers for various diseases. Meticulous study of lipid metabolism has been enabled by implementation of lipidomics. Advent of soft ionization technologies in the 1980s that allowed intricate quantitation and identification of lipids, have made it possible for researchers to delve into a deeper understanding of lipid metabolism, and development of lipidomics (Han & Gross, 2022).

During the early stages of investigating lipid metabolism, researchers predominantly utilized radioactively tagged substances and thin layer chromatography (TLC) as their primary experimental techniques (Deranieh et al., 2013). The utilization of very sensitive mass spectrometry (MS), in conjunction with innovative separation methodologies, has significantly propelled the field of lipidomic investigation (Giera et al., 2022). Gas chromatography (GC) was employed throughout the preliminary stages of the investigation to analyze sterols and fatty acids (Williams et al., 2021). In contrast, the application of liquid chromatography tandem mass spectrometry (LC–MS/MS) has facilitated the efficient separation of lipids from intricate samples (Züllig & Köfeler, 2021). The utilization of triple quadrupole (QQQ) mass spectrometry (MS) analyzers operating in the multiple reaction monitoring mode (MRM) is required for the successful implementation of targeted lipidomics. However, untargeted lipidomics refers to the use of high-resolution mass spectrometry (HRMS), followed by informatics analysis utilizing databases such as MS-DIAL (Tsugawa et al., 2020) and METLIN (Xue et al., 2020).

It is incontrovertible that serious non-communicable cardiovascular diseases (CVD) along with various types of cancer, have high mortality rates if untreated but debilitating neurodegenerative diseases like AD and PD have created a socio-economic quagmire. In the previous decades, genomics and proteomics have been implemented to study these diseases, to gain a better understanding of their mechanism (Castegna et al., 2002; Jungblut et al., 1999). However, lipidomics have opened a new frontier in the quest to understand these diseases and to discover new therapeutic targets and diagnostic procedures for these complex diseases. The advent of technologies in lipidomics has enabled large cohort studies with an extensive dataset, that can be utilized to delve into the etiology of diseases as well as therapeutics. (Meikle et al., 2021).

Lipidomic studies can help in unraveling lipid-lipid interaction and interaction of lipids with other biomolecules such as metabolites and proteins (Barker-Tejeda et al., 2021). In this review article, we are going to focus on analytical methods and advancements in lipid profiling and its significant role in human diseases where aberrations in lipid profile cause serious non communicable diseases like cardiovascular diseases (CVD), few types of cancers and neurodegenerative diseases like Alzheimers disease (AD), Parkinson's disease (PD) (Tables 1 and 2).

2 Lipids are a diverse group of biomolecules

Every lipid molecule is composed of a distinct head group possessing a unique chemical composition, which is then esterified to hydrophobic tails composed of fatty acyl chains

Table 1 Lipidomics applied in neurodegenerative disorders such as PD and AD

S.No	Disease	Sample	Method	Major findings	References
1	PD and GD	Human blood serum (278)	HLPC-MS	Elevated levels of PC, PE, LPE were observed in serum samples of both PD and GD patients. P-PE was increased in serum samples of PD patients. However, PG and LPS were elevated in serum samples of GD patients only	López de Frutos et al. (2022)
2	PD	Mouse liver (5)	GC/MS and UHPLC/MS	Long-chain saturated FAs (C14:0, C15:0 and C20:0), monounsaturated long- and very long-chain FAs (C19:1, C20:1, C22:1, C24:1) and polyunsaturated long- and very long-chain (C18:3, C18:4, C20:2, C20:3, C20:5, C22:4, C22:5, C22:6), PC16:0, PC17:0, PC18:0, PC16:1, PC18:2, PC20:3, PC20:4, PC22:6 and PE16:0, carnitines C6:0 or C18:0 were decreased in mice liver samples	Corral Nieto et al. (2023)
3	PD	Human putamen (30)	ESI-HR-MS	Cer (16:0 and 18:0) and Hydroxyceramide (18:0) levels were reduced in patients with PD)	Beger, Dudzik, et al. (2022)
4	PD	Human CSF (30)	UPLC-ESI-qToF-MS/MS	TG, SAFA, MUFA, PC, Cer, and SM downregulated in PD patients	Fernández-Irigoyen et al. (2021)
5	AD	Human CSF (91)	LC-ESI-qToF-MS/MS	Elevated levels of OxCer(40:6) and decreased levels of OxTG(57:2) in CSF samples of AD patients with severe OSA was observed	Dakterzada et al. (2023)
6	AD	Human plasma (40)	LC-QqQ-MS	Upregulation of GP and Cer was observed. Conversely, SP and some other PL were downregulated in AD patients	Reveglia et al. (2023)
7	AD	Human plasma and frontal brain cortex tissue (229)	UHPLC-MS/MS and FIA-MS/MS	Elevated levels of saturated AC (3:0, 8:0, 10:0, 18:0), polyunsaturated and diacyl PC, LPC, Cer, unsaturated TG, diglycerides, and cholesterol species were observed in AD patients	Kalecký et al. (2022)
8	MCI	Human plasma (1255)	LC/ESI/MS/MS	The levels of C18:0, C23:0, C24:1, C18:0, C24:1, C24:1, C40:3 were significantly altered in patients with MCI, suggesting strong correlation with the disease. These lipids are potential biomarkers for MCI	Wang et al. (2021)

MeSH terms used: 'Lipidomics AND Alzheimers disease AND alteration of lipids' and 'Lipidomics AND Parkinson's disease AND alteration of lipids'

Table 2 Application of lipidomic techniques in cardiovascular diseases for developing better therapeutics

S.No	Disease	Sample	Method	Major findings	References
1	Hypertrophic Cardiomyopathy (HCM)	Myocardial tissue (42)	LC–MS	A significant elevation of free FA, CE, PC, PE, LPC, and LPE levels was observed. Cer and SM levels were also increased in the samples. Levels of TG and all AC were decreased in the HCM myocardial tissue samples	Ranjbarvaziri et al. (2021)
2	CVD and Type II Diabetes	Blood plasma (27,548)	LC–MS/MS	Elevated levels of TG, total cholesterol, and decreased levels of HDLC were observed in the plasma samples from EPIC-Potsdam Cohort Study. However, in the general population, increased levels of CE, FFA, TG, PC, and SM and decreased levels of Cer, dhCer, LacCer, HexCer, PEO, and LPE were found. Several FAs such as FA16:0, FA18:0, FA18:1, FA18:2, and FA20:4 was upregulated, whereas FA18:4, FA22:2, FA26:0, and FA26:1 were downregulated	Eichelmann et al. (2022)
3	Atherosclerosis and Osteoporosis	Blood serum (1494)	LC–MS/MS	12 modules of lipids were studied, out of which 1 lipid module was correlated to both atherosclerosis and osteoporosis. The abundant lipids in this module were GL, GP, SP, and Cer	Mishra et al. (2020)
4	Ischemic cardiomyopathy	Tissue from right ventricle (RV), left ventricle (LV) and infarcted left ventricle (LV INF) of explanted human hearts ischemic cardiomyopathy patients (27)	LC-HRMS	Infarcted tissues were found to have increased levels of SM, HexCer, and CE. Conversely, GP levels decreased	Samouillan et al. (2020)

MeSH terms: 'Lipidomics AND Cardiovascular diseases AND alteration of lipids'

or sphingoid bases (Raghu, 2020). Specific chemical and physical properties of the lipids are responsible for their diverse biological functions. Number of scientific studies have shown that changes in the lipid metabolism and its homeostasis is connected to many serious diseases including cancers, cardiovascular diseases and neurodegenerative diseases amongst many others (Chen et al., 2021; Chiurchiù et al., 2022; Fais et al., 2021; Zhou et al., 2021).

2.1 Lipids to lipidome

During the initial stages of the research on lipids, studies were focused on specific molecules. But the necessity to draw a complete picture of how lipids are crucial for the health and disease of an individual gave rise to 'lipidomics'. The term 'lipidome' refers to the entirety of distinct lipid molecular species present within a biological system, cell, or organ (Kishimoto et al., 2001). The term 'lipidomics' deals with the interaction between lipids and other molecules (Lagarde et al., 2003; Wenk, 2005). Lipidomics encompasses a diverse range of methodologies aimed at the identification of distinct lipid species within a cellular context. This comprehensive approach facilitates the elucidation of the intricate mechanisms governing lipid-lipid interactions and their interactions with other molecules (Han & Gross, 2003). The difference in the very nature of molecules that are under investigation in two different cases is majorly responsible for the differentiation between lipidomics and metabolomics, alongside the techniques involved in both these disciplines (Kostidis et al., 2023). Over an extensive duration, the principal emphasis of metabolomics was zeroed on molecules that are soluble in water, whereas conversely, lipidomics is oriented towards molecules that are insoluble in water. The conglomeration of these features has catalyzed the various advancements achieved in the realm of lipidomics, encompassing an array of analytical techniques and informatics strategies. Similar to other analytical methodologies, lipidomics adheres to a specific workflow that is summarized in the workflow (Fig. 1). The key stages of lipid analysis include (a) the collection of samples through a process known as sampling and the proper storage of samples, (b) the preparation/extraction of samples and sample normalization (c) analytical calibration, (d) the actual analysis through analytical instrument, (e) processing and normalization of data, followed by (f) statistical evaluation and (g) validation of the data (Jurowski et al., 2017; Kvasnička et al., 2023). Unique techniques employed in lipidome studies includes MALDI-IMS comprising Matrix-assisted laser desorption/ionization imaging mass spectrometry (Garrett et al., 2007), has been utilized to detect and identify biological samples, simultaneously (Goto-Inoue et al., 2011). The extraction and purification of lipids, which is the core bottleneck in the workflow, often leads to the loss of lipid distribution in valuable tissues.

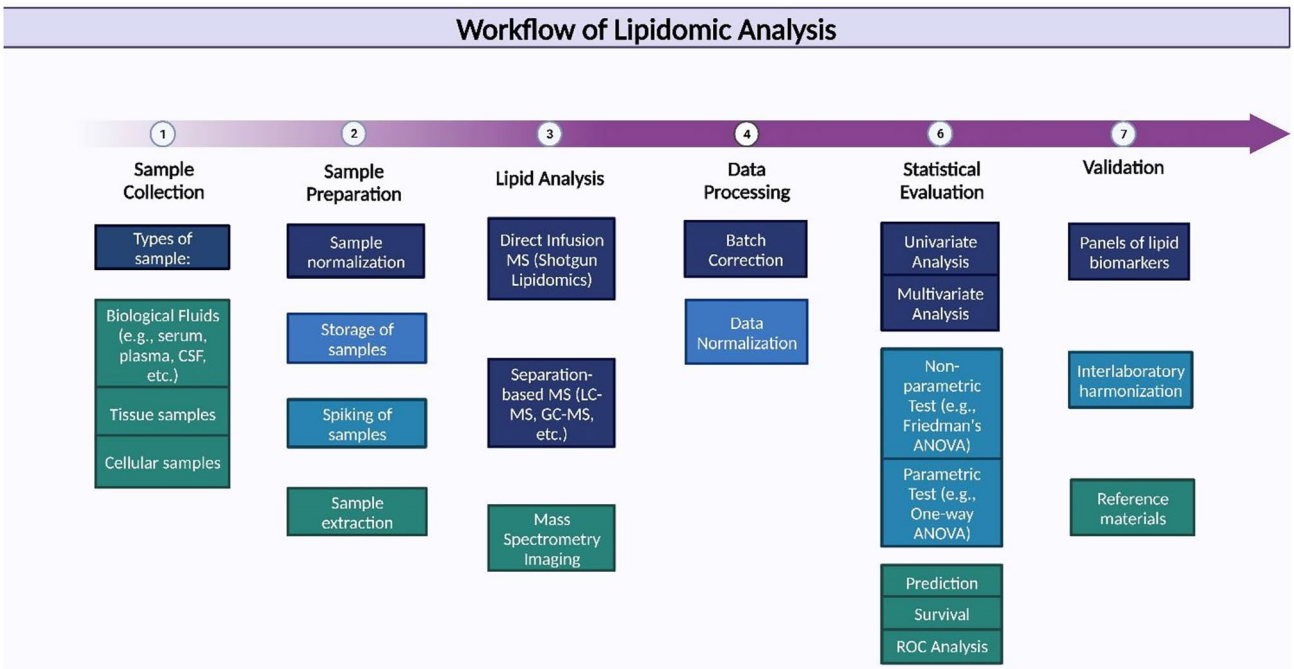


Fig. 1 The workflow showing processes of extraction, analysis and evaluation of lipidome study of biological samples

3 Workflow of lipidomics

3.1 Biological samples

Lipidomic studies employ various biological samples, such as biological fluids, tissue samples, and cellular samples, depending on the specific research objective. Biomarkers are primarily studied using biological fluid samples, while tissue samples are employed to investigate the underlying mechanisms of the pathophysiological process (Chetwynd et al., 2017). It was observed that the predominant sample types utilized in publications were plasma, serum, and tissue and these sample types constituted 38%, 22%, and 16% of the total articles, respectively during the year 2022 (Géhin et al., 2023). While plasma and serum samples have been commonly used in recent publications, the effectiveness of the most popular extraction methods for cerebrospinal fluid (CSF) remains uncertain as the lipid content is significantly less in CSF, when compared to serum. CSF is a crucial biological sample for investigating neurological disorders like Alzheimer's and Parkinson's disease (Reichl et al., 2020). Other unconventional samples such as apocrine sweat (Kvasnička et al., 2021), tears (Cicalini et al., 2019), sebum (E. Sinclair et al., 2021) and saliva (Caterino et al., 2023) have been also used in lipidomic studies.

3.2 Sample normalization

A key objective in quantitative lipidomics is to determine the concentration of individual metabolites across multiple samples, as the quantity of these metabolites can vary based on the shape, size, and weight of the sample. Normalization is crucial for precise lipid quantification and dependable comparison among samples. The desired concentration of lipids in a sample can be achieved by weighing the sample, determining its lipid content, and adjusting the weight or volume accordingly and comprise the initial first steps after sample collection (Wu & Li, 2016).

3.3 Handling and storage of samples

The proper storage and handling of samples are vital steps within the lipidomics workflow. Many investigations have provided evidence indicating that the selection of collecting tubes and the specific anticoagulant utilized can exert a substantial influence on the lipid extraction process and the ionization of blood samples in mass spectrometry (Dorow et al., 2016; Kano et al., 2021; Wolrab et al., 2020). The utilization of formaldehyde for tissue fixation may impact lipid analysis due to the formation of a fixation gradient, wherein the surface layers are more extensively fixed compared to the deeper layers (Bauer et al., 2016). Consequently, this gradient might result in autolytic degradation of the deeper tissue layers (McFadden et al., 2019). Several research findings emphasize the influence of preservation methods on the lipid classes detected, leading to compromised data quality (Beger, Hauther, et al., 2022; Yadav et al., 2022). Thus, evaluation of the preservation techniques prior to their implementation becomes utterly necessary. The concentration of lipids may undergo significant changes if preanalytical conditions are not suitable, necessitating certain precautions to maintain their in vivo concentration. In 2023, a comparative study was conducted on tissue samples collected from the heart, liver, kidney and spleen of mice. The samples were stored in ice water and as a control, some of the samples were also stored at room temperature. It was observed that, after 35 min, the change in lipid ratio was 60% in room temperature, whereas, only about 10% in samples stored in ice water (Dorochow et al., 2023). According to another study conducted on blood sample of 83 individuals, it was observed that 325 and 288 robust lipid species resisted instabilities for up to 24 h at 21 °C and 30 °C, respectively (Wang et al., 2023b). The collected samples should be preserved by subjecting them to freezing conditions in liquid nitrogen at a temperature of −80 °C (Köfeler et al., 2021).

3.4 Spiking of samples

Given the lack of agreement on optimal procedures for lipidomics workflow, it is imperative to establish a consensus within the scientific community on the best practices. This consensus will ensure that lipids do not degrade or undergo changes during the process of sample collection and storage. Implementing standardization protocols can enhance the reliability of the outcome. Inadequate sample methods, inappropriate storage temperatures, and flawed analytical procedures can lead to the deterioration of intricate lipids and the production of oxidized or hydrolyzed metabolites. Hence, it is crucial to consider enzymatic activity and the avoidance of lipid oxidation during sample preparation (Ulmer et al., 2021). During sample preparation antioxidants can be administered to decrease oxidation of lipids. There are numerous ways an antioxidant can prevent or minimize oxidation, such as by neutralizing the oxidation products, by eliminating free radicals, chelating metals and ions and preventing enzyme activation (Blanco & Blanco, 2017; Lü et al., 2010). Some examples of antioxidants include methyl silicone, ascorbic acid, transferrin, deferoxamine etc. (Ulmer et al., 2021). Lipids are very sensitive to temperature, can undergo polymerization as well as hydrolysis, which might interfere with results, due to which spiking of samples is needed especially when comparing samples. The addition of a predetermined quantity of lipid standards to biological samples is vital, as it serves to rectify discrepancies in

extraction efficiency, ionization efficiency, and instrument sensitivity. This practice enables accurate quantification of lipids within the samples. The samples have the potential to be enriched with isotopically labeled lipid standards. (Reichl et al., 2020).

3.5 Sample extraction

The extraction process may be classified into numerous categories, with monophasic and biphasic being the most prevalent methods. Triphasic extraction, also known as Three-phase liquid extraction (3PLE), offers advantages over the widely used Bligh/Dyer Liquid–liquid extraction method. The 3PLE approach is a one-step liquid–liquid extraction process, including an aqueous phase and two organic phases. The use of 3PLE has greatly enhanced the identification of lipids in direct-infusion workflows by reducing ion suppression, resulting in a considerable increase in the quantity of lipids detected. Additionally, it facilitated the detection of less common lipids, such as phosphatidic acid and phosphatidylserine, which are present in lesser quantities. Furthermore, 3PLE demonstrated its usefulness as a suitable instrument for fatty acid profiling using GC/MS, enabling the distinct identification of both neutral and polar fatty acids (Vale et al., 2019). Phospholipids may be detected and isolated by the use of Solid Phase Extraction (SPE), which employs silica gel-aminopropyl-silica gel SPE cartridges for the purpose of separation. This technique has effectively been used for the separation and identification of phosphatidylcholine, lysophosphatidylcholine, phosphatidylethanolamine, phosphatidylglycerol, phosphatidic acid, phosphatidylinositol, phosphatidylserine, cardiolipin, and sphingomyelin. The separation process occurs in four stages, which are determined by the polarity of the headgroup. The sample was obtained using LC–MS technology. Solid-phase extraction (SPE) has been shown to be very effective in removing both polar and non-polar impurities from phospholipids, as well as preventing peak overlap that often results in ion suppression (Fauland et al., 2013). The Folch extraction technique which employs methanol and chloroform is commonly recognized as the standard method for extraction (Géhin et al., 2023). However, the Matyash extraction, which involves a combination of methyl tert-butyl ether (MTBE) and methanol, has demonstrated improved comprehensiveness and repeatability of metabolites and is one of the most used extraction techniques used in 2022 lipidomics studies (Géhin et al., 2023). Additionally, the Matyash extraction aligns with the principles of green chemistry by eliminating the need for chloroform. Although it results in a reduction in the maximum level of intensity (Avela & Sirén, 2020). When dealing with cerebrospinal fluid (CSF) as a sample, it is crucial to employ a highly sensitive extraction technique due to its lower lipid content in comparison to serum or plasma. Research findings have indicated that the modification of the Folch extraction method is very appropriate for extracting several lipid classes from cerebrospinal fluid (CSF), such as glycerophospholipids, glycerolipids, and sphingolipids (Reichl et al., 2020). A comparative analysis of three biphasic extraction methods for the extraction of polar and non-polar compounds. These methods include chloroform/methanol/water, dichloromethane/methanol/water, and MTBE/methanol/water (Southam et al., 2021). In addition, the researchers conducted a comparison between a monophasic extraction approach utilizing a mixture of acetonitrile, methanol, and water for polar component extraction, and a monophasic extraction method employing a combination of isopropanol and water for nonpolar compound extraction. The polar extracts were subjected to analysis using hydrophilic interaction chromatography (HILIC) coupled with ultrahigh-performance liquid chromatography–mass spectrometry (UHPLC–MS), whereas the nonpolar extracts were examined using C18 reversed-phase UHPLC–MS. The researchers discovered that monophasic approaches exhibited superior yield and repeatability compared to biphasic methods. Sarafian and her colleagues conducted a comparison of eight different sample preparation techniques to optimize the extraction and measurement of blood plasma lipids using UPLC-MS lipid profiling. Isopropanol (IPA) was found to be the most resilient solvent, capable of extracting a wide range of lipid species. It is particularly well-suited for efficient and comprehensive lipid profiling utilizing UPLC-MS in high-throughput settings. The scientists found that employing isopropanol precipitation is a more straightforward method that can enhance the effectiveness of protein removal, as well as improve lipid coverage and recovery (Sarafian et al., 2014). Additional research has also demonstrated that monophasic extraction utilizing IPA was simpler and yielded one of the most significant detection responses among all identified lipid classes, with a high level of reproducibility (Calderón et al., 2019; Southam et al., 2020). Therefore, monophasic approaches have been determined to be more efficient, simpler, and more suited for potential automation (Southam et al., 2021) (Fig. 2).

3.6 Separation techniques

Lipidomics research often utilizes gas chromatography (GC) or liquid chromatography (LC)-based separation methods. Initially GC-EI (electron ionization) MS was used to analyze lipids. The implementation of separation strategies serves to mitigate the intricacy inherent in biological matrices. The prevailing method employed for lipidomic investigations is reverse phase liquid chromatography (RPLC). In the year 2022, a significant proportion of published literature, approximately 73%, referred to the

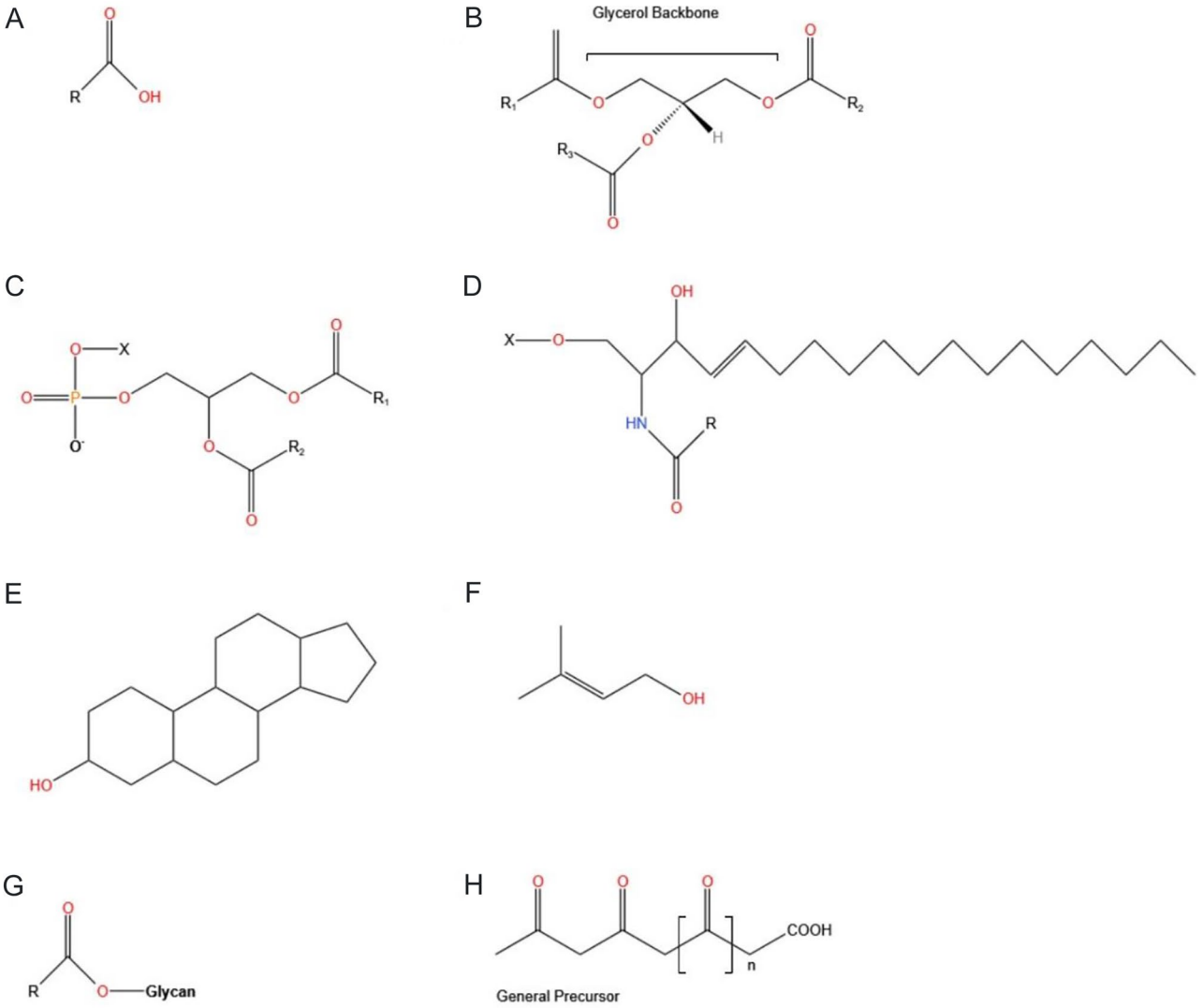


Fig. 2 (**a**) Representation of various Lipid Classes. (A) Fatty Acids (FA), where R represents the acyl chain. (B) Glycerolipid (GL), where R1, R2, and R3 represent various acyl chains. Represented 'Glycerol background' might include monoacylglycerol (MG), diacylglycerol (DG) or triacylglycerol species (TG). (C) Glycerophospholipid/Phospholipid (GP/P) (structure represents phospholipid with a hydrophilic head and hydrophobic tail), where R1 and R2 represent acyl chains. X represents hydrogen/choline(PC)/ethanolamine(PE)/serine(PS)/inositol(PI)/phosphatidylglycerol/glycerol(PG). (D) Sphingolipid (SP), where R represents acyl chain, and X represents Hydrogen(Cer)/phosphocholine(SM)/glucose/galactose/lactose/oligosaccharide/sugar + sulphate. (E) Sterol lipid (ST). (F) Prenol lipid (PR). (G) Saccharolipid (SL), where R represents acyl chain. (H) Polyketide (PK), where n represents carbonyl groups. (All lipid structures are drawn using free version of online tool Kingdraw and arranged on Biorender canvas). (**b**) Examples of various lipid classes and their IUPAC names: (A) Octadecanoic acid. (B) 1,3-dihydroxypropan-2-yl (13Z)-docos-13-enoate. (C) 1-palmitoyl-2-oleoyl phosphatidylethanolamine. (D) N-[(2S,3R,4E)-1,3-dihydroxyoctadec-4-en-2 yl] pentacosanamide. (E) (1S,2R,5S,10S,11S,14R,15R)-2,15-dimethyl-14-[(2R)-6-methylheptan-2-yl]tetracyclo[8.7.0.0^{2,7}.0^{11,15}] heptadec-7-en-5-ol. (F) 2-methyl-3-[(2E,7R,11R)-3,7,11,15-tetramethylhexadec-2-en-1-yl]-1,4-dihydronaphthalene-1,4-dione. (G) [(2R,3S,4R,5R,6R)-5-[(3R)-3-(dodecanoyloxy) tetradecanamido]-6-{[(2R,3S,4R,5R,6R)-3-hydroxy-5-[(3R)-3-hydroxytetradecanamido]-4-{[(3R)-3-hydroxytetradecanoyl]oxy}-6-(phosphonooxy)oxan-2-yl]methoxy}-2-(hydroxymethyl)-4-{[(3R)-3-(tetradecanoyloxy)tetradecanoyl]oxy}oxan-3-yl]oxy}phosphonic acid. (H) (4S,4aS,5aS,6S,12aS)-4-(dimethylamino)-3,6,10,12,12a-pentahydroxy-6-methyl-1,11-dioxo-1,4,4a,5,5a,6,11,12a-octahydrotetracene-2-carboxamide. (All lipid structures are drawn using free version of online tool Chem4draw and arranged on Biorender canvas)

utilization of the RPLC separation approach. The other separation techniques employed include hydrophilic interaction liquid chromatography (HILIC) in 5% of the studies, and gas chromatography in 5% of the studies (Géhin et al., 2023). A recent study assessed the quantification of lipid concentration using HILIC and RPLC methodologies. The study also contrasted the results determined for the same

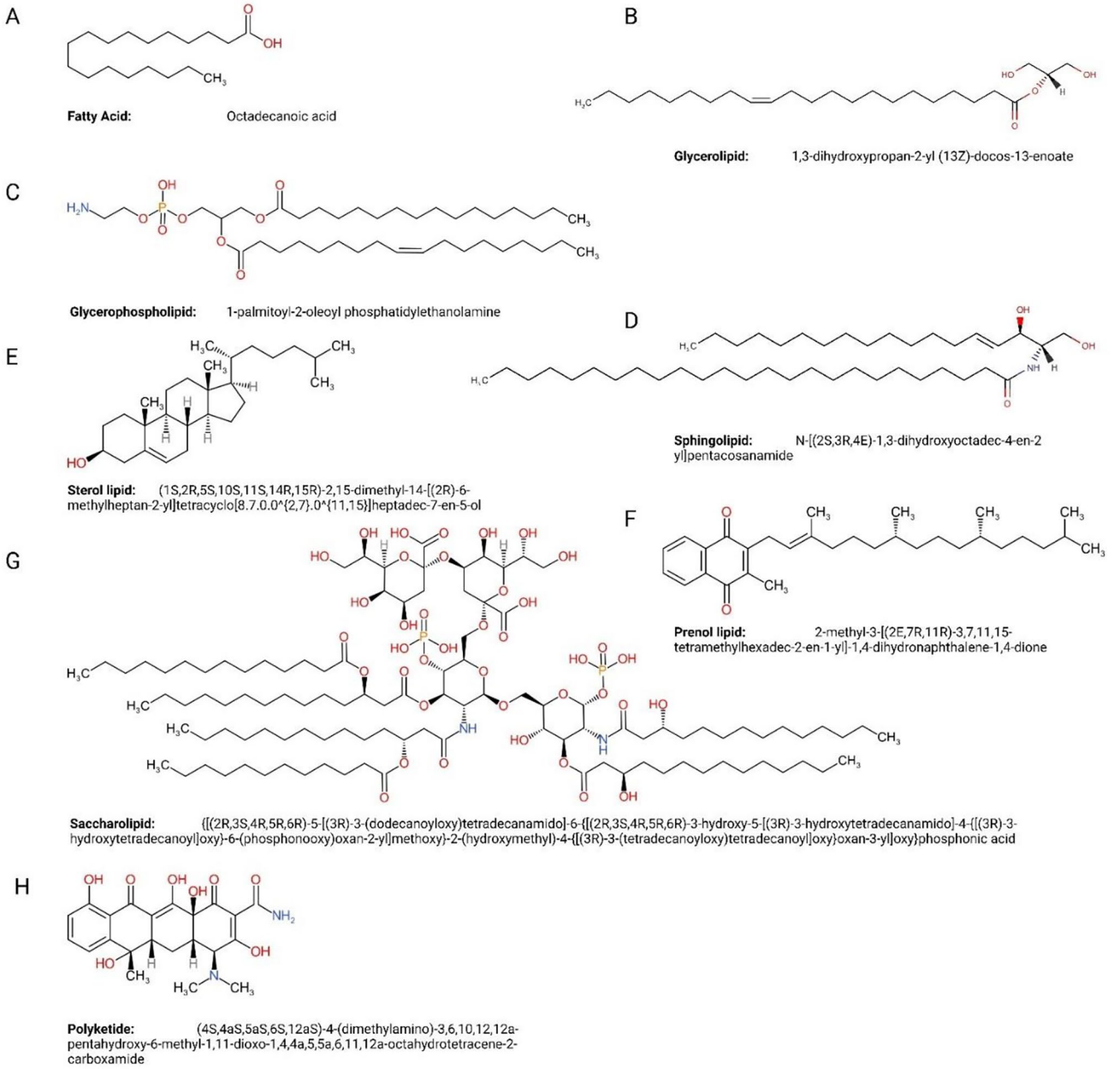


Fig. 2 (continued)

lipid species in NIST SRM 1950 human blood with those acquired in a previously reported multi-laboratory inquiry. The researchers have shown that, despite differences in the matrix effects, both procedures yield similar outcomes for PE, LPE, and SM, which align with the existing consensus values. Nevertheless, when measuring the amounts of LPC lipids, the HILIC approach produced greater quantities in comparison to RPLC MS, especially for PC lipids that are highly unsaturated (Lange & Fedorova, 2020).

3.7 Lipidome analysis

Mass spectrometers are often preferred as detectors because of their exceptional specificity and sensitivity. Furthermore, the mass spectrometers have a broad range of applicability, enabling the identification of a diverse array of lipids (Züllig et al., 2020). A significant proportion of the published literature, approximately 95%, referred to the utilization of Mass Spectrometry (MS) as a detection technique. Three of the most used MS techniques used in current studies involve

direct infusion MS (also called "shotgun lipidomics"), chromatographic techniques coupled with MS and more recently mass spectrometry imaging (MSI) (Géhin et al., 2023). Separation of lipid ions in the gas phase was made possible by a gas phase electrophoretic technique which is, ion-mobility mass spectrometry (IMS) (Paglia et al., 2015). The separation of lipid ions occurs within a chamber that is pressured and contains a buffer gas, such as Nitrogen (Lapthorn et al., 2013). IMS, when amalgamated with MS, has a number of benefits. The combination of these two techniques enables determination of the collision cross section (CCS), which enhances the accuracy of lipid identification. The peak capacity and signal-to-noise ratio of IMS-MS is superior to the traditional techniques. The IMS-MS combination is suggested to improve the specificity of MS/MS-based approach (Paglia et al., 2015).

3.7.1 Targeted lipidomics

Targeted lipidomics is a methodology employed to find and quantify distinct lipid compounds through the utilization of discovery experiments and relevant literature. When doing targeted lipidomics, a predetermined group of lipids is analyzed in a quantitative manner. The quadrupole linear ion trap is commonly employed in conjunction with multiple reaction monitoring (MRM) collection because to its extraordinary characteristics, such as its wide linear range, enhanced sensitivity, and amazing stability (Lin et al., 2019). MRM, also known as multiple reaction monitoring, is a quantitative mass spectrometry approach that is primarily concerned with the monitoring of particular precursor ions and their matching product ions. In the process of multiple reaction monitoring (MRM), a particular transition, namely precursor-to-product ion pairs, is typically chosen to specifically target the lipids that are of interest. The utilization of liquid chromatography-multiple reaction monitoring (LC-MRM) is frequently observed in tandem with lipid separation and quantification processes (He et al., 2021). In recent research, there has been an increased utilization of parallel reaction monitors (PRM), quadrupole time-of-flight instruments, and orbitraps, which have demonstrated improved efficacy (Park et al., 2020). The data collecting strategy employed in targeted lipidomics is characterized by its simplicity, as seen by several recent research that have utilized readily accessible technologies like Skyline (Adams et al., 2020) and XCMS-MRM (Park et al., 2020). MRM performed on a high-resolution mass spectrometer (HRMS) offers prospective advantages in terms of resolving power and sensitivity. This analytical technique allows for the identification of a substantial quantity of low molecular weight compounds, generally those with a mass below 600 Daltons (Da). The MRM method demonstrated a notable level of specificity and sensitivity when compared to the Single Ion Monitoring (SIM) technique, as well as a broad linear dynamic range. Nevertheless, the analysis of lipids may be susceptible to matrix effects, which have the potential to impact the precision and reliability of results. MS/MS/MS (MRM3) has some advantages upon classic MRM quantification (Guironnet et al., 2022).

An additional approach, known as Parallel Reaction Monitoring (PRM), is a quantitative mass spectrometry method that enables the concurrent monitoring of all precursor ions and their corresponding product ions within a certain mass range. The technology offers data with a high level of resolution and selectivity. The adoption of PRM in lipidomics is becoming increasingly prevalent due to its capacity to offer extensive lipid profile. The analysis of intricate lipid mixtures, such as those present in biological materials like cells and tissues, might yield significant insights (van Bentum & Selbach, 2021). PRM is being used to augment the existing understanding of the sphingolipidome in zebrafish, the researchers employed PRM-based LC–MS methodology to comprehensively quantify ceramides in zebrafish (Zhang et al., 2019). Similarly, PRM was also used for lipidomic study in yeast and *Enterococcus faecalis* (Tague et al., 2019). One of the foremost benefits of employing PRM in lieu of MRM is the marked reduction in the occurrence of erroneous positive outcomes. The utilization of HRMS-based PRM exhibits a notable degree of precision, effectively discerning precursor ions with a high level of accuracy. The task at hand proved to be unattainable for a triple quadrupole mass spectrometer utilizing multiple reaction monitoring. However, one of the most significant limitations of PRM pertains to its low scan rate, thereby impeding expeditious and efficient analysis (Xu et al., 2020).

3.7.2 Untargeted lipidomics

The high-resolution mass spectrometry (HRMS) technology is widely employed in untargeted lipidomics investigations. Currently, the full scan, data-independent acquisition (DIA), and data-dependent acquisition (DDA) modes of HRMS acquisitions are widely employed. During the full scan mode, a range of m/z data is acquired inside a specific window to create ions corresponding to various molecular species (Defossez et al., 2023). During the DIA acquisition mode, the HRMS conducts a comprehensive scan on the first mass spectrometry (MS1) and then analyzes all precursor ions. The proposal to enhance the selectivity of DIA techniques involves the use of sequential window of all theoretical fragment-ion spectra (SWATH) acquisition (Bonner & Hopfgartner, 2019). In the DDA mode, the HRMS does a comprehensive scan on MS1 and subsequently conducts an analysis of specifically chosen precursor ions. One of the primary advantages of DIA mode over DDA mode is that under-sampling of peaks

does not occur due to its quick acquisition rate (Defossez et al., 2023). The continuous improvement in the capacity and accuracy of MS equipment necessitates the development of novel data processing technologies. Various data analysis tools have shown their usefulness in processing untargeted lipidomics data. Examples of such data analysis tools include Mzmine3 (Schmid et al., 2023), MSDIAL4 (Tsugawa et al., 2020), and Lipostar (Goracci et al., 2017).

3.7.3 Shotgun lipidomics

Shotgun lipidomics does not require a preliminary separation procedure before mass spectrometric analysis. This method is conducted under controlled experimental conditions, maintaining a consistent concentration of lipid solution (Ejsing et al., 2009; Han & Gross, 2003; Hsu, 2018). In addition to reducing the impact of variables that might hinder the accurate identification and measurement of specific lipid species, shotgun lipidomics offers other benefits over LC–MS methods. It can effectively eliminate chromatographic abnormalities and ion-pairing alterations (Han et al., 2012). In addition to that, a thorough tandem MS analysis can be conducted as constant infusion concentration can provide researchers ample time to improve mass spectral signal/noise ratios (Han et al., 2012). The earliest ionization technique employed in shotgun lipidomics is direct infusion-based electrospray ionization. The technical approach has been broadened by the advancement of MALDI matrices that are specific for small molecules (Ibrahim et al., 2017; Shanta et al., 2011). The scope of shotgun lipidomics is further expanded by the advancement of analytical techniques that include direct desorption or imaging analysis, such as desorption electrospray ionization (DESI), liquid extraction surface analysis-mass spectrometry (LESA-MS), and mass spectrometry imaging (MSI) (Ellis et al., 2013; Hall et al., 2017).

Nevertheless, this lipidomic technique is not without its own constraints. The first limitation of the approach is ion suppression. Ion suppression in shotgun lipidomics can manifest in two distinct forms: intraclass ion suppression and interclass ion suppression. The phenomenon of ion suppression renders the signals of lipid species with low abundance and/or poor ionizability nearly undetectable (Hu et al., 2020). Secondly, shotgun lipidomics is unable to distinguish between specific lipid species due to the overlap in their isobaric mass, which hinders the clear identification of lipids. Thirdly, in-source fragmentation is consistently observed in ESI–MS. This approach is unable to distinguish some types of isomers that have a comparable or identical pattern of fragmentation (Hu et al., 2019, 2020).

3.7.4 MRM-based lipidomics

Targeted lipidomics is a specialized analytical approach employed to precisely quantify individual lipids that are integral to specific metabolic pathways. The lipids identified through this process have undergone extensive pre-screening and scholarly examination, indicating that they are likely to serve as a drug target or a promising biomarker. The employment of MS-based multi-reaction monitors (MRMs) and parallel reaction monitors (PRMs) acquisition modes is ubiquitous in both shotgun and LC–MS-based targeted lipidomics. The utilization of ESI in conjunction with triple-quadrupole (QQQ) MRM-based MDMS shotgun lipidomics for targeted lipid detection is widely regarded as a potent methodology due to its exceptional sensitivity, resolution, efficiency, and expansive scope. This methodology empowers lipid researchers to effectively leverage the distinctive benefits inherent in mass spectrometry for lipid examination, and to fully capitalize on the singular physicochemical characteristics of lipid varieties in order to achieve optimal separation and ionization while minimizing ion suppression (Wang & Han, 2016) In the realm of targeted lipidomics, the quadrupole linear ion trap is utilized in conjunction with MRM acquisition, in addition to the triple quadruple MS, due to their exceptional attributes, including its expansive linear range, heightened sensitivity, and remarkable stability (Lin et al., 2019). Even with the manifold benefits, it is essential to acknowledge that MRM-based techniques are subject to certain limitations due to their inherent drawbacks. Owing to the limited resolution of the quadrupole, false positive identifications and inaccurate quantification may arise (Liu et al., 2013). The acquisition of MRM data is subject to a constraint on dwell time, which consequently imposes an upper limit on the ion pair that can be detected. The incorporation of a minimum of two MRM transitions has been observed to yield enhanced outcomes (Cajka & Fiehn, 2016). Contemporary technological progress has enabled the realization of numerous MRM transitions (Giles et al., 2018).

3.7.5 PRM-based lipidomics

In addition to QQQ-based MRM, the utilization of PRM on HRMS presents a viable methodology. However, it is important to note that MRM is widely regarded as the benchmark technique for targeted lipidomics analysis. At present, the utilization of PRM-based targeted lipidomics is being widely implemented across various domains of scientific inquiry. In 2017, Zhou and his colleagues demonstrated the use of the PRM acquisition strategy on a Q-TOF platform for targeted lipidomics analysis in human serum (Zhou et al., 2017). The PRM methodology to augment the existing understanding of the sphingolipidome in zebrafish, the researchers employed

PRM-based LC–MS methodology to comprehensively quantify ceramides in zebrafish (Zhang et al., 2019). Similarly, PRM was used for lipidomic study in yeast and *Enterococcus faecalis* (Rampler et al., 2017; Tague et al., 2019). One of the foremost benefits of employing PRM in lieu of MRM is the marked reduction in the occurrence of erroneous positive outcomes. The utilization of HRMS-based PRM exhibits a notable degree of precision, effectively discerning precursor ions with a high level of accuracy. The task at hand proved to be unattainable for a triple quadrupole mass spectrometer utilizing multiple reaction monitoring. However, one of the most significant limitations of PRM pertains to its low scan rate, thereby impeding expeditious and efficient analysis (Xu et al., 2020). To surmount this challenge, it is imperative to enhance the speed of the scanning process. Thankfully, contemporary Quadrupole Time-of-Flight (QTOF) instruments can execute as many as 100 PRM experiments in a single cycle, thereby enabling extensive monitoring of precursor and product ions on a grand scale (Yu et al., 2018). In light of the respective strengths and weaknesses inherent in both PRM and MRM, some researchers have posited that a synergistic approach that capitalizes on the superior precision of PRM and the expedited pace of MRM may yield optimal outcomes. It has been proposed that following the identification of MS2 spectra via PRM, the ion pairs list may be transferred to MRM for rapid scanning, thereby enabling high-throughput quantitative analysis (Zhou et al., 2016).

3.7.6 Role of internal standards and harmonization in lipidomics

Mass spectrometry (MS) has emerged as the favored technique for conducting quantitative lipid analysis owing to its remarkable sensitivity, molecular specificity, and unparalleled resolution in comparison to nuclear magnetic resonance (NMR). Owing to the intricacies associated with a substantial sample complexity, the absence of a corresponding internal standard can prove to be a genuine hindrance, potentially resulting in quantitative inaccuracies (O'Donnell et al., 2020). Researchers employ criteria and recommendations in order to ensure the best workflow of lipidomics that allows an accurate and efficient study of a wide spectrum of interconnected lipids. The Lipidomics Standards Initiative is a collaborative effort aimed at coordinating the creation of best practice recommendations in lipidomics. It operates under the framework of the International Lipidomics Society (Köfeler et al., 2021; McDonald et al., 2022).

The Lipidomics Standards Initiative (LSI) has put forth a proposal encompassing three distinct categories of quantitation in MS-based lipidomics. At the foundational level, the process involves aligning internal standards (IS) in a manner that adheres to established criteria, while also considering the unique analytical response exhibited by different species. In essence, this implies a preference for utilizing species-specific internal standards (SILL) during the analytical procedure. Progressing to the second level, it necessitates the alignment of internal criteria with the corresponding lipid class as the analyte under investigation. Finally, the third level encompasses the application of non-congruent internal standards, wherein the analytes are standardized in relation to other lipid class compounds. In order to improve the accuracy of data generated through targeted and untargeted methods, it is imperative to consider the isomeric diversity of specific lipids, particularly fatty acids, as well as the disparities among mass spectrometer ion sources (Luque de Castro & Quiles-Zafra, 2020). Ongoing scholarly investigations are currently focused on a nascent realm of analysis, commonly referred to as lipid mediator (LM) metabolomics or metabololipidomics (Serhan, 2017).

For targeted lipidomics, errors are minimized by introducing stable isotope-labeled internal standards. The ratio of the analyte to the internal standards is then measured as a response. Conversely, in untargeted lipidomics, the normalization procedures mostly depend on model-driven approaches (Ejigu et al., 2013). The limited availability of leveled compounds is a significant obstacle to the effective use of ISs in untargeted profiling. However, globally U-13C labelled samples have demonstrated encouraging outcomes (Bueschl et al., 2014; Rampler et al., 2017). Utilizing a substantial number of internal standards is typically deemed appropriate for untargeted lipidomics profiling (Wang et al., 2017).It has been noticed that the use of stable isotope tagged internal standards for specific lipid classes does not provide consistent findings across various laboratories globally. This discrepancy can be attributed to variations in sample preparation processes, diverse sample introduction techniques and MS instruments utilized, as well as differences in analytical platforms (Triebl et al., 2020).

A comprehensive global lipidomics investigation conducted across many laboratories utilizing their preferred mass spectrometry-based techniques revealed substantial discrepancies in the reported lipid concentrations across the participants (Bowden et al., 2017).The comparison investigation relied on a single reference sample [National Institute of Standards and Technology standard reference material (NIST SRM) 1950 (Phinney et al., 2013)] In order to reduce discrepancies in outcomes, Triebl and his colleagues suggest that lipidomics studies should include appropriate reference materials, such as laboratory-specific long-term reference (LTR) or commercially available standards (e.g., NIST SRM 1950). This will mitigate method-specific quantitative biases and improve the comparability of results (Triebl et al., 2020).

3.7.7 Current technologies in lipidomics

3.7.7.1 Mass spectrometry with magnetic resonance imaging A remarkable development was made by combining magnetic resonance imaging and mass spectrometry (MRI-MS) and has emerged as prominent technological breakthroughs in contemporary lipid detection methodologies. The use of MRI and MRS-based techniques holds significant promise in the comprehension of breast cancer. The utilization of in vivo proton (^{1}H) magnetic resonance spectroscopy (MRS) is prevalent in distinguishing breast malignancies from benign conditions through the quantification of increased choline-containing chemicals. Moreover, the utilization of hyperpolarized ^{13}C and ^{31}P magnetic resonance spectroscopy (MRS) has contributed to the advancement of knowledge about glucose and phospholipid metabolism. Additional multi-center research is required to investigate the utilization of MRI and MRS methodologies and their integration into clinical environments (Sharma & Jagannathan, 2022). Magnetic resonance imaging (MRI) is a medical imaging technology that employs high magnetic fields and radio waves to obtain detailed pictures of cross sections from the target sample's tissues (Ho et al., 2017). MRI allows for the acquisition of a three-dimensional anatomical structure of a specific sample with high resolution, providing an accurate representation of the sample shape. MRI and MSI were used to examine the spatial patterns of alkaloid distribution in two separate areas of developing areca nuts (the seeds of *Areca catechu*). Furthermore, a separate investigation used MSI to identify gadoteridol (an MRI contrast agent) in human gliomas using DESI-MS imaging after doing MRI analysis (Tata et al., 2015).

3.7.7.2 Matrix-assisted laser desorption/ionization coupled with mass spectrometry (MALDI-MS) (a) MALDI coupled with trapped ion mobility spectrometry (TIMS)

The development of a new technique MALDI-TIMS, a MALDI quadrupole time-of-flight (Q-TOF) mass spectrometer integrated with trapped ion mobility spectrometry (TIMS) results in a significant enhancement of over 250% in the peak capacity seen during ion mobility spectrometry (IMS) studies (Djambazova et al., 2020). In MALDI TIMS analysis, TOF ion mobility spectrometry is used which provides additional structural and conformational data. The process of data interpretation is quite intricate due to the incorporation of isotopes and isobars. The integration of ion mobility separations enhances the ability to resolve complex mixtures and address the challenges inherent in lipid ion mobility spectrometry. A recent study on deep lipidotyping to elucidate the structural features showed that the acquisition rate for both C = C and sn-position isomers in biological tissues may be significantly improved by high-pressure-OzID in MALDI-MS/MS imaging (Zhang et al., 2022b).

(b) MALDI coupled with imaging mass spectrometry (MALDI-IMS)

Matrix-assisted laser desorption/ionization (MALDI) imaging mass spectrometry (IMS) is a novel and captivating two-dimensional MALDI-MS technique (Goto-Inoue et al., 2011) that enables the direct mapping of lipids inside tissue creating spatial maps inside tissues analyzed. Various matrices (Altelaar et al., 2006; Astigarraga et al., 2008; Cha & Yeung, 2007; Chan et al., 2009; Jun et al., 2010; Meriaux et al., 2010; Shanta et al., 2011; Shrivas et al., 2010), application techniques (Baluya et al., 2007; Bouschen et al., 2010; Franck et al., 2009; Grove et al., 2011; Hankin et al., 2007; Puolitaival et al., 2008; Shimma et al., 2007), and matrix modifiers (Cerruti et al., 2011; Sugiura & Setou, 2009) have been used in MALDI IMS investigations to determine the efficacy and parameters of these method modifications for lipid analysis. Considerable progress has been made in addressing the technical obstacles associated with the identification and measurement of molecules in the field of matrix-assisted laser desorption/ionization-imaging mass spectrometry (MALDI-IMS). By incorporating novel quick peak alignment techniques, this approach exhibits a notable degree of dependability. Moreover, the scope of its application may be extended to include a wide range of human medical conditions. (Gameiro-Ros et al., 2023).

3.7.7.3 Tissue microarray matrix-assisted laser desorption/ionization imaging mass spectrometry (TMA MALDI-IMS) The technique employs the integration of tissue micro-array (TMA), a technological approach enabling researchers to generate a singular microscope slide including several tissue samples, typically organized in an array configuration. This facilitates the concurrent examination of several tissue samples, resulting in increased throughput (Gameiro-Ros et al., 2023). TMA approach has been successfully applied to studies in AD (Sjöbeck et al., 2003), malignancies due to changes in gene expression (Casadonte et al., 2017; Luu et al., 2009), and other oncological studies (Cole & Clench, 2015). The use of this technique is often seen in scientific research pertaining to cancer, neurology, and other disciplines that prioritize the examination of lipid spatial distribution. The TMA MALDI-IMS technique offers several benefits, such as enhanced data integrity and resilience, along with greater efficiency in workload management. The investigation of tumor infiltrating lymphocytes (TILs) in colorectal cancer (CRC) tissues is now a subject of active research. This study aimed to evaluate the potential of using spatial lipidomics by MALDI-MSI to differentiate CRC tissue samples based on their TIL concentration (Denti et al., 2021). When combined with the implementation of innovative quick peak alignment techniques, this methodology demonstrates a high level of reliability. Furthermore, its

applicability may be expanded to encompass many human medical conditions. (Gameiro-Ros et al., 2023).

3.7.8 Data normalization and processing

One often utilized method for data normalization involves the use of a singular normalizing factor, such as biomass, internal standard, mean, median, or total intensity of characteristics, throughout a specific sample. This approach guarantees that the distribution of intensities remains unchanged. Typically, lipid intensities are frequently normalized by the utilization of either spiked-in internal standards that accurately represent the majority of the essential lipid classes, or by taking into account the wet weight of the sample. Different normalizing processes modify the distribution of intensities by applying a distinct normalization factor to each peak in every sample (Smirnov et al., 2021). The high throughput nature of untargeted lipidomics results in the generation of substantial amounts of data, sometimes referred to as "big data." Consequently, the analysis of this data becomes very complex. Therefore, in the absence of specific targeting, lipidomics studies must depend on computer algorithms, statistical testing, and mathematical treatments. Various software programs, such as Progenesis QI, can be employed to initially transform raw data into a suitable format for subsequent processing (Lacalle-Bergeron et al., 2023) which can be read by softwares such as MetaboAnalyst (Pang et al., 2021) after removing complications using softwares like Mzmine (Pluskal et al., 2010) A peak detection tool called "NeatMS" was developed in order to address the prevailing issues of irreproducibility and peak overpicking encountered in the post-acquisition phase of omics data analysis (Gloaguen et al., 2022). To interpret these data in context of clinical information several statistical tools are used. Machine learning (ML) has become more popular in the context of the big data revolution, since it enables the construction of models such as diagnostic tests that facilitate the translation of research findings into clinical practice.

4 Lipids: a key player in diseases

Lipids have a crucial role in cellular physiology. Not only lipids are the fundamental constituents of cellular membranes, but they are also responsible for cellular oxidation. Lipids act as an energy powerhouse, by storing excess chemical energy that can be utilized by the cells during energy depletion. In addition, lipids have important functions in controlling cellular bioenergetics by coordinating oxidative metabolic processes (Michalik et al., 2006). They also regulate systemic energy balance by producing eicosanoids and lysolipids (Skoura & Hla, 2009; Vegiopoulos et al., 2010). Furthermore, lipids play a role in regulating the flow and efficiency of the mitochondrial electron transport chain, such as through cardiolipin and fatty acids (Zhang et al., 2002). Lipid membranes also act as molecular structures that support effective interactions between membrane-associated components, which control cellular signaling. This enables the transmission of biological information across cell membranes, between different parts within a cell, or to neighboring cells. Moreover, the behavior and characteristics of membrane bilayers play a crucial role in influencing the functions of transmembrane proteins, including ion channels and ion pumps (Gross & Han, 2011; Schmidt & MacKinnon, 2008). Alteration in lipid levels can be potent biomarkers for diseases. Bioactive lipid mediators are synthesized due to the breakdown of lipid constituents of the cellular membranes. Prolonged alteration in lipid pathways lead to cellular stress which propels the accumulation of allostatic load, which represents the initial stage of a clinical condition (Devaki et al., 2013). If the organism fails to recover from the stressed condition, it leads to an imbalance in the production of metabolic pathway biomarkers, which can be measured using modern lipid analyzers (Avela & Sirén, 2020). The analysis of the specific outcomes resulting from different lipid species in physiological pathways has the potential to provide a conceptual framework for comprehending recently identified targets that govern lipid homeostasis. These findings possess noteworthy ramifications for the therapeutic management of metabolic disorders. The examination of abnormalities in the metabolism of fatty acids encompasses a broad range of human illnesses. A significant proportion of human cells have a restricted ability to efficiently regulate the excessive buildup of lipids. Saturated fatty acids have been shown to have a detrimental impact on cellular integrity, therefore initiating a wide range of unfavorable cellular responses, including inflammation, reactive oxygen species (ROS) generation, and apoptosis (Šrámek et al., 2021). Inquiries are made into the examination of lipid-related toxicity and the intricate pathways involved in several organs, including the kidney, liver, heart, skeletal muscle, bone, pancreas, and brain (Michel et al., 2011).

4.1 Lipid involvement in neurodegenerative and brain diseases

Lipids are the most abundant biological macromolecules present in the brain accounting for almost 60% of its dried mass (Legido-Quigley, 2021). A connection between imbalance in the dietary intake of essential fatty acids and impaired brain development or disease is observed in many clinical studies (Melo et al., 2019). Lipids play some extremely crucial roles in the brain, for example: proper functional maturation of retina and visual cortex requires decosahexaenoic acid (DHA) (Sinclair, 2019). Almost about 25% of body's total cholesterol is in the brain (Björkhem & Meaney, 2004).

Cholesterol plays a primary role in synaptogenesis which is crucial for healthy brain functioning. Besides cholesterol, sphingolipids are also abundant in the brain (Hussain et al., 2019). Sphingolipids are formed by the metabolic conversion of sphingomyelin. However, de novo synthesis of sphingolipids occurs in the endoplasmic reticulum (ER). The formation of dihydrosphingosine occurs via the combination of serine and palmitoyl-CoA. Dihydrosphingosine undergoes binding with a fatty acyl CoA, resulting in the formation of dihydroceramide. Ceramide synthases catalyze this process. Other than that, sphingolipids are also synthesized by the salvage pathway, in lysosomes (Mandik & Vos, 2021). The development of schizophrenia and metabolic syndrome may be attributed to the pathological alterations in the typical metabolism of SP and its homeostasis (Hussain et al., 2019). Given the substantial presence of lipids inside the brain and their capacity to exert impact on cellular processes, it is very probable that they undergo modifications in many brain disorders. However, the extent of our understanding pertaining to the relationship between lipid modification and several neurological illnesses remains significantly constrained. The incomplete comprehension may be attributed, in part, to the challenges associated with investigating the vast array of lipids present in the brain.

4.1.1 Alzheimer's disease

Alzheimer's Disease (AD) is the most common form of dementia, which has the highest mortality rate among neurodegenerative diseases. According to the recent data, the number of cases will be twice the current number in Europe itself, and triple worldwide (Nichols et al., 2022). The brain exhibits a significant abundance of lipids, and disturbances in lipid homeostasis have been implicated in AD. The process of aging is correlated with changes in the composition of lipids. Alteration of fatty acids inside lipid rafts and brain lipid peroxidation have been seen during the first phase of AD (Kao et al., 2020). The initial stages of AD, also known as the cellular phase, is characterized by the accumulation of soluble and insoluble amyloid β (van Dyck et al., 2023) Extracellular aggregates of amyloid β, also known as senile plaques, are formed by the breakdown of Amyloid precursor protein (APP) (Breijyeh & Karaman, 2020) by β-secretase and γ-secretase. The most common form Aβ peptide that constitutes the senile plaque is the 42 amino acid form, due to their low solubility and higher tendency to assemble into fibrils (Madnani, 2023). Another important hallmark of AD is the abnormal entanglement of hyperphosphorylated tau proteins, leing to the formation of intracellular neurofibrillary tangles (NFTs) (Breijyeh & Karaman, 2020; Madnani, 2023).

In a research done in 2022, Hwangbo along with their colleagues observed elevation of SM(d18:1/18:1), CE(16:1), CE(20:1), and PC(18:0/20:3) in the cerebrospinal fluid (CSF) of 57 patients with AD compared to the control group (n = 85). In contrast, the levels of PE(P-18:0/22:6), PE(18:0/20:4), and PE(18:0/22:6) were shown to be decreased in individuals diagnosed with AD. Both untargeted and targeted lipid analysis were completed using liquid chromatography coupled with electrospray ionization tandem mass spectrometry using a triple qurupole analyzer (LC(HILIC)-ESI–MS/MS(QqQ)). Statistical analysis was performed using logistic regression, receiver operating curve (ROC), Area Under the ROC Curve (AUC), and Principal Component Analysis (PCA) using the R package (Hwangbo et al., 2022) (Fig. 3).

A study conducted on 82 blood plasma samples from the Sydney MAS Cohort. Among these samples, 40 individuals were diagnosed with AD, while the remaining individuals were cognitively normal controls. The researchers conducted untargeted lipidomic analysis using liquid chromatography coupled–mass spectrometry (LC–MS/MS) and observed changes in different lipid classes. Statistical analysis included the utilization of the receiver operating curve (ROC) and area under ROC (AUC) obtained using the R package pROC. Upregulated lipids in plasma samples of patients include Cer(d18:0_16:0), SM(d35:4), PC(16:0_22:6), PE(16:0p_22:6), PI (18:0_18:3),

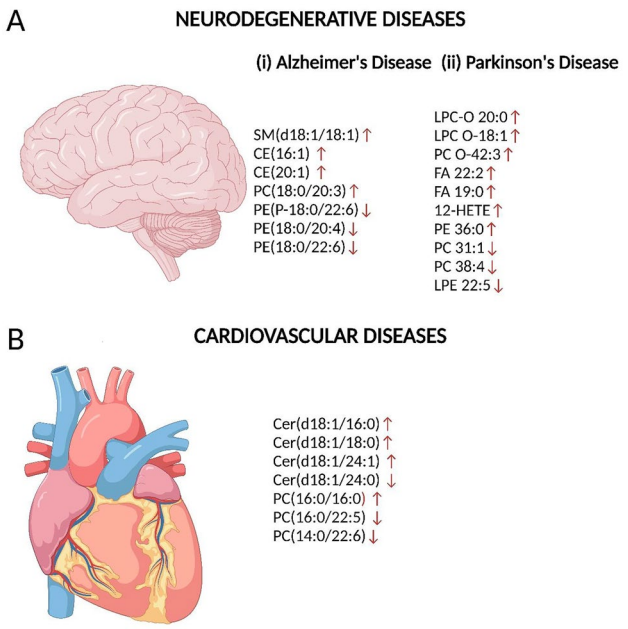


Fig. 3 Representation of lipidome study and the changes in the lipid profiles observed in Alzheimer's Disease (AD), Parkinson's Disease (PD) and Cardiovascular Diseases (CVD) lipidome according to recent studies (**A** and **B**) (Created with BioRender.com). (**A**) Changes in lipids in AD (Hwangbo et al., 2022) and PD (Dahabiyeh et al., 2023) as deduced by various lipidome analysis. (**B**) Lipidome profiling in cardiovascular diseases (Hilvo et al., 2020)

DG(16:0_18:3), and TG(18:1_17:1_18:3). Conversely, Cer(d18:1_23:0), SM(d41:1), PC (20:2_18:2), PE (18:0_18:1), DG(18:1_20:4), and TG(18:1_12:0_14:0) were downregulated in patients compared to the control group (Liu et al., 2021).

An untargeted lipidomic analysis on cerebrospinal fluid samples from 17 individuals with dementia, 15 individuals with Mild Cognitive Impairment (MCI), and 18 healthy controls. UHPLC-MS/MS was used to analyze the lipid content in the samples. The study discovered increased levels of total ceramides in the cerebrospinal fluid (CSF) of patients with AD, while monohexosylceramide (MHC) was found to be reduced. In patients, there was a significant decrease in the levels of specific subsets of MHC, namely d18:1/18:0-, d18:1/20:0-, d18:1/24:1-, d18:2/18:0-, d18:2/22:0-, d18:2/24:0-, and d18:2/24. This study is significant as it is the first to identify changes in MHC levels in cerebrospinal fluid (CSF) samples of patients with AD (Byeon et al., 2021).

In addition to the aforementioned research, there are further studies that provide evidence of recurrent dysregulation of certain categories of lipids in individuals with AD. Upregulation of LDL-C has been observed in patients (Iqbal et al., 2020; Liu et al., 2020; Sáiz-Vazquez et al., 2020; Wu et al., 2019; Zhou et al., 2020). Sphingolipids such as sphingomyelin, ceramide, sulfatide, and sphingosine and phospholipids such as phosphatidylcholine, plasmogens, phosphatidylinositol are major constituents of lipid raft. These lipids play a significant role in the formation of beta-amyloid, aggravating. This fact is backed up by a study conducted in 2017, that exhibits upregulation of sphingomyelin and ceramides in CSF samples of patients (Wong et al., 2017). Therefore, LDL-C, sphingolipids and phospholipids can be potential biomarkers for AD.

Although, the advent of modern technologies to facilitate comprehensive lipid analysis has enabled us to gain deeper knowledge on lipids which me it possible to identify biomarkers for prognosis, diagnosis, and discovery of novel therapeutic approaches. However, there are still some challenges and limitations in the current lipidomics research, such as the heterogeneity of the samples, the variability of the analytical methods, and the complexity of the data interpretation. Therefore, more standardized and comprehensive lipidomics studies are needed to validate and expand the existing knowledge and to explore new avenues for AD research.

4.1.2 Parkinson's disease

Parkinson's Disease (PD) is an age-dependent neurodegenerative disorder that is increasingly affecting the global population. It is speculated that 17.5 million people will be affected with PD by 2040 and will most probably lead to a "PD Pandemic" (Klæstrup et al., 2022).

Lipids play an important role in the early diagnosis and prognosis of PD and other neurological disorders. Although, the exact etiology of PD yet to be solidified, it has been observed that brain, which is heavily lipid-laden, is pathologically influenced by a protein called α-synuclein (αS), coded by the SNCA gene (Fanning et al., 2019). αS is accumulated into proteinaceous filamentous aggregates, known as 'Lewy Bodies'. The accumulation of 'Lewy bodies' in the brainstem, limbic system, and cortical areas lead to the dopaminergic neuronal death in the striatum and substantia nigra (Fan et al., 2021). This degeneration subsequently leads to the impairment of motor functions, such as bradykinesia, rigidity, compromised postural balance, and the development of a distinct resting tremor. Patients also develop dementia as the disease progresses (Fan et al., 2021). During the advanced phase of PD, it is common to see non-motor symptoms such as symptomatic postural hypotension, constant reliance on laxatives for constipation, and urinary incontinence (Neag et al., 2020).

In 2023, a study was conducted on 10 *Macaca mulatta* primates, examining their brain samples. In this study, 5 of the primates were injected with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) to induce symptoms like Parkinson's disease, while the remaining primates received saline injections as a control. Using a MALDI-Fourier-transform ion cyclotron resonance (FTICR)-MSI in dual polarity, researchers observed a decrease in long-chain hydroxylated sulfatides with polyunsaturated chains (SHexCer t41:2, t42:2, t42:3, and t43:2) in the GPi, GPe, and SNR regions of the brain in the MPTP-lesioned group compared to the control group. Conversely, certain long-chain non-hydroxylated sulfatides (SHexCer d40:1, d40:2, d42:1, and d41:1) showed an increase. Further data processing and statistical analysis was also performed using SCiLS Lab, SIMCA 15.0 and GraphPad Prism. The authors of this study concluded that the observed differences between control and MPTP-lesioned brain tissues may be linked to the development of Parkinson's disease caused by MPTP. (Kaya et al., 2023).

Another study conducted on serum samples from a cohort of 50 patients diagnosed with idiopathic PD at various phases (early, mid, or advanced), as well as 45 age-matched controls. The researchers used untargeted liquid chromatography–tandem mass spectrometry (LC–MS/MS) and detected substantial increases in LPC-O 20:0, LPC O-18:1, PC O-42:3, FA 22:2, FA 19:0, 12-HETE, and PE 36:0 as PD progressed, in comparison to the control group. Additionally, Partial Least Squares Discriminant analysis, heat maps, volcano plots, and receiver operating curve (ROC) were used to perform statistical analysis. Nevertheless, the values of PC 31:1, PC 38:4, and LPE 22:5 exhibited a decline as the disease advanced. The authors have reached a conclusion that

the alteration of several serum lipid classes, such as phosphatidylcholines (PCs), fatty acids (FAs), lysophosphatidylcholines (LPCs), phosphatidylethanolamines (PEs), and hydroxyeicosatetraenoic acids (HETEs), during the progression of the disease indicates their potential use in monitoring the course of PD. (Dahabiyeh et al., 2023) (Fig. 3).

Other noteworthy investigations involved examination of sebum samples from a cohort of 274 individuals, of whom 56 were controls, 80 were PD patients who had not previously taken any medication, and the remaining were medicated PD patients. TAG (50:5) and Cer (42:0, 40:0, 38:1) have been found to be downregulated in PD patients by the researchers, using Ultra-High-Performance Liquid Chromatography Quadrupole Time-of-Flight Tandem Mass Spectrometry (UHPLC-qToF-MS/MS). Additionally, the researchers used MATLAB and Origin to carry out Partial Least Squares Discriminant analysis and univariate receiver operating characteristic analysis, respectively. (Sinclair et al., 2021).

Besides the previous studies, there are other publications demonstrating repeated dysregulation of certain classes of lipids in PD patients. Several research studies have provided more extensive data about significant lipid dysregulation linked to Parkinson's Disease. Researchers have observed a rise in the levels of HETE and isofurans in the plasma and substantia nigra (SN) of patients diagnosed with PD (Fessel et al., 2003; Lee et al., 2009; Seet et al., 2010). Elevated concentrations of sulfatides have been seen in the plasma and visual cortex of individuals with PD, as well as in the substantia nigra (SN) of male PD patients (Cheng et al., 2011; Kurup & Kurup, 2003; Seyfried et al., 2018). Patients with PD have elevated plasma concentrations of GM3 gangliosides and N-acetylneuraminic acid-3 (NANA-3) gangliosides, compared to those without the condition (Chan et al., 2017; Zhang J et al., 2017). Plasma samples from individuals with PD have shown reduced levels of carnitine and long-chain acylcarnitine (Crooks et al., 2018; Saiki et al., 2017; Zhao et al., 2018). Serum and plasma levels of TAG are reduced in male patients with Parkinson's disease (Cereda et al., 2012; Chan et al., 2017; Gregório et al., 2013; Guo et al., 2015; Sääksjärvi et al., 2015; Wei et al., 2013; Zhang J et al., 2017). PD patients have reduced plasma concentrations of PE 34:2. Reduced levels of total PE have been seen in the substantia nigra of individuals with PD before to therapy, only in males following treatment, and in the primary visual cortex (Cheng et al., 2011; Riekkinen et al., 1975; Seyfried et al., 2018). Plasma and frontal brain samples from individuals with PD have shown reduced levels of PC 34:2 and 46:2, PC 34:5, 36:5, and 38:5, as well as total PC. In addition, only male PD patients have shown decreased levels of these compounds in the substantia nigra (SN) (Seyfried et al., 2018; Wood et al., 2018; Zhang J et al., 2017). PD has been linked to reduced levels of plasma cholesterol, as shown by numerous studies (Cereda et al., 2012; Guo et al., 2015; Ikeda et al., 2011; Kirbas et al., 2014; Wei et al., 2018; Zhang L et al., 2017). Elevated levels of LDL-cholesterol are linked to an increased risk of Parkinson's disease (Benn et al., 2017; Guo et al., 2015; Huang et al., 2007, 2008; Ikeda et al., 2011; Kirbas et al., 2014; Zhang L et al., 2017).

The recent investigations have effectively elucidated the lipid alterations linked to the advancement of PD via extensive research. From the aforementioned studies, it can be concluded that the lipid signatures have facilitated the acquisition of a deeper understanding of the etiology of the disease, as well as establishing a strong basis for future research endeavors aimed at enhancing the diagnosis and prognosis of PD.

4.2 Cardiovascular diseases and growing role of lipidomics

Cardiovascular diseases (CVD) are responsible for the greatest number of deaths worldwide. A staggering total of 928,741 fatalities due to CVD was recorded in the year 2020, in United States alone (Tsao et al., 2023). As per the findings of the American Heart Association (AHA), it has been established that CVD surpasses the collective mortality rates of various cancer types and Chronic Lower Respiratory Disease (CLRD) within the United States (Tsao et al., 2023). Hence, it becomes imperative to establish biomarkers that can proficiently discern and evaluate the potential risk associated with CVD. The cardinal manifestation of CVD is the perturbation in lipid homeostasis. But the knowledge about changes in the concentration of well-established lipid markers including low density lipoproteins cholesterol (LDL-C), high-density lipoproteins cholesterol (HDL-C), triglycerides, and total cholesterol (Tabassum & Ripatti, 2021) is not enough to establish novel biomarkers. Enhancement of the prognosis can only be attained by using lipidomic assessment with large population-based cohort along with prolonged observational monitoring. Identification of disparities in lipid homeostasis can serve as a catalyst for individuals to enhance their lifestyle choices. It will facilitate timely detection and pharmacological intervention, ultimately leading to a significant reduction in mortality rates. Further exploration of lipidomics is imperative to enhance the consistency of information and mitigate the presence of incongruous data.

A recent untargeted lipidomic study was conducted on 1057 individuals with Coronary Artery Disease (CAD), using LC–MS. The researchers were able to identify 767 lipid species in the platelets lipidome of the participants, out of which lysophosphatidylserine, lysophosphatidylethanolamine, and phosphatidylethanolamine with MUFA or PUFA were significantly upregulated in patients (Harm et al., 2023).

In another study, investigation was conducted into the potential synergistic relationship between ceramide and phosphatidylcholines (PCs) in predicting cardiovascular disease (CVD) events. The study focused on patients with atherosclerotic coronary heart disease and utilized data from three distinct cohort studies: WECAC (The Western Norway Coronary Angiography Cohort) (N = 3789), LIPID (Long-Term Intervention with Pravastatin in Ischaemic Disease) trial (N = 5991), and KAROLA (Langzeiterfolge der KARdiOLogischen Anschlussheilbehandlung) (N = 1023). The researchers utilized liquid chromatography-mass spectrometry (LC–MS) to determine that a risk score based on ceramide and phospholipid levels, which may effectively predict the likelihood of residual cardiovascular disease (CVD) events in individuals diagnosed with coronary artery disease. R software was utilized for statistical computations in all of the studies. (Hilvo et al., 2020) (Fig. 3).

In a population-based cohort study of lipids on a group of older adults residing in four different communities in the United States was conducted on plasma samples using RPLC coupled with electrospray ionization tandem mass spectrometry (QQQ). Additionally, statistical analysis was done, employing cox regression. The study revealed a heightened susceptibility to heart failure in plasma samples exhibiting elevated concentrations of Cer(d18:1/16:0) and SM(d18:1/16:0). On the other hand, it was shown that plasma samples exhibiting heightened concentrations of Cer(d18:1/22:0), SM(d18:1/20:0), SM(d18:1/22:0), and SM(d18:1/24:0) were correlated with a reduced likelihood of developing heart failure. (Lemaitre et al., 2019).

Besides the aforementioned studies, it is evident from several studies that total cholesterol (TC), LDL-cholesterol (LDL-C), and HDL-cholesterol (HDL-C) has been successfully used as a marker to determine the risk of developing cardiovascular diseases. However, further investigations have allowed the evaluation of new markers, such as sphingolipids and phospholipids, to determine CVD risk. These lipids have been previously linked with atherosclerosis (Havulinna et al., 2016; Laaksonen et al., 2016; Mundra et al., 2018; Tarasov et al., 2014). Clinics and diagnostic laboratories have developed tests based on LC–MS based prognostic and diagnostic markers. CERT2 is a ceramide- and phospholipid-based risk test, which efficiently predicts CVD and CAD mortality risk. In a study conducted in 2022, a CERT2 test was conducted on 1260 elderly participants aged more than or equal to 64 years, utilizing LC–MS to analyze the lipids. The aim of the study was to perform a risk assessment of developing CVD, CAD and stroke with a follow-up period of 18 years. In order to determine the effectiveness of CERT2, the results were compared with those of conventional lipids such as LDL-C and HDL-C. It was observed during the 18-year follow-up period that a higher CERT2 score showed significant association with CVD, CAD and stroke, but failed to exhibit a strong association with conventional lipids (Katajamäki et al., 2022). CERT2 test is included in diagnostic portfolio of Zora Biosciences (Finland) to assess the risk of heart attack and Type 2 Diabetes (https://zora.fi/diagnostic-portfolio/). Use of LC–MS to analyze Sphingolipids, such as Cer (d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/24:0), Cer(d18:1/24:1), Cer16:0, Cer18:0, Cer24:0, Cer24:1, N-palmitoyl-sphingosine, N-stearoyl-sphingosine, N-nervonoyl-sphingosine, N-lignoceroyl-sphingosine are primarily tested in CERAM test, conducted in Mayo Clinic Laboratories, to assess the risk of coronary revascularization, myocardial infarction, acute coronary syndrome hospitalization and mortality within 5 years (https://www.mayocliniclabs.com/test-catalog/overview/606777).

Although many studies have enabled the identification of potential lipid biomarkers and therapeutic targets for CVD diagnosis, prognosis, and treatment, there are still gaps in lipidomics studies due to the immense variation in studies which hinders the progress in identifying biomarkers. The anticipation of analytical and clinical validation, as well as clinical utility studies, is high as researchers anxiously anticipate the results that will investigate the potential benefit of biomarker panels when implemented in real-world clinical settings.

4.3 Diagnosing lipids in cancers and their role in development of therapeutics

The cancer cells consist of many heterogeneous cells making up the cancerous tumor tissue, however the study of tumor cannot be limited to the study of cells in the tumor but also the tumor microenvironment which consists of immune cells, blood vessels, extracellular matrix (ECM), fibroblasts, lymphocytes, bone marrow-derived inflammatory cells, and signaling molecules (Del Prete et al., 2017; Spill et al., 2019). Cancer cells alter the signaling pathways to sustain their growth and avoid cell death/apoptosis. Along with alterations in signaling pathway cancer cells tend to alter the metabolic pathways like production of lactate in presence of oxygen while limiting the energy production to glycolysis (Schiliro & Firestein, 2021) and generation of high levels of α-ketoglutarate and citrate in the Krebs cycle due to increased glutamine metabolism (Yoo et al., 2020). It was found evident that cancer cells alter the fatty acid metabolism which increases tumor invasion and migration (Bergers & Fendt, 2021; Huang & Freter, 2015). The alterations in the various signaling and metabolic pathways related to lipids can help to increase in demands for energy and building blocks for rapid proliferation (Manfreda et al., 2023), that can support tumor progression improving the growth, survival, and adaptability of the cancer cells along with helping the tumor microenvironment for promoting

Table 3 Application of lipidomics in Cancer therapeutics to understand the role of lipids and lipid pathways in cancer progression and treatment

S.No	Disease	Sample	Method	Major findings	References
1	Prostate cancer	Prostate cancer tissues from patients (111)	ESI–MS/MS–based lipidomics	Tumors have more monounsaturated lipids and longer phosphatidylinositol and phosphatidylserine fatty acid chains. Patient tissues that reacted to AR inhibition had altered phospholipid composition	Butler et al. (2021)
2	Prostate Cancer	Urine samples from patients (119)	MALDI-TOF/MS	High ratio of phosphatidylcholines/lysophosphatidylcholine ratio suggests association between phosphatidylcholines/lysophosphatidylcholine ratio and prostrate cancer	Li et al. (2021)
3	Lung cancer	Plasma from blood samples (311)	LC–MS–based targeted lipidomics assay using MRM mode	GP metabolism was the most changed lipid metabolism pathway. LysoPC (16:0, 18:0, and 20:4), PC (16:0–18:1, 16:0–18:2, 18:0–18:1, and 16:0–22:6), and TG (16:0–18:1–18:1) were the most significant indicators for early diagnosis	Wang et al. (2022)
4	Colorectal cancer	Tumor tissues	UHPLC and TQ-MS	Rectal cancer had elevated sphingosine levels and reduced ceramide content compared to adjacent healthy tissue, while colon cancer displayed increased sphingosine, sphinganine, sphingosine-1-phosphate, and specific ceramides without a decrease in assessed sphingolipids. Distinct sphingolipid profiles in colon and rectal cancer, suggesting their potential role in the development and progression of colorectal cancer	Markowski et al. (2023)
5	Pancreatic cancer	Serum from blood samples Phase I (364 samples), Phase II (554 samples), and Phase III (830 samples)	UHPSFC/MS, shotgun MS (LR), shotgun MS (HR), RP-UHPLC/MS	There was dysregulation of very long chain SM, Cer, and lysoPC	Wolrab et al. (2022)
6	Breast cancer	MDA-MB-231	GC–MS and nanoESI-MS	Significantly high levels of PC and PE was observered and low levels of phosphatidylinositol was observed. Additionally, enhanced radiosensitivity was achieved by inhibition of GSH biosynthesis in radioresistant MDA-MB-231 cells	Lee et al. (2022)

MeSH terms: 'Lipidomics AND Cancer AND alteration of lipids'

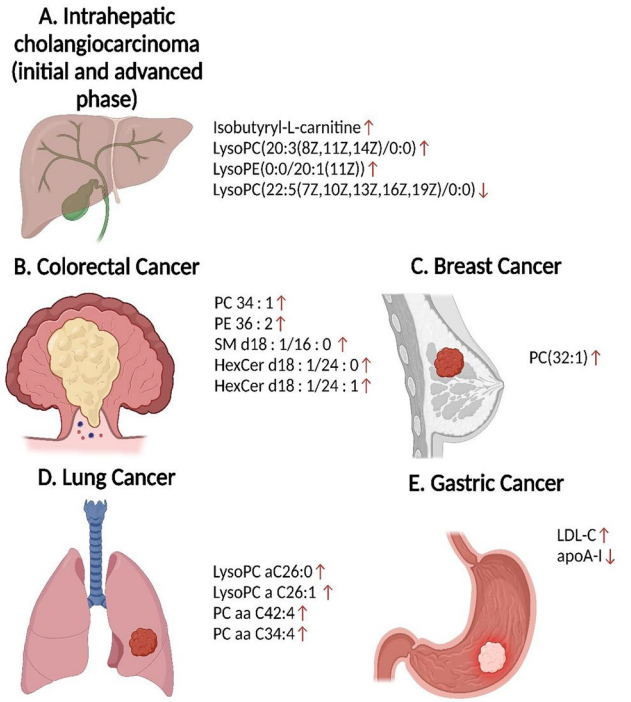


Fig. 4 Representation of lipidome study in various cancers and the changes in the lipid profiles observed in lipidome according to recent studies (**A**–**E**) (Created with BioRender.com). (**A**) Intrahepatic cholangiocarcinoma (initial and advanced phase) (Chen et al., 2022). (**B**) Colorectal Cancer (Elmallah et al., 2022). (**C**) Breast Cancer (Rosini Silva et al., 2020). (**D**) Lung Cancer (Klupczynska et al., 2019). (**E**) Gastric Cancer (Pih et al., 2020)

tumor progression. Utilization of mass spectrometry for quantitative lipid analysis in cancer research shows that upregulation and downregulation of dysregulated lipids that can be associated with tumor progression provides potential future use of lipidomic analysis in early cancer diagnosis and find targets for developing therapeutics (Wolrab et al., 2019). Hence, understanding the role of lipids can give us a novel way to fight cancer and cancer related diseases with less side effects and more efficiency (Table 3).

4.3.1 Lung cancer

Lung cancer is the leading cause of deaths 1.8 million deaths in both the genders (18%) due to malignancy and has the second highest incidence rate 2.2 million cases (11.4%) among other cancers (Sung et al., 2021). Lipidome screening in lung cancer indicates choline-containing phospholipids like lysoPC aC26:0, lysoPC a C26:1, PC aa C42:4, and PC aa C34:4, were present in high concentrations in the serum indicating lipidomics will have impactful results in study of potential therapeutic targets as they indicate the presence of a disease, the disease's progression, or the effectiveness of a treatment (Klupczynska et al., 2019) (Fig. 4). Identifying elevated choline-containing phospholipids during lung cancer lipidome screening may guide therapeutic approaches by targeting enzymes involved in their synthesis or breakdown, potentially influencing disease progression or treatment response. Altered lipid metabolism was observed using UHPLC-Q-TOF/MS (quadrupole time-of-flight mass spectrometry) in phosphatidylethanolamines metabolism and three lipids FA (20:4), FA (20:0), LPE (20:4) were found to have potential to help diagnosing by its capability to distinguish nonsmoking female Lung cancer with adequate sensitivity and specificity, and also has a satisfactory sorting effectiveness for early-stage lung cancer (Noreldeen et al., 2020). According to a study the identification of cancer at an early stage relies on a particular combination of lipids, specifically in three classes which were confirmed with the help of matrix-assisted laser desorption/ionization MS imaging (Wang et al., 2022). These lipid classes include phosphatidylcholines with combinations of fatty acid chains such as 16:0_18:1, 16:0_18:2, 18:0_18:1, 18:0_18:2, and 16:0_22:6. Additionally, lysophosphatidylcholines with fatty acid chains 16:0, 18:0, and 20:4, as well as triglycerides with the combination 16:0_18:1_18:1, play an essential role in the early detection of cancer. Using LC–MS/MS on lung tumor tissues revealed notable changes in lipid profiles, particularly affecting ceramides (Cer) and sphingomyelins (SM). Very long-chain sphingolipids were notably reduced in non-small cell lung cancer (NSCLC) tissues compared to nonmalignant samples. Lipidomic analyses showed disruptions in glycerophospholipids, sphingolipids, and cholesteryl esters in NSCLC tissues, indicating significant alterations in these lipid classes. Paired analysis highlighted distinct shifts in the metabolism of specific lipids like phosphatidylcholines (PC), phosphatidylserines (PS), phosphatidic acids (PA), and phosphatidylinositols (PI) in NSCLC, providing insights into the pathobiochemical processes underlying the condition (Cífková et al., 2022). The detection of all the lipid molecules which has potential to serve as biomarker can revolutionize the management and prevention of lung cancer with earlier detection of the disease, precise diagnosis, better customized treatment approaches, and better patient outcome after treatment. However, these claims require validation through larger-scale clinical studies, especially considering the relatively small sample sizes in the above-mentioned studies ($n < 100$). For instance, serum samples from a group of 138 individuals underwent LC–MS/MS analysis to examine compounds like mristoyl-sn-glycero-3-phosphocholine, 16b-hydroxyestradiol, 3-phosphoserine, cholesteryl sulfate, D-lyxose, dioctyl phthalate, DL-lactate, and Leu-Phe (Shang et al., 2023). The diverse insights from lipidomic studies in lung cancer offer promising avenues for early detection,

personalized treatment, and improved patient outcomes, yet the validation through larger-scale clinical studies remains pivotal for their transformative potential in lung cancer management and prevention.

4.3.2 Pancreatic cancer

In pancreatic ductal adenocarcinoma, a study found atypical decrease in cholesterol and LDL concentrations from 18 to 6 months before diagnosed (Sah et al., 2019). However, increase in levels of LDL cholesterol showed increase in cancer progression by activating signal transducer and activator of transcription (STAT)-3 phosphorylation which helps with tumor survival and progression by regulating various hallmarks of cancer like cancer cell survival, invasion, and tumor progression (Jung et al., 2021). Some clinical studies suggest that decreased expression of LDLR leads to decrease in viability of cancer cells and recurrence of the patients with pancreatic cancer (Lu et al., 2020). These results pave the way for identification of new therapeutic targets and better understanding of the role of lipid metabolism in pancreatic cancer leading to improved diagnostic and treatment strategies for patients. Another study suggests that the maintenance of KRAS-mediated HSL regulation and the consequent modulation of lipid storage, utilization, and metabolism can contribute to development of therapeutics for suppressing metastasis and enhance survival of the patient (Rozeveld et al., 2020). A study showed KRAS-driven metabolic switch can get altered due to changes in sphingolipids concentrations in patients with Pancreatic Ductal Adenocarcinoma. The measurements and assessment for this work were carried out in several labs, including the groups located in Pardubice, Regensburg, and Singapore. Various mass spectrometry (MS)-based procedures, including ultra-high performance supercritical fluid chromatography/mass spectrometry (UHPSFC/MS), shotgun low-resolution mass spectrometry (LR-MS), shotgun high-resolution mass spectrometry (HR-MS), reversed-phase ultra-high performance liquid chromatography/mass spectrometry (RP-UHPLC/MS), and matrix-assisted laser desorption/ionization mass spectrometry (MALDI-MS), were used in this investigation. (Wolrab et al., 2022). These studies have highlighted the role of lipid molecules in KRAS related metabolic pathways where alteration in concentration of the lipid molecules can promote tumor progression and enhance the invasive properties of pancreatic cancer. Another study elucidates that the study of alteration in glycosphingolipids concentration by using LC/ESI-MS2 can contribute to identification of new biomarkers in Pancreatic Ductal Adenocarcinoma and help in developing new therapeutic strategies (Hořejší et al., 2023). Lipidica, a.s. (Czech Republic) aims to globally advance non-invasive, laboratory-based, and early diagnosis for malignant neoplasms. Their focus lies in fundamental research utilizing lipidome analysis, alongside mathematical modeling and artificial intelligence algorithms. Lipidica is geared towards collaborating continuously with top clinical and research institutions to implement diagnostic methods, fostering potential life-saving impacts (*LIPIDICA. COM – New Method for Early Pancreatic Carcinoma Detection*). LC–MS/MS analysis was conducted on 361 Pancreatic Ductal Adenocarcinoma patients, focusing on sphingomyelins (SM) and ceramides (CER) as key lipid markers. These lipid species play roles in signaling, impacting cancer cell fate, chemotherapy response, and resistance mechanisms. Elevated ceramide levels, identified in PDAC tissue and serum of patients with lymph node metastases, implicate their involvement in metastasis. Additionally, cholesteryl esters (CE) were studied as markers. Inhibiting cholesterol biosynthesis has been linked to driving epithelial-to-mesenchymal transition (EMT) in pancreatic tumor cells, contributing to a more aggressive tumor phenotype (Mahajan et al., 2021). The collective findings across pancreatic ductal adenocarcinoma studies underscore the critical role of lipid metabolism in cancer progression, offering potential avenues for therapeutic intervention and improved diagnostic strategies, shaping the future of pancreatic cancer management and patient outcomes.

4.3.3 Breast cancer

Breast cancer is one of the foremost leading causes of deaths in females (6.9%) and highest incidence rate 11.7% (Sung et al., 2021). Serum fatty acid profiling of patients with breast cancer recorded significant changes in FA profile after 12 months of treatment, further beneficial changes like increased BCFA and OCFA levels, and improved n-6/n-3 PUFA ratio were also seen suggesting breast cancer patients lack normal lipid concentrations (Pakiet et al., 2023). Unsaturated phosphatidylcholines (PC ae 16:0_20:4, PC ae 18:0_20:5, PC ae 16:0_20:5, and PC ae 18:0_20:6) are overexpressed in breast cancer survivors and found decreased with the metformin treatment using untargeted LC–QTOF-MS metabolomics, targeted LC–MS metabolomics, and gas chromatography phospholipid fatty acid assay (Bellerba et al., 2022). This shows that the metformin treatment may prevent the cancer cell growth to avoid obesity related breast cancer by altering the metabolism of phosphatidylcholines and phospholipid, and lipid desaturase activity. At a mechanistic level, the release of oleic acid by adipocytes demonstrated inhibition of lipid peroxidation and ferroptosis in triple-negative breast cancer cells when ACSL3 was present providing new therapeutic targets for treating breast cancer (Xie et al., 2022). At a mechanistic level, the release of oleic acid by adipocytes demonstrated inhibition of lipid peroxidation and ferroptosis in triple-negative breast cancer cells when ACSL3 was present (Xiao et al., 2022). Lipidomics

analysis has demonstrated that the activation of ACSL4 plays a role in catalyzing the biosynthesis of lipids containing polyunsaturated fatty acid; this activation further leads to the accumulation of lipid peroxidation products, ultimately contributing to the induction of ferroptosis (Zhang et al., 2022a). Hence, inducing programmed cell death by iron-dependent lipid peroxidation and help in suppressing the tumor growth and avoiding chemoresistance. Three separate studies have detected higher levels of PC(32:1) in the serum of women with breast cancer when compared to women without the condition (Rosini Silva et al., 2020) (Fig. 4). A study revealed that the study of Triple-negative Breast Cancer metabolomics is of clinical importance and suggest new therapeutics targets and helps fighting recurrence of cancer (Xiao et al., 2022). The research unveiled the presence of five distinct lipid categories in TNBC samples: fatty acyls (FA), glycerolipids (GL), glycerophospholipids (GP), sphingolipids (SP), and sterol lipids (ST), however specific lipid markers weren't explicitly detailed in the study. Another study was conducted with 166 plasma samples and a panel with 19 lipids proved to be effective in distinguishing early-stage triple-negative breast cancer (TNBC) cases from control subjects (Eghlimi et al., 2020). In this study, DG 34:2 and Cer 38:1 (2) sustained significance across various subtype comparisons in distinguishing TNBC from controls, while LPC O-18:1 and PC 34:1 lost their significance in differentiating other BC subtypes from controls. The final diagnostic panel of 19 lipids remained significant in discerning TNBC from controls and other BC or non-TNBC subtypes, contributing to an effective OPLS-DA model that accurately differentiated TNBC and identified early-stage TNBC among control subjects. Utilizing TMA MALDI-IMS, a study uncovered the existence of tumor-related polylactosamine glycans in both primary and metastatic breast cancer tissues, offering fresh perspectives on the evolution and advancement of breast cancer that can be potentially targeted for therapy (Scott et al., 2019). In a study of 330 TNBC samples using MS/MS, 594 polar metabolites and 1944 lipids were analyzed. Using statistical tests, 452 metabolites (417 higher, 35 lower in tumors) showed significant differences. Notably, metabolites related to oxidation and glycosyl transfer (e.g., oxidized glutathione [GSSG], uridine diphosphate glucose [UDP] were enriched in tumors. Additionally, phosphatidylinositols, fatty acids (FAs), and ceramides were identified as enriched lipids in TNBCs (Xiao et al., 2022). Overall, we can see that lipidomics serves as a tool to improve the diagnostics and help in venturing more into discovery of new therapeutic targets in breast cancer.

4.3.4 Hepatocellular cancer

In the past few decades Hepatocellular cancer has become one of the major reasons for death due to malignancy (Rawla et al., 2018). A study suggests that lipogenesis mechanism regulated by USP22, involving the PPARγ-ACLY/ACC axis, in the development of hepatocellular carcinoma. A total of 47 metabolites have been identified as being changed in hepatocellular carcinoma tissue. These metabolites include several types, including fatty acids (FAs), phosphatidylcholine (PC), lysophosphatidylcholine (LPC), phosphatidylethanolamine (PE), lysophosphatidylethanolamine (LPE), and sphingomyelin (SM). An additional study was conducted to enrich the pathway utilizing 47 differential metabolites. The results indicated that the production of PC, cardiolipin, phospholipids, PE, and triacylglycerol exhibited enrichment in cancerous tissue. (Ning et al., 2022). A study in Intrahepatic cholangiocarcinoma suggested through UHPLC-Q-TOF–MS/MS that 14 potential biomarkers on AKT/YapS127A co-expression-induced ICC mouse model, where it was established that disturbance in regulation of amino acid metabolism and lipid metabolism have effect on hepatocellular cancer. Isobutyryl-L-carnitine, LPC 20:3(8Z,11Z,14Z), and LPE 20:1(11Z) exhibited an upward trajectory throughout the initial and advanced phases of ICC, whereas LPC 22:5(7Z,10Z,13Z,16Z,19Z) demonstrated a declining pattern. However, throughout the process of ICC formation, there was a decrease observed in the relative content of two potential metabolisms, namely betaine and LPE 1 8:2(9Z,12Z). In contrast, an increase in the relative content of two other possible metabolisms, namely LPC 18:1(9Z) and LPC 20:1(11Z), was found. (Chen et al., 2022) (Fig. 4). The result from these studies underscores the complexity and importance of understanding the role of mTORC2 and its relationship with lipid metabolism to develop potential therapeutic strategies for treating hepatocellular cancer. In a Europe based Cohort, analysis of pre-diagnostic serum samples from Hepatocellular cancer cases and matched controls uncovered a distinct metabolic pattern linked to disease risk. This pattern involved changes in fatty acid oxidation, amino acid, lipid, and carbohydrate metabolism. Sixteen metabolites, including tyrosine, phenylalanine, glutamate, citrate, glucose, and propylene glycol, correlated with higher Hepatocellular cancer risk, while leucine, isoleucine, choline, N-acetyl glycoproteins, unsaturated lipids, and VLDL showed an inverse association with Hepatocellular cancer. The identified metabolic signature effectively differentiated between Hepatocellular cancer cases and controls, varying based on the time from blood collection to diagnosis, hepatitis infection status, and liver function. This distinct metabolic profile has the potential to enhance HCC diagnosis, surpassing the utility of traditional biomarkers like AFP and liver enzyme levels (Fages et al., 2015). Similarly in a study with 521 Hepatocellular cancer patients found relationships between different lipid components (total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides)

and important characteristics of hepatocellular carcinoma (HCC) such as tumor size, portal vein thrombosis, tumor multiplicity, and alpha-fetoprotein levels. High-density lipoprotein cholesterol (HDL) was notably linked to the Tumor Aggressiveness Index (TAI) in a multiple linear regression model, suggesting a connection between HDL levels and HCC aggressiveness. Elevated HDL levels were associated with a higher risk of death compared to lower levels and showed significant connections with the TAI and portal vein thrombosis. Conversely, lower HDL cholesterol levels were tied to better survival rates among HCC patients. Notably, the study observed no significant differences in HDL levels among HCC patients with varying underlying causes (Carr et al., 2018). The culmination of studies in hepatocellular carcinoma sheds light on the intricate relationship between lipid metabolism, metabolic signatures, and cancer aggressiveness, underlining the potential for novel therapeutic targets and improved diagnostic strategies, shaping the landscape of hepatocellular cancer treatment and prognosis.

4.3.5 Gastric cancer

Gastric cancer patients exhibit reduced levels of high-density lipoprotein cholesterol (HDL-C), elevated levels of low-density lipoprotein cholesterol (LDL-C), and decreased levels of apolipoprotein A-I (apoA-I) elucidating the role of lipid profiles in development of cancer (Pih et al., 2020) (Fig. 4). A study showed in both in vitro and in vivo LINC00924 was essential for Gastric Cancer (GC) cell growth and regulated GC cell lipid metabolic reprogramming along with its ability to regulate the p38 MAPK/PPARα signaling pathway to stop peritoneal metastasis which is a major cause of lethality (He et al., 2022). Through lipidome pseudo-targeted metabolomics analysis it was found that levels of sphingolipid metabolism between GC tumor tissue have notable variations, sphingolipid molecules such as sphingosine (d16:1) and the cluster of compounds referred to as ceramides were also validated as biomarkers for gastric cancer (Zeng et al., 2022). These studies open the scope of extensive research on elucidating how therapeutic responses gets affected by lipid metabolism and need for further clinical studies to determine the diagnostic values of such molecules or lipids for their usefulness as targets for therapeutic interventions in Gastric cancer. Through lipid profiling and isotope tracing analyses showed that intestinal-type gastric cancers (GCs) exhibit an inability to produce arachidonic acid (AA) and adrenic acid (AdA) from linoleic acid and inhibition of GPX4 (a key enzyme that protects cells from lipid peroxidation) can lead to ferroptotic cell death suggesting biosynthesis pathway of polyunsaturated fatty acids is important to determine the sensitivity of gastric cancer (Lee et al., 2020). Another study showed applying UPLC-MS/MS knockdown of SREBP-1c downregulated SCD1 and FASN, as well as the upregulated ELOVL6 which inhibited the proliferation, invasiveness, and migration of gastric cancer cells (Sun et al., 2020). When mass spectrometry imaging-based spatial metabolomics and lipidomics with microarray-based spatial transcriptomics were integrated to visualize intratumor metabolic heterogeneity and cell metabolic interactions in gastric cancer samples, tumor-associated alteration of metabolism is observed at both the metabolic and transcriptional levels demonstrating the integration of metabolite, lipid, and gene expression signatures have the potential to characterize complex tumor metabolic remodeling and tumor-microenvironment metabolic interactions (Sun et al., 2023). These studies provide insights into cancer-associated metabolic dependencies and lipid profile alterations that could be targeted for cancer therapy and help in effective prognosis and diagnosis of gastric cancer. (Lee et al., 2020). A two-step large cohort study (400 subjects) using targeted lipidomics profiling on plasma samples using ultra high-performance liquid chromatography-mass spectrometry (LC–MS) highlighted crucial lipid markers: phosphatidylcholines, phosphatidylethanolamines, and sphingomyelins. Among the 142 lipids linked to GC risk, 15 demonstrated consistency in validation, while 11 lipids (FFA18:0, FFA18:3, FFA20:4, LysoPC18:3, LysoPC20:3, Linoleic acid, Palmitic acid, and Phospholipids containing PUFAs) indicated progression from precancerous lesions, showcasing their potential significance in early detection and understanding disease advancement (Liu et al., 2022). The collective exploration of lipid profiles in gastric cancer unveils intricate metabolic dependencies and alterations, illuminating potential targets for therapeutic intervention and paving the way for improved diagnostic and prognostic approaches in gastric cancer.

4.3.6 Colorectal cancer

In colorectal cancer, several potential biomarkers were identified due to their noteworthy difference in concentrations in cancer cells when compared with normal cells such as glycerolipids, glycerophospholipids, and sphingolipids; sphingomyelin and triacylglycerol these observations can lead to novel therapeutic strategies by improving the understanding of the cancer-associated glycerolipid and sphingolipid metabolism (Ecker et al., 2021). Upon evaluation of cancer subsites, it was found that concentration of triglyceride levels was found to be linked to an elevated risk of cancer in the caecum and transverse colon, and higher levels of apolipoprotein A were associated with a reduced risk of cancer specifically in the hepatic flexure however these findings need confirmation through further studies (Fang et al., 2020). A study found that elevated levels of PC(C-36:3) plasmalogen were correlated with a reduced risk of conventional adenomas, subsequently an increased risk of serrated polyps was found to be associated with triglyceride

(TAG) levels, and Phenylacetylglutamine (PAG) levels were linked to a decreased the risk of advent of advance adenomas (Hang et al., 2022). By applying LC–MS molecules that can help in diagnosis of colorectal cancer were identified in two categories the primary set is for non-metastatic colorectal cancer (PC(34:1), PE(36:2), SM(d18:1/16:0), HexCer(d18:1/24:0), and HexCer(d18:1/24:1) and the second set is for metastatic colorectal (PE 34:2, PE 36:2, pPE 16:0/20:4, and Cer d18:1/24:1) which were identified through their alteration in their profiles. Exosomes derived from primary cancer patients and nonmetastatic cells, when compared to exosomes from healthy donors and control cells, exhibited a significant increase in the levels of PC(34: 1), PE(36: 2), SM(d18: 1/16: 0), HexCer(d18: 1/24: 0), and HexCer(d18: 1/24: 1). It is noteworthy that the aforementioned lipid species exhibited a reduction in both the metastatic cell line and the patients under investigation. Additionally, the levels of PE(34: 2), PE(36: 2), and phosphorylated PE(p16: 0/20: 4) exhibited a considerable drop in metastatic circumstances as compared to their nonmetastatic counterparts. The only molecular species that exhibited a significant increase in metastatic circumstances, as seen in both patients and cells, in comparison to control groups, was Cer (d18: 1/24: 1) (Elmallah et al., 2022) (Fig. 4). An additional noteworthy application of recent technological advancements involves the analysis of Formalin-fixed paraffin-embedded tissue samples obtained from the human thymus and tonsil. In this study, MALDI-MSI was employed to generate a carefully curated mass list from a collection of individual positive T lymphocytes. The putative identities of these lymphocytes were then annotated using a lipidomic approach based on LC–MS. Subsets of T cells were then differentiated according to their level of maturation and differentiation inside human thymus and tonsil tissue. Subsequently, when implemented on a CRC TMA comprising varying levels of T lymphocyte infiltration, cases exhibiting a substantial TIL composition were discernible from those with a lesser TIL composition, particularly within the tumor microenvironment. Notably, three lipid signals (PI(20:4/18:1), PS(44:1), and PI(O-40:3)) were identified as having the most significant influence on this differentiation ($p < 0.05$) (Denti et al., 2021). Using imaging mass spectrometry study identified elevated PC(16:0/16:1) levels in advanced colorectal cancer, the findings suggested LPCAT4's role in dysregulating PC(16:0/16:1) in CRC, supported by its overexpression in CRC tissues. This indicates potential clinical use of PC(16:0/16:1) as a CRC biomarker, implicating LPCAT4 in its heightened expression within the disease (Kurabe et al., 2013). A large Europe based cohort study revealed several associations between specific fatty acids and colorectal cancer risk. Elevated concentrations of stearic acid in red blood cells were linked to a higher risk of colorectal cancer, while eicosapentaenoic acid (EPA) showcased an inverse relationship, indicating a potential protective effect from fish consumption. Arachidonic acid (AA) displayed a positive association with colorectal cancer risk, especially in higher quintiles, and docosatetraenoic acid (C22:4n6) was significantly linked to colorectal cancer incidence. Other saturated fatty acids or cis monounsaturated fatty acids did not show significant associations. Moreover, the content of EPA, DHA, and the sum of n-3 PUFA in RBC membrane lipids demonstrated an inverse correlation with colorectal cancer risk. Importantly, these associations remained consistent across various tumor sites, including the colon, proximal colon, distal colon, and rectal cancer (Linseisen et al., 2021). The intricate profiling of lipidomic alterations in colorectal cancer not only provides insights into potential biomarkers but also unravels novel therapeutic strategies, underscoring the significance of lipid metabolism in the disease's progression and proposing promising avenues for targeted interventions in colorectal cancer.

4.3.7 Leukemia

In acute lymphoblastic leukemia elevated TG, reduced HDL-C, and reduced ApoA1 concentrations were found (Leahy et al., 2017). A study applying quantitative shotgun lipidomics in acute myeloid leukemia illustrated that treatment with S63845 increases ceramide (Cer) levels in the MV4-11 and KG1 cell lines at the expense of downstream sphingolipids, while increasing hexosylceramide (HexCer) levels in the HL60 cell line at the expense of Cer and sphingomyelin (SM) (Yandim & Bilgin, 2022). Fatty acid desaturases 1 and 2 (FADS1 and FADS2) were found to be upregulated in relapsed acute myeloid leukemia cells, leading to increased fatty acid desaturation, Fatty acid desaturation was implicated in cancer stem cell (CSC) pathogenesis and therapeutic resistance, suggesting its potential as a therapeutic target (Culp-Hill et al., 2023). A study identified a specific metabolic vulnerability in mIDH1 acute myeloid leukemia and solid tumors, suggesting the potential of targeting alternative metabolic pathways like ACC1 alongside mutation-specific 2HG inhibitors, and elucidated the need for further research in preleukemic stem cells and clonal hematopoiesis (Thomas et al., 2023). A cohort study identified 14 ferroptosis-related genes (FRGs) associated with prognostic significance in chronic lymphocytic leukemia (CLL). These genes exhibited higher expression in cluster 1, linked with better overall survival (OS). Utilizing LASSO analysis, an eight-gene signature (TP63, STEAP3, NQO1, ELAVL1, PRKAA1, HELLS, FANCD2, and CDKN2A) effectively stratified CLL patients into high- and low-risk groups. This signature proved reliable through Cox regression and ROC analysis. The risk score of this gene signature correlated significantly with immune scores and proportions of specific immune cell types, such as resting monocytes and NK cells. Moreover,

validation in an external cohort (GSE22762) confirmed the robustness of the risk model. The study also encompassed enrichment analysis and genomic mutation analysis (Gong et al., 2022). These studies alterations in lipid profiles and metabolic pathways in various types of leukemia, which may have implications for understanding disease mechanisms and potential therapeutic targets.

4.3.8 Renal cell carcinoma

The lipidomic analysis of clear cell renal cell carcinoma (ccRCC) tissue versus normal renal cortex samples using LC-TOFMS and LC-MSMS highlighted significant lipid profile variations. Over 70% of detected lipids exhibited distinct differences, indicating higher levels of specific lipids like ether-type phospholipids, cholesterol esters, and triacylglycerols in the cancerous tissue. Increased lipid classes in ccRCC included phosphatidylcholines (PCs), ether-type phosphatidylcholines (ePCs), ether-type phosphatidylethanolamines (ePEs), ceramides (Cers), sulfatides (Suls), cholesterol esters (ChE), and triacylglycerols (TGs). Conversely, ccRCC tissue showed reduced levels of other lipid types like phosphatidylethanolamines (PEs), phosphatidylinositols (PIs), cardiolipins (CLs), sphingomyelins (SMs), diacylglycerols (DGs), polyunsaturated fatty acids (PUFAs), lipoxygenase (LOX) metabolites, and cytochrome P450 (P450) metabolites. These lipidomic shifts in ccRCC offer crucial insights into the altered metabolism within renal cancerous tissue, enhancing our understanding of ccRCC pathophysiology (Saito et al., 2016). Distinct alterations in sulfatide and sphingomyelin concentrations were observed in plasma and urine samples from renal cell carcinoma (RCC) patients compared to healthy controls, reflecting changes in the lipid profiles across body fluids and tissues in RCC. These shifts correlated with tumor stage and grade progression. Dysregulated lipid patterns in plasma and urine allowed for the creation of classifiers aiding in early-stage RCC detection. In tumor tissues, there was a decline observed in hydroxylated sulfatides and specific sphingomyelins (SM 41:1;O2), whereas SHex2Cer species (including SHexCer 42:2;O2, SHexCer 42:3;O2) showcased elevated levels. Notably, plasma analysis revealed a reduction in certain sphingomyelins (SM 41:1;O2, SM 40:1;O2, SM 39:1;O2, SM 38:1;O2, SM 33:1;O2, SM 32:1;O2) and sulfatides (such as SHexCer 40:1;O3, SHexCer 41:1;O3, SHexCer 42:1;O3, SHexCer 40:1;O2) among individuals with cancer. However, sulfatides containing multiple double bonds (SHexCer 42:3;O2, SHexCer 42:3;O3, SHexCer 42:2;O2) displayed an increase in cancer patients. Additionally, sterol sulfates were upregulated in RCC patients but downregulated in control subjects (Jirásko et al., 2022). A cohort study of 912 patients identified 14 ferroptosis-related genes (FRGs) associated with prognostic significance in chronic lymphocytic leukemia (CLL). These genes exhibited higher expression in cluster 1, linked with better overall survival (OS). Utilizing LASSO analysis, an eight-gene signature (TP63, STEAP3, NQO1, ELAVL1, PRKAA1, HELLS, FANCD2, and CDKN2A) effectively stratified CLL patients into high- and low-risk groups. This signature proved reliable through Cox regression and ROC analysis. The risk score of this gene signature correlated significantly with immune scores and proportions of specific immune cell types, such as resting monocytes and NK cells. Moreover, validation in an external cohort (GSE22762) confirmed the robustness of the risk model. The study also encompassed enrichment analysis and genomic mutation analysis (Guo et al., 2016). The comprehensive lipidomic insights into renal cell carcinoma underscore the intricate lipid alterations within cancerous tissues and body fluids, emphasizing the need for ongoing large-scale cohort studies to refine early detection methods, elucidate pathophysiological mechanisms, and develop targeted interventions for improved clinical outcomes in kidney cancer.

4.3.9 Therapies developed based on lipidomics

A pan-cancer *in-silico* study suggested that changes in major lipid metabolic processes lead to tumorigenesis and highlighted the correlation between lipid metabolism and immune response (Hao et al., 2019). This study opened the path for further investigation in molecular based studies to understand lipid regulation in cancer. In triple negative breast cancer (TNBC), one of the fatty acid transporting proteins FABP5 were found to be overexpressed which can be related to tumor formation and poor prognosis, FABP/EET/CYP-associated metastatic signaling network could be a novel approach to combat metastatic TNBC (Apaya et al., 2020). Similarly in pancreatic cancer, it was hypothesized that increase in activity of PPARβ/δ increases tumor progression (Levi et al., 2015) and FABP5 was found to be upregulated that caused the tumor to progress and proliferate (Corn et al., 2020). Another pan-cancer study oncogenic role of FABP5 overexpression with poor prognosis in multiple tumor types, relation of FABP5 with immune checkpoints (CD274, CTLA4, HAVCR2, LAG3, PDCD1, and TIGIT) shows the relevance of fatty acid associated pathway to immunotherapy (Wang et al., 2023a). ATP citrate lyase (ACLY), a significant enzyme which serves an important role in lipid biogenesis and acts as a catalyst in conversion of citrate into oxaloacetate and Acetyl-CoA. Downregulation of concentrations or decreasing activity of ACLY lead to reduction in growth rate of glioblastoma, colorectal cancer, breast cancer, non-small cell lung cancer and hepatocellular carcinoma (Khwairakpam et al., 2015). Inhibition of acetyl-CoA carboxylases (ACC) through chemical inhibitors stops synthesis of fatty acids and reduces phospholipid concentration in cancer cells which leads to death of cancer cells (Mallick

et al., 2023) These studies pave the way for therapies that involve lipogenesis or associated pathways in cells for treatment of cancers, however they need to be verified through clinical studies performed in large number of cohorts.

Despite the continuous advancement in our comprehension of cancer metabolism, it is disheartening to note that clinical trials pertaining to cancer metabolism therapy have yielded predominantly unfavorable outcomes, save for the notable exception of isocitrate dehydrogenase 1-inhibitors. Considerable focus has been directed towards the lipid metabolism, presumably due to its role in furnishing fundamental constituents crucial for sustaining tumor growth, as well as potentially serving as an alternative means of generating adenosine triphosphate (ATP). Fatty acid synthase (FASN) assumes a pivotal role in the proliferation and viability of tumors exhibiting lipogenic characteristics, in addition to its function as a central controller of lipid metabolism. FASN stands out as a prominently pursued lipogenic enzyme in the context of breast cancer, owing to its persistent overexpression. The preclinical studies have shown that inhibiting FASN, whether through genetic methods or pharmacological interventions, effectively reduces cellular proliferation in controlled laboratory settings and hinders tumor growth in living organisms with different types of breast cancer. Additionally, it is important to highlight the existence of reputable scholarly reviews that extensively cover this topic (Fhu & Ali, 2020). As of now, TVB-2640 stands as the sole FASN inhibitor that has progressed to a phase II clinical trial for breast cancer. The trial NCT03179904 is currently evaluating the effectiveness of TVB-2640 in combination with paclitaxel and Trastuzumab among breast cancer patients with metastatic HER2 + disease (ClinicalTrials.gov, 2023). Statin drugs hold promise as a therapeutic target, particularly for advanced HER2 + and TNBC cases that show increased reliance on cholesterol. Additionally, diabetic drugs are being explored for their potential in breast cancer treatment. Metformin, the widely used diabetes medication, influences hepatic glucose production and insulin sensitivity by inhibiting mitochondrial complex 1 and activating the AMPK pathway showing its possible role in cancer. Currently, there are 18 clinical trials involving Metformin for breast cancer, with some investigating its effectiveness as a neoadjuvant treatment (ClinicalTrials.gov, 2020, 2021, 2022). Metformin reduced viability, migration, and stemness in MDA-MB-231 metastatic cells, suppressed anti-apoptotic genes (BCL2, Bcl-xL), mesenchymal genes (vimentin, N-cadherin, Zeb1, Zeb2), and enhanced apoptotic (caspase 3, Bax) and epithelial genes (E-cadherin, keratin 19), indicating its inhibitory effects on tumorigenesis (Homayoonfal et al., 2023; Kabakov et al., 2020; Sharma et al., 2019). Therefore, the development therapeutics based on lipids which helps in the inhibition of cancer growth and invasion is the need of the hour. The studies so far have shown the alteration in lipid concentration during various cancer types, however further clinical trials conducted in large cohorts can establish the potential biomarkers which can help in prognosis and diagnosis of cancer along with pave the way for identification of new targets for therapeutics.

5 Conclusion

Recent development of analytical techniques has boosted the versatility of lipidomic studies. High-throughput assays have enabled accurate quantification of lipids in altered physiological conditions such as diseases. In this review, we have elucidated the significance of lipidomics in disease prognosis, including Parkinson's disease, Alzheimer's disease, cardiovascular diseases and various cancers. The use of several methodologies like MRI, NMR coupled with LC, and the more recent TMA MALDI IMS expands the scope of lipidomics in a broader range of fields. However, plenty of well-designed cohort studies of pristine quality are required in order to add new and meaningful direction to this field of research. (Yoon et al., 2022) Cancer studies, on the other hand, demand significant betterment of techniques such as optical spectroscopy, biophysical characterization, and immuno-based assays, as a potent quantification technique of lipidic signatures (Stromberg et al., 2020). Cancer cells exhibit significant modifications in lipid homeostasis, encompassing various processes such as remodeling, reprogramming, metabolism, and signaling. Therefore, it is potential to undertake more advanced and enduring cohort studies, which may facilitate the administration of preventative medications to individuals exhibiting early indications of neurodegenerative disorders, therefore enhancing their quality of life. The utilization of a high throughput lipidomics approach presents novel opportunities for the investigation of diagnostic and treatment approaches (Pan et al., 2021). Using high throughput lipidomic assays, we can significantly improve the quality of prognosis by efficiently analyzing the lipid biomarkers associated with ASCVD (Nurmohamed et al., 2023). The involvement of Artificial intelligence (AI) based lipidomics and machine learning (ML) approaches can aid in holistic analysis of the large number of data produced by the state-of-art approaches in MS. For instance, in the case of brain studies, the utilization of the techniques will allow the amalgamation of lipidomics with other omics thereby sealing the gap between the molecular networks and their respective physical manifestations (Yoon et al., 2022).

Therefore, in conclusion, the role of lipidomics in disease studies is indispensable and it has become increasingly clear that technological advancement benefits the disease prognosis, diagnosis and aids in the development of biomarkers and therapeutics in seemingly fatal non communicable and neurodegenerative diseases.

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Declarations

Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

Adams, K. J., Pratt, B., Bose, N., Dubois, L. G., St. John-Williams, L., Perrott, K. M., Ky, K., Kapahi, P., Sharma, V., MacCoss, M. J., Moseley, M., Colton, C. A., MacLean, B. X., Schilling, B., & Thompson, J. W. (2020). Skyline for small molecules: A unifying software package for quantitative metabolomics. *Journal of Proteome Research, 19*(4), 1447–1458. https://doi.org/10.1021/acs.jproteome.9b00640

Altelaar, A. F. M., Klinkert, I., Jalink, K., De Lange, R. P. J., Adan, R. A. H., Heeren, R. M. A., & Piersma, S. R. (2006). Gold-enhanced biomolecular surface imaging of cells and tissue by SIMS and MALDI mass spectrometry. *Analytical Chemistry, 78*(3), 734–742. https://doi.org/10.1021/AC0513111

Apaya, M. K., Hsiao, P. W., Yang, Y. C., & Shyur, L. F. (2020). Deregulating the CYP2C19/Epoxy-eicosatrienoic acid-associated FABP4/FABP5 signaling network as a therapeutic approach for metastatic triple-negative breast cancer. *Cancers, 12*(1), 199. https://doi.org/10.3390/CANCERS12010199

Astigarraga, E., Barreda-Gómez, G., Lombardero, L., Fresnedo, O., Castaño, F., Giralt, M. T., Ochoa, B., Rodríguez-Puertas, R., & Fernández, J. A. (2008). Profiling and imaging of lipids on brain and liver tissue by matrix-assisted laser desorption/ionization mass spectrometry using 2-mercaptobenzothiazole as a matrix. *Analytical Chemistry, 80*(23), 9105–9114. https://doi.org/10.1021/AC801662N

Avela, H. F., & Sirén, H. (2020). Advances in lipidomics. *Clinica Chimica Acta, 510*, 123–141. https://doi.org/10.1016/j.cca.2020.06.049

Baluya, D. L., Garrett, T. J., & Yost, R. A. (2007). Automated MALDI matrix deposition method with inkjet printing for imaging mass spectrometry. *Analytical Chemistry, 79*(17), 6862–6867. https://doi.org/10.1021/ac070958d

Barker-Tejeda, T. C., Villaseñor, A., Gonzalez-Riano, C., López-López, Á., Gradillas, A., & Barbas, C. (2021). In vitro generation of oxidized standards for lipidomics. Application to major membrane lipid components. *Journal of Chromatography A, 1651*, 462254. https://doi.org/10.1016/j.chroma.2021.462254

Bauer, D. R., Stevens, B., Chafin, D., Theiss, A. P., & Otter, M. (2016). Active monitoring of formaldehyde diffusion into histological tissues with digital acoustic interferometry. *Journal of Medical Imaging, 3*(1), 017002. https://doi.org/10.1117/1.JMI.3.1.017002

Beger, A. W., Dudzik, B., Woltjer, R. L., & Wood, P. L. (2022). Human brain lipidomics: Pilot analysis of the basal ganglia sphingolipidome in PD and Lewy body disease. *Metabolites, 12*(2), 187. https://doi.org/10.3390/metabo12020187

Beger, A. W., Hauther, K. A., Dudzik, B., Woltjer, R. L., & Wood, P. L. (2022). Human brain lipidomics: Investigation of formalin fixed brains. *Frontiers in Molecular Neuroscience*, *15*. https://doi.org/10.3389/fnmol.2022.835628

Bellerba, F., Chatziioannou, A. C., Jasbi, P., Robinot, N., Keski-Rahkonen, P., Trolat, A., Vozar, B., Hartman, S. J., Scalbert, A., Bonanni, B., Johansson, H., Sears, D. D., & Gandini, S. (2022). Metabolomic profiles of metformin in breast cancer survivors: A pooled analysis of plasmas from two randomized placebo-controlled trials. *Journal of Translational Medicine, 20*(1), 1–16. https://doi.org/10.1186/S12967-022-03809-6/FIGURES/4

Benn, M., Nordestgaard, B. G., Frikke-Schmidt, R., & Tybjærg-Hansen, A. (2017). Low LDL cholesterol, PCSK9 and HMGCR genetic variation, and risk of AD and Parkinson's disease: Mendelian randomisation study. *BMJ (clinical Research Ed.), 357*, j1648. https://doi.org/10.1136/BMJ.J1648

Bergers, G., & Fendt, S. M. (2021). The metabolism of cancer cells during metastasis. *Nature Reviews Cancer, 21*(3), 162–180. https://doi.org/10.1038/s41568-020-00320-2

Berná, G., López-Bermudo, L., Escudero-López, B., & Martín, F. (2023). *We are what we eat: The role of lipids in metabolic diseases* (pp. 173–219). https://doi.org/10.1016/bs.afnr.2022.11.004

Björkhem, I., & Meaney, S. (2004). Brain cholesterol: Long secret life behind a barrier. *Arteriosclerosis, Thrombosis, and Vascular Biology, 24*(5), 806–815. https://doi.org/10.1161/01.ATV.0000120374.59826.1b

Blanco, A., & Blanco, G. (2017). Antioxidants. In *Medical biochemistry* (pp. 205–214). Elsevier. https://doi.org/10.1016/B978-0-12-803550-4.00010-0

Bonner, R., & Hopfgartner, G. (2019). SWATH data independent acquisition mass spectrometry for metabolomics. *TrAC Trends in Analytical Chemistry, 120*, 115278. https://doi.org/10.1016/j.trac.2018.10.014

Bouschen, W., Schulz, O., Eikel, D., & Spengler, B. (2010). Matrix vapor deposition/recrystallization and dedicated spray preparation for high-resolution scanning microprobe matrix-assisted laser desorption/ionization imaging mass spectrometry (SMALDI-MS) of tissue and single cells. *Rapid Communications in Mass Spectrometry, 24*(3), 355–364. https://doi.org/10.1002/rcm.4401

Bowden, J. A., Heckert, A., Ulmer, C. Z., Jones, C. M., Koelmel, J. P., Abdullah, L., Ahonen, L., Alnouti, Y., Armando, A. M., Asara, J. M., Bamba, T., Barr, J. R., Bergquist, J., Borchers, C. H., Brandsma, J., Breitkopf, S. B., Cajka, T., Cazenave-Gassiot, A., Checa, A., et al. (2017). Harmonizing lipidomics: NIST interlaboratory comparison exercise for lipidomics using SRM 1950–Metabolites in Frozen Human Plasma. *Journal of Lipid Research, 58*(12), 2275–2288. https://doi.org/10.1194/jlr.M079012

Breijyeh, Z., & Karaman, R. (2020). Comprehensive review on AD: Causes and treatment. *Molecules, 25*(24), 5789. https://doi.org/10.3390/molecules25245789

Bueschl, C., Kluger, B., Lemmens, M., Adam, G., Wiesenberger, G., Maschietto, V., Marocco, A., Strauss, J., Bödi, S., Thallinger, G. G., Krska, R., & Schuhmacher, R. (2014). A novel stable isotope labelling assisted workflow for improved untargeted LC–HRMS based metabolomics research. *Metabolomics, 10*(4), 754–769. https://doi.org/10.1007/s11306-013-0611-0

Butler, L. M., Mah, C. Y., Machiels, J., Vincent, A. D., Irani, S., Mutuku, S. M., Spotbeen, X., Bagadi, M., Waltregny, D.,

Moldovan, M., Dehairs, J., Vanderhoydonc, F., Bloch, K., Das, R., Stahl, J., Kench, J. G., Gevaert, T., Derua, R., Waelkens, E., et al. (2021). Lipidomic profiling of clinical prostate cancer reveals targetable alterations in membrane lipid composition. *Cancer Research, 81*(19), 4981–4993. https://doi.org/10.1158/0008-5472.CAN-20-3863

Byeon, S. K., Madugundu, A. K., Jain, A. P., Bhat, F. A., Jung, J. H., Renuse, S., Darrow, J., Bakker, A., Albert, M., Moghekar, A., & Pandey, A. (2021). Cerebrospinal fluid lipidomics for biomarkers of AD. *Molecular Omics, 17*(3), 454–463. https://doi.org/10.1039/d0mo00186d

Cajka, T., & Fiehn, O. (2016). Toward merging untargeted and targeted methods in mass spectrometry-based metabolomics and lipidomics. *Analytical Chemistry, 88*(1), 524–545. https://doi.org/10.1021/acs.analchem.5b04491

Calderón, C., Sanwald, C., Schlotterbeck, J., Drotleff, B., & Lämmerhofer, M. (2019). Comparison of simple monophasic versus classical biphasic extraction protocols for comprehensive UHPLC-MS/MS lipidomic analysis of Hela cells. *Analytica Chimica Acta, 1048*, 66–74. https://doi.org/10.1016/j.aca.2018.10.035

Carr, B. I., Giannelli, G., Guerra, V., Giannini, E. G., Farinati, F., Rapaccini, G. L., Di Marco, M., Zoli, M., Caturelli, E., Masotto, A., Virdone, R., Sacco, R., & Trevisani, F. (2018). Plasma cholesterol and lipoprotein levels in relation to tumor aggressiveness and survival in HCC patients. *The International Journal of Biological Markers, 33*(4), 423–431. https://doi.org/10.1177/1724600818776838

Casadonte, R., Longuespée, R., Kriegsmann, J., & Kriegsmann, M. (2017). MALDI IMS and cancer tissue microarrays. *Advances in Cancer Research, 134*, 173–200. https://doi.org/10.1016/BS.ACR.2016.11.007

Castegna, A., Aksenov, M., Aksenova, M., Thongboonkerd, V., Klein, J. B., Pierce, W. M., Booze, R., Markesbery, W. R., & Butterfield, D. A. (2002). Proteomic identification of oxidatively modified proteins in AD brain. Part I: Creatine kinase BB, glutamine synthase, and ubiquitin carboxy-terminal hydrolase L-1. *Free Radical Biology and Medicine*, *33*(4), 562–571. https://doi.org/10.1016/S0891-5849(02)00914-0

Caterino, M., Fedele, R., Carnovale, V., Castaldo, A., Gelzo, M., Iacotucci, P., Ruoppolo, M., & Castaldo, G. (2023). Lipidomic alterations in human saliva from cystic fibrosis patients. *Scientific Reports, 13*(1), 600. https://doi.org/10.1038/s41598-022-24429-6

CERAM – Overview: MI-Heart Ceramides, Plasma. (n.d.). Retrieved December 21, 2023, from https://www.mayocliniclabs.com/test-catalog/overview/606777

Cereda, E., Cassani, E., Barichella, M., Spadafranca, A., Caccialanza, R., Bertoli, S., Battezzati, A., & Pezzoli, G. (2012). Low cardiometabolic risk in PD is independent of nutritional status, body composition and fat distribution. *Clinical Nutrition, 31*(5), 699–704. https://doi.org/10.1016/J.CLNU.2012.02.004

Cerruti, C. D., Touboul, D., Guérineau, V., Petit, V. W., Laprévote, O., & Brunelle, A. (2011). MALDI imaging mass spectrometry of lipids by adding lithium salts to the matrix solution. *Analytical and Bioanalytical Chemistry, 401*(1), 75–87. https://doi.org/10.1007/S00216-011-4814-9

Cha, S., & Yeung, E. S. (2007). Colloidal graphite-assisted laser desorption/ionization mass spectrometry and MSn of small molecules. 1. Imaging of cerebrosides directly from rat brain tissue. *Analytical Chemistry, 79*(6), 2373–2385. https://doi.org/10.1021/AC062251H

Chan, K., Lanthier, P., Liu, X., Sandhu, J. K., Stanimirovic, D., & Li, J. (2009). MALDI mass spectrometry imaging of gangliosides in mouse brain using ionic liquid matrix. *Analytica Chimica Acta, 639*(1–2), 57–61. https://doi.org/10.1016/J.ACA.2009.02.051

Chan, R. B., Perotte, A. J., Zhou, B., Liong, C., Shorr, E. J., Marder, K. S., Kang, U. J., Waters, C. H., Levy, O. A., Xu, Y., Shim, H., Pe'er, I., Di Paolo, G., & Alcalay, R. M. (2017). Elevated GM3 plasma concentration in idiopathic Parkinson's disease: A lipidomic analysis. *PLoS ONE, 12*(2), e0172348. https://doi.org/10.1371/journal.pone.0172348

Chen, W., Wang, Q., Zhou, B., Zhang, L., & Zhu, H. (2021). Lipid Metabolism profiles in rheumatic diseases. *Frontiers in Pharmacology*, *12*. https://doi.org/10.3389/fphar.2021.643520

Chen, X., Liu, H., Shen, L., Li, D., Zhang, B., Ji, X., Tian, X., Qiu, Z., Zheng, G., & Hu, J. (2022). Untargeted UPLC-MS-based metabolomics analysis reveals the metabolic profile of intrahepatic cholangiocarcinoma process and the intervention effect of Osthole in mice. *Pharmacological Research-Modern Chinese Medicine, 3*, 100096. https://doi.org/10.1016/j.prmcm.2022.100096

Cheng, D., Jenner, A. M., Shui, G., Cheong, W. F., Mitchell, T. W., Nealon, J. R., Kim, W. S., McCann, H., Wenk, M. R., Halliday, G. M., & Garner, B. (2011). Lipid pathway alterations in PD primary visual cortex. *PLoS ONE, 6*(2), e17299. https://doi.org/10.1371/journal.pone.0017299

Chetwynd, A. J., Dunn, W. B., & Rodriguez-Blanco, G. (2017). *Collection and preparation of clinical samples for metabolomics* (pp. 19–44). https://doi.org/10.1007/978-3-319-47656-8_2

Chiurchiù, V., Tiberi, M., Matteocci, A., Fazio, F., Siffeti, H., Saracini, S., Mercuri, N. B., & Sancesario, G. (2022). Lipidomics of bioactive lipids in Alzheimer's and Parkinson's diseases: Where are we? *International Journal of Molecular Sciences, 23*(11), 6235. https://doi.org/10.3390/ijms23116235

Cicalini, I., Rossi, C., Pieragostino, D., Agnifili, L., Mastropasqua, L., di Ioia, M., De Luca, G., Onofrj, M., Federici, L., & Del Boccio, P. (2019). Integrated lipidomics and metabolomics analysis of tears in multiple sclerosis: An insight into diagnostic potential of lacrimal fluid. *International Journal of Molecular Sciences, 20*(6), 1265. https://doi.org/10.3390/ijms20061265

Cífková, E., Brumarová, R., Ovčačíková, M., Dobešová, D., Mičová, K., Kvasnička, A., Vaňková, Z., Šiller, J., Sákra, L., Friedecký, D., & Holčapek, M. (2022). Lipidomic and metabolomic analysis reveals changes in biochemical pathways for non-small cell lung cancer tissues. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids*, *1867*(2), 159082. https://doi.org/10.1016/J.BBALIP.2021.159082

ClinicalTrials.gov. (2020). *Neoadjuvant chemotherapy with or without metformin in early breast cancer. – Full text view* . https://classic.clinicaltrials.gov/ct2/show/NCT04387630

ClinicalTrials.gov. (2021). *Randomized trial of neo-adjuvant chemotherapy with or without metformin for HER2 positive operable breast cancer – Full text view* . https://classic.clinicaltrials.gov/ct2/show/NCT03238495

ClinicalTrials.gov. (2022). *Role of adding metformin to neoadjuvant chemotherapy in patients with breast cancer (METNEO) – Full text view* . https://classic.clinicaltrials.gov/ct2/show/NCT04170465

ClinicalTrials.gov. (2023). *FASN inhibitor TVB-2640 and trastuzumab in combination with paclitaxel or endocrine therapy for the treatment of HER2 positive metastatic breast cancer*. https://classic.clinicaltrials.gov/ct2/show/NCT03179904

Cole, L. M., & Clench, M. R. (2015). Mass spectrometry imaging tools in oncology. *Biomarkers in Medicine, 9*(9), 863–868. https://doi.org/10.2217/bmm.15.61

Corn, K. C., Windham, M. A., & Rafat, M. (2020). Lipids in the tumor microenvironment: From cancer progression to treatment. *Progress in Lipid Research, 80*, 101055. https://doi.org/10.1016/J.PLIPRES.2020.101055

Corral Nieto, Y., Yakhine-Diop, S. M. S., Moreno-Cruz, P., Manrique García, L., Gabrielly Pereira, A., Morales-García, J. A., Niso-Santano, M., González-Polo, R. A., Uribe-Carretero, E., Durand, S., Maiuri, M. C., Paredes-Barquero, M., Alegre-Cortés, E.,

Canales-Cortés, S., López de Munain, A., Pérez-Tur, J., Pérez-Castillo, A., Kroemer, G., Fuentes, J. M., & Bravo-San Pedro, J. M. (2023). Changes in liver lipidomic profile in G2019S-LRRK2 mouse model of Parkinson's disease. *Cells, 12*(5), 806. https://doi.org/10.3390/cells12050806

Crooks, S. A., Bech, S., Halling, J., Christiansen, D. H., Ritz, B., & Petersen, M. S. (2018). Carnitine levels and mutations in the SLC22A5 gene in Faroes patients with Parkinson's disease. *Neuroscience Letters, 675*, 116–119. https://doi.org/10.1016/J.NEULET.2018.03.064

Culp-Hill, R., Stevens, B. M., Jones, C. L., Pei, S., Dzieciatkowska, M., Minhajuddin, M., Jordan, C. T., & D'Alessandro, A. (2023). Therapy-resistant acute myeloid leukemia stem cells are resensitized to venetoclax + azacitidine by targeting fatty acid desaturases 1 and 2. *Metabolites, 13*(4), 467. https://doi.org/10.3390/METABO13040467/S1

Dahabiyeh, L. A., Nimer, R. M., Rashed, M., Wells, J. D., & Fiehn, O. (2023). Serum-based lipid panels for diagnosis of idiopathic Parkinson's disease. *Metabolites, 13*(9), 990. https://doi.org/10.3390/metabo13090990

Dakterzada, F., Benítez, I. D., Targa, A., Carnes, A., Pujol, M., Jové, M., Mínguez, O., Vaca, R., Sánchez-de-la-Torre, M., Barbé, F., Pamplona, R., & Piñol-Ripoll, G. (2023). Cerebrospinal fluid lipidomic fingerprint of obstructive sleep apnoea in AD. *Alzheimer's Research & Therapy, 15*(1), 134. https://doi.org/10.1186/s13195-023-01278-7

Defossez, E., Bourquin, J., von Reuss, S., Rasmann, S., & Glauser, G. (2023). Eight key rules for successful data-dependent acquisition in mass spectrometry-based metabolomics. *Mass Spectrometry Reviews, 42*(1), 131–143. https://doi.org/10.1002/mas.21715

Del Prete, A., Schioppa, T., Tiberio, L., Stabile, H., & Sozzani, S. (2017). Leukocyte trafficking in tumor microenvironment. *Current Opinion in Pharmacology, 35*, 40–47. https://doi.org/10.1016/J.COPH.2017.05.004

Denti, V., Mahajneh, A., Capitoli, G., Clerici, F., Piga, I., Pagani, L., Chinello, C., Bolognesi, M. M., Paglia, G., Galimberti, S., Magni, F., & Smith, A. (2021). Lipidomic typing of colorectal cancer tissue containing tumour-infiltrating lymphocytes by MALDI mass spectrometry imaging. *Metabolites, 11*(9), 599. https://doi.org/10.3390/metabo11090599

Deranieh, R. M., Joshi, A. S., & Greenberg, M. L. (2013). *Thin-layer chromatography of phospholipids* (pp. 21–27). https://doi.org/10.1007/978-1-62703-487-6_2

Devaki, M., Nirupama, R., & Yajurvedi, H. N. (2013). Chronic stress-induced oxidative damage and hyperlipidemia are accompanied by atherosclerotic development in rats. *Stress, 16*(2), 233–243. https://doi.org/10.3109/10253890.2012.719052

Djambazova, K. V., Klein, D. R., Migas, L. G., Neumann, E. K., Rivera, E. S., Van de Plas, R., Caprioli, R. M., & Spraggins, J. M. (2020). Resolving the complexity of spatial lipidomics using MALDI TIMS imaging mass spectrometry. *Analytical Chemistry, 92*(19), 13290–13297. https://doi.org/10.1021/acs.analchem.0c02520

Dorochow, E., Gurke, R., Rischke, S., Geisslinger, G., & Hahnefeld, L. (2023). Effects of different storage conditions on lipid stability in mice tissue homogenates. *Metabolites, 13*(4), 504. https://doi.org/10.3390/metabo13040504

Dorow, J., Becker, S., Kortz, L., Thiery, J., Hauschildt, S., & Ceglarek, U. (2016). Preanalytical investigation of polyunsaturated fatty acids and eicosanoids in human plasma by liquid chromatography-tandem mass spectrometry. *Biopreservation and Biobanking, 14*(2), 107–113. https://doi.org/10.1089/bio.2015.0005

Ecker, J., Benedetti, E., Kindt, A. S. D., Höring, M., Perl, M., Machmüller, A. C., Sichler, A., Plagge, J., Wang, Y., Zeissig, S., Shevchenko, A., Burkhardt, R., Krumsiek, J., Liebisch, G., & Janssen, K. P. (2021). The colorectal cancer lipidome: Identification of a robust tumor-specific lipid species signature. *Gastroenterology, 161*(3), 910–923. https://doi.org/10.1053/j.gastro.2021.05.009

Eghlimi, R., Shi, X., Hrovat, J., Xi, B., & Gu, H. (2020). Triple negative breast cancer detection using LC–MS/MS lipidomic profiling. *Journal of Proteome Research, 19*(6), 2367–2378. https://doi.org/10.1021/acs.jproteome.0c00038

Eichelmann, F., Sellem, L., Wittenbecher, C., Jäger, S., Kuxhaus, O., Prada, M., Cuadrat, R., Jackson, K. G., Lovegrove, J. A., & Schulze, M. B. (2022). Deep lipidomics in human plasma: Cardiometabolic disease risk and effect of dietary fat modulation. *Circulation, 146*(1), 21–35. https://doi.org/10.1161/CIRCULATIONAHA.121.056805

Ejigu, B. A., Valkenborg, D., Baggerman, G., Vanaerschot, M., Witters, E., Dujardin, J.-C., Burzykowski, T., & Berg, M. (2013). Evaluation of normalization methods to pave the way towards large-scale LC-MS-based metabolomics profiling experiments. *OMICS: A Journal of Integrative Biology*, *17*(9), 473–485. https://doi.org/10.1089/omi.2013.0010

Ejsing, C. S., Sampaio, J. L., Surendranath, V., Duchoslav, E., Ekroos, K., Klemm, R. W., Simons, K., & Shevchenko, A. (2009). Global analysis of the yeast lipidome by quantitative shotgun mass spectrometry. *Proceedings of the National Academy of Sciences, 106*(7), 2136–2141. https://doi.org/10.1073/pnas.0811700106

Ellis, S. R., Brown, S. H., Panhuis, M., Blanksby, S. J., & Mitchell, T. W. (2013). Surface analysis of lipids by mass spectrometry: More than just imaging. *Progress in Lipid Research, 52*(4), 329–353. https://doi.org/10.1016/j.plipres.2013.04.005

Elmallah, M. I. Y., Ortega-Deballon, P., Hermite, L., Pais-De-Barros, J. P., Gobbo, J., & Garrido, C. (2022). Lipidomic profiling of exosomes from colorectal cancer cells and patients reveals potential biomarkers. *Molecular Oncology, 16*(14), 2710–2718. https://doi.org/10.1002/1878-0261.13223

Fages, A., Duarte-Salles, T., Stepien, M., Ferrari, P., Fedirko, V., Pontoizeau, C., Trichopoulou, A., Aleksandrova, K., Tjønneland, A., Olsen, A., Clavel-Chapelon, F., Boutron-Ruault, M. C., Severi, G., Kaaks, R., Kuhn, T., Floegel, A., Boeing, H., Lagiou, P., Bamia, C., et al. (2015). Metabolomic profiles of hepatocellular carcinoma in a European prospective cohort. *BMC Medicine, 13*(1), 242. https://doi.org/10.1186/S12916-015-0462-9

Fais, M., Dore, A., Galioto, M., Galleri, G., Crosio, C., & Iaccarino, C. (2021). Parkinson's disease-related genes and lipid alteration. *International Journal of Molecular Sciences, 22*(14), 7630. https://doi.org/10.3390/ijms22147630

Fan, T.-S., Liu, S.C.-H., & Wu, R.-M. (2021). Alpha-synuclein and cognitive decline in Parkinson disease. *Life, 11*(11), 1239. https://doi.org/10.3390/life11111239

Fang, Z., He, M., & Song, M. (2020). Serum lipid profiles and risk of colorectal cancer: A prospective cohort study in the UK Biobank. *British Journal of Cancer, 124*(3), 663–670. https://doi.org/10.1038/s41416-020-01143-6

Fanning, S., Haque, A., Imberdis, T., Baru, V., Barrasa, M. I., Nuber, S., Termine, D., Ramalingam, N., Ho, G. P. H., Noble, T., Sandoe, J., Lou, Y., Landgraf, D., Freyzon, Y., Newby, G., Soldner, F., Terry-Kantor, E., Kim, T.-E., Hofbauer, H. F., et al. (2019). Lipidomic analysis of α-synuclein neurotoxicity identifies stearoyl CoA desaturase as a target for parkinson treatment. *Molecular Cell, 73*(5), 1001–1014. https://doi.org/10.1016/j.molcel.2018.11.028

Fauland, A., Trötzmüller, M., Eberl, A., Afiuni-Zadeh, S., Köfeler, H., Guo, X., & Lankmayr, E. (2013). An improved SPE method for fractionation and identification of phospholipids. *Journal of Separation Science, 36*(4), 744–751. https://doi.org/10.1002/jssc.201200708

Feijó Delgado, F., Cermak, N., Hecht, V. C., Son, S., Li, Y., Knudsen, S. M., Olcum, S., Higgins, J. M., Chen, J., Grover, W. H., &

Manalis, S. R. (2013). Intracellular water exchange for measuring the dry mass, water mass and changes in chemical composition of living cells. *PLoS ONE, 8*(7), e67590. https://doi.org/10.1371/journal.pone.0067590

Fernández-Irigoyen, J., Cartas-Cejudo, P., Iruarrizaga-Lejarreta, M., & Santamaría, E. (2021). Alteration in the cerebrospinal fluid lipidome in Parkinson's disease: A post-mortem pilot study. *Biomedicines, 9*(5), 491. https://doi.org/10.3390/biomedicines9050491

Fessel, J. P., Hulette, C., Powell, S., Roberts, L. J., & Zhang, J. (2003). Isofurans, but not F_2 -isoprostanes, are increased in the substantia nigra of patients with PD and with dementia with Lewy body disease. *Journal of Neurochemistry, 85*(3), 645–650. https://doi.org/10.1046/j.1471-4159.2003.01709.x

Fhu, C. W., & Ali, A. (2020). Fatty acid synthase: An emerging target in cancer. *Molecules, 25*(17), 3935. https://doi.org/10.3390/molecules25173935

Franck, J., Arafah, K., Barnes, A., Wisztorski, M., Salzet, M., & Fournier, I. (2009). Improving tissue preparation for matrix-assisted laser desorption ionization mass spectrometry imaging. Part 1: Using microspotting. *Analytical Chemistry, 81*(19), 8193–8202. https://doi.org/10.1021/ac901328p

Hertta. (n.d.). Retrieved December 21, 2023, from https://hertta.fi/en/

Gameiro-Ros, I., Noble, L., Tong, M., Yalcin, E. B., & de la Monte, S. M. (2023). Tissue microarray lipidomic imaging mass spectrometry method: Application to the study of alcohol-related white matter neurodegeneration. *Applied Biosciences, 2*(2), 173–193. https://doi.org/10.3390/applbiosci2020013

Garrett, T. J., Prieto-Conaway, M. C., Kovtoun, V., Bui, H., Izgarian, N., Stafford, G., & Yost, R. A. (2007). Imaging of small molecules in tissue sections with a new intermediate-pressure MALDI linear ion trap mass spectrometer. *International Journal of Mass Spectrometry, 260*(2–3), 166–176. https://doi.org/10.1016/j.ijms.2006.09.019

Géhin, C., Fowler, S. J., & Trivedi, D. K. (2023). Chewing the fat: How lipidomics is changing our understanding of human health and disease in 2022. *Analytical Science Advances, 4*(3–4), 104–131. https://doi.org/10.1002/ansa.202300009

Giera, M., Yanes, O., & Siuzdak, G. (2022). Metabolite discovery: Biochemistry's scientific driver. *Cell Metabolism, 34*(1), 21–34. https://doi.org/10.1016/j.cmet.2021.11.005

Giles, C., Takechi, R., Lam, V., Dhaliwal, S. S., & Mamo, J. C. L. (2018). Contemporary lipidomic analytics: Opportunities and pitfalls. *Progress in Lipid Research, 71*, 86–100. https://doi.org/10.1016/j.plipres.2018.06.003

Gloaguen, Y., Kirwan, J. A., & Beule, D. (2022). Deep learning-assisted peak curation for large-scale LC-MS metabolomics. *Analytical Chemistry, 94*(12), 4930–4937. https://doi.org/10.1021/acs.analchem.1c02220

Gong, H., Li, H., Yang, Q., Zhang, G., Liu, H., Ma, Z., Peng, H., Nie, L., Xiao, X., & Liu, J. (2022). A ferroptosis molecular subtype-related signature for predicting prognosis and response to chemotherapy in patients with chronic lymphocytic leukemia. *BioMed Research International*, *2022*. https://doi.org/10.1155/2022/5646275

Goracci, L., Tortorella, S., Tiberi, P., Pellegrino, R. M., Di Veroli, A., Valeri, A., & Cruciani, G. (2017). Lipostar, a comprehensive platform-neutral cheminformatics tool for lipidomics. *Analytical Chemistry, 89*(11), 6257–6264. https://doi.org/10.1021/acs.analchem.7b01259

Goto-Inoue, N., Hayasaka, T., Zaima, N., & Setou, M. (2011). Imaging mass spectrometry for lipidomics. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids*, *1811*(11), 961–969. https://doi.org/10.1016/j.bbalip.2011.03.004

Gregório, M. L., Pinhel, M. A. S., Sado, C. L., Longo, G. S., Oliveira, F. N., Amorim, G. S., Nakazone, M. A., Florim, G. M., Mazeti, C. M., Martins, D. P., Tognola, W. A., Brandão, A. C., Júnior, S. P., De Godoy, M. F., & Souza, D. R. S. (2013). Impact of genetic variants of apolipoprotein e on lipid profile in patients with parkinson's disease. *BioMed Research International*, *2013*. https://doi.org/10.1155/2013/641515

Gross, R. W., & Han, X. (2011). Lipidomics at the interface of structure and function in systems biology. *Chemistry & Biology, 18*(3), 284–291. https://doi.org/10.1016/j.chembiol.2011.01.014

Grove, K. J., Frappier, S. L., & Caprioli, R. M. (2011). Matrix precoated MALDI MS targets for small molecule imaging in tissues. *Journal of the American Society for Mass Spectrometry, 22*(1), 192–195. https://doi.org/10.1007/s13361-010-0013-8

Guironnet, A., Wiest, L., & Vulliet, E. (2022). Advantages of MS/MS/MS (MRM3) vs classic MRM quantification for complex environmental matrices: Analysis of beta-lactams in WWTP sludge. *Analytica Chimica Acta, 1205*, 339773. https://doi.org/10.1016/j.aca.2022.339773

Guo, S., He, X., Chen, Q., Yang, G., Yao, K., Dong, P., Ye, Y., Chen, D., Zhang, Z., Qin, Z., Liu, Z., Li, Z., Xue, Y., Zhang, M., Liu, R., Zhou, F., & Han, H. (2016). The effect of preoperative apolipoprotein a-I on the prognosis of surgical renal cell carcinoma a retrospective large sample study. *Medicine (United States)*, *95*(12). https://doi.org/10.1097/MD.0000000000003147

Guo, X., Song, W., Chen, K., Chen, X. P., Zheng, Z., Cao, B., Huang, R., Zhao, B., Wu, Y., & Shang, H. F. (2015). The serum lipid profile of PD patients: A study from China. *International Journal of Neuroscience, 125*(11), 838–844. https://doi.org/10.3109/00207454.2014.979288

Hall, Z., Chu, Y., & Griffin, J. L. (2017). Liquid extraction surface analysis mass spectrometry method for identifying the presence and severity of nonalcoholic fatty liver disease. *Analytical Chemistry, 89*(9), 5161–5170. https://doi.org/10.1021/acs.analchem.7b01097

Han, X., & Gross, R. W. (2003). Global analyses of cellular lipidomes directly from crude extracts of biological samples by ESI mass spectrometry: A bridge to lipidomics. *Journal of Lipid Research, 44*(6), 1071–1079. https://doi.org/10.1194/jlr.R300004-JLR200

Han, X., & Gross, R. W. (2022). The foundations and development of lipidomics. *Journal of Lipid Research, 63*(2), 100164. https://doi.org/10.1016/j.jlr.2021.100164

Han, X., Yang, K., & Gross, R. W. (2012). Multi-dimensional mass spectrometry-based shotgun lipidomics and novel strategies for lipidomic analyses. *Mass Spectrometry Reviews, 31*(1), 134–178. https://doi.org/10.1002/mas.20342

Hang, D., Zeleznik, O. A., Lu, J., Joshi, A. D., Wu, K., Hu, Z., Shen, H., Clish, C. B., Liang, L., Eliassen, A. H., Ogino, S., Meyerhardt, J. A., Chan, A. T., & Song, M. (2022). Plasma metabolomic profiles for colorectal cancer precursors in women. *European Journal of Epidemiology, 37*(4), 413–422. https://doi.org/10.1007/S10654-021-00834-5/METRICS

Hankin, J. A., Barkley, R. M., & Murphy, R. C. (2007). Sublimation as a method of matrix application for mass spectrometric imaging. *Journal of the American Society for Mass Spectrometry, 18*(9), 1646–1652. https://doi.org/10.1016/j.jasms.2007.06.010

Hao, Y., Li, D., Xu, Y., Ouyang, J., Wang, Y., Zhang, Y., Li, B., Xie, L., & Qin, G. (2019). Investigation of lipid metabolism dysregulation and the effects on immune microenvironments in pan-cancer using multiple omics data. *BMC Bioinformatics, 20*(7), 29–39. https://doi.org/10.1186/S12859-019-2734-4/FIGURES/4

Harm, T., Dittrich, K., Brun, A., Fu, X., Frey, M., Petersen Uribe, A., Schwarz, F.-J., Rohlfing, A.-K., Castor, T., Geisler, T., Rath, D., Lämmerhofer, M., & Gawaz, M. P. (2023). Large-scale lipidomics profiling reveals characteristic lipid signatures associated with an increased cardiovascular risk. *Clinical Research in Cardiology, 112*(11), 1664–1678. https://doi.org/10.1007/s00392-023-02260-x

Havulinna, A. S., Sysi-Aho, M., Hilvo, M., Kauhanen, D., Hurme, R., Ekroos, K., Salomaa, V., & Laaksonen, R. (2016). Circulating ceramides predict cardiovascular outcomes in the population-based FINRISK 2002 cohort. *Arteriosclerosis, Thrombosis, and Vascular Biology, 36*(12), 2424–2430. https://doi.org/10.1161/ATVBAHA.116.307497

He, Q., Yang, C., Xiang, Z., Huang, G., Wu, H., Chen, T., Dou, R., Song, J., Han, L., Song, T., Wang, S., & Xiong, B. (2022). LINC00924-induced fatty acid metabolic reprogramming facilitates gastric cancer peritoneal metastasis via hnRNPC-regulated alternative splicing of Mnk2. *Cell Death & Disease*, *13*(11). https://doi.org/10.1038/s41419-022-05436-x

He, X., Li, Z., & Zhang, Q. (2021). A UPLC-MRM-MS method for comprehensive profiling of Amadori compound-modified phosphatidylethanolamines in human plasma. *Analytical and Bioanalytical Chemistry, 413*(2), 431–443. https://doi.org/10.1007/s00216-020-03012-w

Hilvo, M., Meikle, P. J., Pedersen, E. R., Tell, G. S., Dhar, I., Brenner, H., Schöttker, B., Lääperi, M., Kauhanen, D., Koistinen, K. M., Jylhä, A., Huynh, K., Mellett, N. A., Tonkin, A. M., Sullivan, D. R., Simes, J., Nestel, P., Koenig, W., Rothenbacher, D., et al. (2020). Development and validation of a ceramide- and phospholipid-based cardiovascular risk estimation score for coronary artery disease patients. *European Heart Journal, 41*(3), 371–380. https://doi.org/10.1093/eurheartj/ehz387

Ho, Y., Shu, L., & Yang, Y. (2017). Imaging mass spectrometry for metabolites: Technical progress, multimodal imaging, and biological interactions. *WIREs Systems Biology and Medicine*, *9*(5). https://doi.org/10.1002/wsbm.1387

Homayoonfal, M., Gilasi, H., Asemi, Z., Khaksary Mahabady, M., Asemi, R., & Yousefi, B. (2023). Quercetin modulates signal transductions and targets non-coding RNAs against cancer development. *Cellular Signalling, 107*, 110667. https://doi.org/10.1016/J.CELLSIG.2023.110667

Hořejší, K., Jin, C., Vaňková, Z., Jirásko, R., Strouhal, O., Melichar, B., Teneberg, S., & Holčapek, M. (2023). Comprehensive characterization of complex glycosphingolipids in human pancreatic cancer tissues. *Journal of Biological Chemistry*, *299*(3). https://doi.org/10.1016/J.JBC.2023.102923/ATTACHMENT/2123634D-3B90-4A89-9AC9-3D799C339B62/MMC1.PDF

Hsu, F.-F. (2018). Mass spectrometry-based shotgun lipidomics – A critical review from the technical point of view. *Analytical and Bioanalytical Chemistry, 410*(25), 6387–6409. https://doi.org/10.1007/s00216-018-1252-y

Hu, C., Duan, Q., & Han, X. (2020). Strategies to improve/eliminate the limitations in shotgun lipidomics. *Proteomics*, *20*(11). https://doi.org/10.1002/pmic.201900070

Hu, C., Wang, C., He, L., & Han, X. (2019). Novel strategies for enhancing shotgun lipidomics for comprehensive analysis of cellular lipidomes. *TrAC Trends in Analytical Chemistry, 120*, 115330. https://doi.org/10.1016/j.trac.2018.11.028

Huang, C., & Freter, C. (2015). Lipid metabolism, apoptosis and cancer therapy. *International Journal of Molecular Sciences, 16*(1), 924–949. https://doi.org/10.3390/IJMS16010924

Huang, X., Abbott, R. D., Petrovitch, H., Mailman, R. B., & Ross, G. W. (2008). Low LDL cholesterol and increased risk of Parkinson's disease: Prospective results from Honolulu-Asia aging study. *Movement Disorders, 23*(7), 1013–1018. https://doi.org/10.1002/MDS.22013

Huang, X., Chen, H., Miller, W. C., Mailman, R. B., Woodard, J. L., Chen, P. C., Xiang, D., Murrow, R. W., Wang, Y. Z., & Poole, C. (2007). Lower low-density lipoprotein cholesterol levels are associated with Parkinson's disease. *Movement Disorders, 22*(3), 377–381. https://doi.org/10.1002/MDS.21290

Hussain, G., Wang, J., Rasul, A., Anwar, H., Imran, A., Qasim, M., Zafar, S., Kamran, S. K. S., Razzaq, A., Aziz, N., Ahmad, W., Shabbir, A., Iqbal, J., Baig, S. M., & Sun, T. (2019). Role of cholesterol and sphingolipids in brain development and neurological diseases. *Lipids in Health and Disease, 18*(1), 26. https://doi.org/10.1186/s12944-019-0965-z

Hwangbo, N., Zhang, X., Raftery, D., Gu, H., Hu, S.-C., Montine, T. J., Quinn, J. F., Chung, K. A., Hiller, A. L., Wang, D., Fei, Q., Bettcher, L., Zabetian, C. P., Peskind, E. R., Li, G., Promislow, D. E. L., Davis, M. Y., & Franks, A. (2022). Predictive modeling of Alzheimer's and PD using metabolomic and lipidomic profiles from cerebrospinal fluid. *Metabolites, 12*(4), 277. https://doi.org/10.3390/metabo12040277

Ibrahim, H., Jurcic, K., Wang, J.S.-H., Whitehead, S. N., & Yeung, K.K.-C. (2017). 1,6-Diphenyl-1,3,5-hexatriene (DPH) as a novel matrix for MALDI MS imaging of fatty acids, phospholipids, and sulfatides in brain tissues. *Analytical Chemistry, 89*(23), 12828–12836. https://doi.org/10.1021/acs.analchem.7b03284

Ikeda, K., Nakamura, Y., Kiyozuka, T., Aoyagi, J., Hirayama, T., Nagata, R., Ito, H., Iwamoto, K., Murata, K., Yoshii, Y., Kawabe, K., & Iwasaki, Y. (2011). Serological profiles of urate, paraoxonase-1, ferritin and lipid in Parkinson's disease: Changes linked to disease progression. *Neurodegenerative Diseases, 8*(4), 252–258. https://doi.org/10.1159/000323265

Iqbal, G., Braidy, N., & Ahmed, T. (2020). Blood-based biomarkers for predictive diagnosis of cognitive impairment in a pakistani population. *Frontiers in Aging Neuroscience*, *12*. https://doi.org/10.3389/fnagi.2020.00223

Jirásko, R., Idkowiak, J., Wolrab, D., Kvasnička, A., Friedecký, D., Polański, K., Študentová, H., Študent, V., Melichar, B., & Holčapek, M. (2022). Altered plasma, urine, and tissue profiles of sulfatides and sphingomyelins in patients with renal cell carcinoma. *Cancers, 14*(19), 4622. https://doi.org/10.3390/CANCERS14194622/S1

Jun, J. H., Song, Z., Liu, Z., Nikolau, B. J., Yeung, E. S., & Lee, Y. J. (2010). High-spatial and high-mass resolution imaging of surface metabolites of *Arabidopsis thaliana* by laser desorption-ionization mass spectrometry using colloidal silver. *Analytical Chemistry, 82*(8), 3255–3265. https://doi.org/10.1021/AC902990P

Jung, Y. Y., Ko, J. H., Um, J. Y., Chinnathambi, A., Alharbi, S. A., Sethi, G., & Ahn, K. S. (2021). LDL cholesterol promotes the proliferation of prostate and pancreatic cancer cells by activating the STAT3 pathway. *Journal of Cellular Physiology, 236*(7), 5253–5264. https://doi.org/10.1002/JCP.30229

Jungblut, P. R., Zimny-Arndt, U., Zeindl-Eberhart, E., Stulik, J., Koupilova, K., Pleißner, K.-P., Otto, A., Müller, E.-C., Sokolowska-Köhler, W., Grabher, G., & Stöffler, G. (1999). Proteomics in human disease: Cancer, heart and infectious diseases. *Electrophoresis, 20*(10), 2100–2110. https://doi.org/10.1002/(SICI)1522-2683(19990701)20:10%3c2100::AID-ELPS2100%3e3.0.CO;2-D

Jurowski, K., Kochan, K., Walczak, J., Barańska, M., Piekoszewski, W., & Buszewski, B. (2017). Analytical techniques in lipidomics: State of the art. *Critical Reviews in Analytical Chemistry, 47*(5), 418–437. https://doi.org/10.1080/10408347.2017.1310613

Kabakov, A., Yakimova, A., & Matchuk, O. (2020). Molecular chaperones in cancer stem cells: Determinants of stemness and potential targets for antitumor therapy. *Cells, 9*(4), 892. https://doi.org/10.3390/CELLS9040892

Kalecký, K., German, D. C., Montillo, A. A., & Bottiglieri, T. (2022). Targeted metabolomic analysis in AD plasma and brain tissue in non-hispanic whites. *Journal of AD, 86*(4), 1875–1895. https://doi.org/10.3233/JAD-215448

Kano, K., Matsumoto, H., Kono, N., Kurano, M., Yatomi, Y., & Aoki, J. (2021). Suppressing postcollection lysophosphatidic acid metabolism improves the precision of plasma LPA quantification. *Journal of Lipid Research, 62*, 100029. https://doi.org/10.1016/j.jlr.2021.100029

Kao, Y.-C., Ho, P.-C., Tu, Y.-K., Jou, I.-M., & Tsai, K.-J. (2020). Lipids and AD. *International Journal of Molecular Sciences, 21*(4), 1505. https://doi.org/10.3390/ijms21041505

Katajamäki, T. T., Koivula, M.-K., Hilvo, M., Lääperi, M. T. A., Salminen, M. J., Viljanen, A. M., Heikkilä, E. T. M., Löppönen, M. K., Isoaho, R. E., Kivelä, S.-L., Jylhä, A., Viikari, L., Irjala, K. M., Pulkki, K. J., & Laaksonen, R. M. H. (2022). Ceramides and phosphatidylcholines associate with cardiovascular diseases in the elderly. *Clinical Chemistry, 68*(12), 1502–1508. https://doi.org/10.1093/clinchem/hvac158

Kaya, I., Nilsson, A., Luptáková, D., He, Y., Vallianatou, T., Bjärterot, P., Svenningsson, P., Bezard, E., & Andrén, P. E. (2023). Spatial lipidomics reveals brain region-specific changes of sulfatides in an experimental MPTP PD primate model. *Npj Parkinson's Disease, 9*(1), 118. https://doi.org/10.1038/s41531-023-00558-1

Khwairakpam, A., Shyamananda, M., Sailo, B., Rathnakaram, S., Padmavathi, G., Kotoky, J., & Kunnumakkara, A. (2015). ATP citrate lyase (ACLY): A promising target for cancer prevention and treatment. *Current Drug Targets, 16*(2), 156–163. https://doi.org/10.2174/1389450115666141224125117

Kirbas, A., Kirbas, S., & Cure, M. (2014). Paraoxonase and arylesterase activity and total oxidative/anti-oxidative status in patients with idiopathic Parkinson's disease. *Elsevier, 21*(3), 451–455. https://doi.org/10.1016/j.jocn.2013.04.025

Kishimoto, K., Urade, R., Ogawa, T., & Moriyama, T. (2001). Nondestructive quantification of neutral lipids by thin-layer chromatography and laser-fluorescent scanning: Suitable methods for "lipidome" analysis. *Biochemical and Biophysical Research Communications, 281*(3), 657–662. https://doi.org/10.1006/bbrc.2001.4404

Klæstrup, I. H., Just, M. K., Holm, K. L., Alstrup, A. K. O., Romero-Ramos, M., Borghammer, P., & Van Den Berge, N. (2022). Impact of aging on animal models of Parkinson's disease. *Frontiers in Aging Neuroscience, 14*, 909273. https://doi.org/10.3389/fnagi.2022.909273

Klupczynska, A., Plewa, S., Kasprzyk, M., Dyszkiewicz, W., Kokot, Z. J., & Matysiak, J. (2019). Serum lipidome screening in patients with stage I non-small cell lung cancer. *Clinical and Experimental Medicine, 19*(4), 505–513. https://doi.org/10.1007/S10238-019-00566-7/FIGURES/2

Köfeler, H. C., Ahrends, R., Baker, E. S., Ekroos, K., Han, X., Hoffmann, N., Holčapek, M., Wenk, M. R., & Liebisch, G. (2021). Recommendations for good practice in MS-based lipidomics. *Journal of Lipid Research, 62*, 100138. https://doi.org/10.1016/j.jlr.2021.100138

Kostidis, S., Sánchez-López, E., & Giera, M. (2023). Lipidomics analysis in drug discovery and development. *Current Opinion in Chemical Biology, 72*, 102256. https://doi.org/10.1016/j.cbpa.2022.102256

Kurabe, N., Hayasaka, T., Ogawa, M., Masaki, N., Ide, Y., Waki, M., Nakamura, T., Kurachi, K., Kahyo, T., Shinmura, K., Midorikawa, Y., Sugiyama, Y., Setou, M., & Sugimura, H. (2013). Accumulated phosphatidylcholine (16:0/16:1) in human colorectal cancer; possible involvement of LPCAT4. *Cancer Science, 104*(10), 1295–1302. https://doi.org/10.1111/CAS.12221

Kurup, R. K., & Kurup, P. A. (2003). Hypothalamic digoxin-mediated model for Parkinson's disease. *International Journal of Neuroscience, 113*(4), 515–536. https://doi.org/10.1080/00207450390162263

Kvasnička, A., Friedecký, D., Tichá, A., Hyšpler, R., Janečková, H., Brumarová, R., Najdekr, L., & Zadák, Z. (2021). SLIDE—Novel approach to apocrine sweat sampling for lipid profiling in healthy individuals. *International Journal of Molecular Sciences, 22*(15), 8054. https://doi.org/10.3390/ijms22158054

Kvasnička, A., Najdekr, L., Dobešová, D., Piskláková, B., Ivanovová, E., & Friedecký, D. (2023). Clinical lipidomics in the era of the big data. *Clinical Chemistry and Laboratory Medicine (CCLM), 61*(4), 587–598. https://doi.org/10.1515/cclm-2022-1105

Laaksonen, R., Ekroos, K., Sysi-Aho, M., Hilvo, M., Vihervaara, T., Kauhanen, D., Suoniemi, M., Hurme, R., März, W., Scharnagl, H., Stojakovic, T., Vlachopoulou, E., Lokki, M.-L., Nieminen, M. S., Klingenberg, R., Matter, C. M., Hornemann, T., Jüni, P., Rodondi, N., et al. (2016). Plasma ceramides predict cardiovascular death in patients with stable coronary artery disease and acute coronary syndromes beyond LDL-cholesterol. *European Heart Journal, 37*(25), 1967–1976. https://doi.org/10.1093/eurheartj/ehw148

Lacalle-Bergeron, L., Goterris-Cerisuelo, R., Beltran, J., Sancho, J. V., Navarro-Moreno, C., Martinez-Garcia, F., & Portolés, T. (2023). Untargeted metabolomics approach using UHPLC-IMS-QTOF MS for surface body samples to identify low-volatility chemosignals related to maternal care in mice. *Talanta, 258*, 124389. https://doi.org/10.1016/j.talanta.2023.124389

Lagarde, M., Géloën, A., Record, M., Vance, D., & Spener, F. (2003). Lipidomics is emerging. *Biochimica et Biophysica Acta (BBA) – Molecular and Cell Biology of Lipids*, *1634*(3), 61. https://doi.org/10.1016/j.bbalip.2003.11.002

Lange, M., & Fedorova, M. (2020). Evaluation of lipid quantification accuracy using HILIC and RPLC MS on the example of NIST® SRM® 1950 metabolites in human plasma. *Analytical and Bioanalytical Chemistry, 412*(15), 3573–3584. https://doi.org/10.1007/s00216-020-02576-x

Lapthorn, C., Pullen, F., & Chowdhry, B. Z. (2013). Ion mobility spectrometry-mass spectrometry (IMS-MS) of small molecules: Separating and assigning structures to ions. *Mass Spectrometry Reviews, 32*(1), 43–71. https://doi.org/10.1002/mas.21349

Leahy, J., Fournier, M., Lamarche, B., Garofalo, C., Grimard, G., Poulain, F., Delvin, E., Laverdière, C., Krajinovic, M., Drouin, S., Sinnett, D., Marcil, V., Levy, E., Morel, S., Leahy, J., Fournier, M., Lamarche, B., Garofalo, C., Grimard, G., et al. (2017). Lipid and lipoprotein abnormalities in acute lymphoblastic leukemia survivors[S]. *Journal Lipid Research, 58*, 982–993. https://doi.org/10.1194/jlr.M072207

Lee, C.-Y.J., Seet, R. C. S., Huang, S. H., Long, L. H., & Halliwell, B. (2009). Different patterns of oxidized lipid products in plasma and urine of dengue fever, stroke, and PD patients: Cautions in the use of biomarkers of oxidative stress. *Antioxidants & Redox Signaling, 11*(3), 407–420. https://doi.org/10.1089/ars.2008.2179

Lee, H., To, N. B., Kim, M., Nguyen, Y. T. K., Cho, S. K., & Choi, H. K. (2022). Metabolic and lipidomic characterization of radioresistant MDA-MB-231 human breast cancer cells to investigate potential therapeutic targets. *Journal of Pharmaceutical and Biomedical Analysis, 208*, 114449. https://doi.org/10.1016/J.JPBA.2021.114449

Lee, J. Y., Nam, M., Son, H. Y., Hyun, K., Jang, S. Y., Kim, J. W., Kim, M. W., Jung, Y., Jang, E., Yoon, S. J., Kim, J., Kim, J., Seo, J., Min, J. K., Oh, K. J., Han, B. S., Kim, W. K., Bae, K. H., Song, J., et al. (2020). Polyunsaturated fatty acid biosynthesis pathway determines ferroptosis sensitivity in gastric cancer. *Proceedings of the National Academy of Sciences of the United States of America, 117*(51), 32433–32442. https://doi.org/10.1073/PNAS.2006828117/SUPPL_FILE/PNAS.2006828117.SD03.XLSX

Legido-Quigley, C. (2021). Lipidomics and the quest for brainy lipids. *eBioMedicine, 65*, 103256. https://doi.org/10.1016/j.ebiom.2021.103256

Lemaitre, R. N., Jensen, P. N., Hoofnagle, A., McKnight, B., Fretts, A. M., King, I. B., Siscovick, D. S., Psaty, B. M., Heckbert, S. R., Mozaffarian, D., & Sotoodehnia, N. (2019). Plasma ceramides and sphingomyelins in relation to heart failure risk. *Circulation: Heart Failure*, *12*(7). https://doi.org/10.1161/CIRCHEARTFAILURE.118.005708

Levi, L., Wang, Z., Doud, M. K., Hazen, S. L., & Noy, N. (2015). Saturated fatty acids regulate retinoic acid signalling and suppress tumorigenesis by targeting fatty acid-binding protein 5. *Nature Communications, 6*(1), 1–10. https://doi.org/10.1038/ncomms9794

Li, X., Nakayama, K., Goto, T., Kimura, H., Akamatsu, S., Hayashi, Y., Fujita, K., Kobayashi, T., Shimizu, K., Nonomura, N., Ogawa, O., & Inoue, T. (2021). High level of phosphatidylcholines/lysophosphatidylcholine ratio in urine is associated with prostate cancer. *Cancer Science, 112*(10), 4292–4302. https://doi.org/10.1111/CAS.15093

Lin, M., Wang, Z., Wang, D., Chen, X., & Zhang, J.-L. (2019). Mathematical model-assisted UHPLC-MS/MS method for global profiling and quantification of cholesteryl esters in hyperlipidemic golden hamsters. *Analytical Chemistry, 91*(7), 4504–4512. https://doi.org/10.1021/acs.analchem.8b05337

Linseisen, J., Grundmann, N., Zoller, D., Kuhn, T., Jansen, E. H. J. M., Chajes, V., Fedirko, V., Weiderpass, E., Dahm, C. C., Overvad, K., Tjønneland, A., Boutron-Ruault, M. C., Rothwell, J. A., Severi, G., Kaaks, R., Schulze, M. B., Aleksandrova, K., Sieri, S., Panico, S., et al. (2021). Red blood cell fatty acids and risk of colorectal cancer in The European Prospective Investigation into Cancer and Nutrition (EPIC). *Cancer Epidemiology, Biomarkers & Prevention : A Publication of the American Association for Cancer Research, Cosponsored by the American Society of Preventive Oncology, 30*(5), 874–885. https://doi.org/10.1158/1055-9965.EPI-20-1426

LIPIDICA.COM – New method for early pancreatic carcinoma detection. (n.d.). Retrieved December 2, 2023, from https://www.lipidica.com/

Liu, Y., Su, Y., & Wang, X. (2013). Phosphatidic acid-mediated signaling. *Advances in Experimental Medicine and Biology, 991*, 159–176. https://doi.org/10.1007/978-94-007-6331-9_9/COVER

Liu, Y., Thalamuthu, A., Mather, K. A., Crawford, J., Ulanova, M., Wong, M. W. K., Pickford, R., Sachdev, P. S., & Braidy, N. (2021). Plasma lipidome is dysregulated in AD and is associated with disease risk genes. *Translational Psychiatry, 11*(1), 344. https://doi.org/10.1038/s41398-021-01362-2

Liu, Y., Zhong, X., Shen, J., Jiao, L., Tong, J., Zhao, W., Du, K., Gong, S., Liu, M., & Wei, M. (2020). Elevated serum TC and LDL-C levels in AD and mild cognitive impairment: A meta-analysis study. *Brain Research, 1727*, 146554. https://doi.org/10.1016/j.brainres.2019.146554

Liu, Z.-C., Wu, W.-H., Huang, S., Li, Z.-W., Li, X., Shui, G.-H., Man Lam, S., Li, B.-W., Li, Z.-X., Zhang, Y., Zhou, T., You, W.-C., Pan, K.-F., & Li, W.-Q. (2022). Plasma lipids signify the progression of precancerous gastric lesions to gastric cancer: A prospective targeted lipidomics study. *Theranostics, 2022*(10), 4671–4683. https://doi.org/10.7150/thno.74770

López de Frutos, L., Almeida, F., Murillo-Saich, J., Conceição, V. A., Guma, M., Queheberger, O., Giraldo, P., & Miltenberger-Miltenyi, G. (2022). Serum phospholipid profile changes in gaucher disease and Parkinson's disease. *International Journal of Molecular Sciences, 23*(18), 10387. https://doi.org/10.3390/ijms231810387

Lü, J., Lin, P. H., Yao, Q., & Chen, C. (2010). Chemical and molecular mechanisms of antioxidants: Experimental approaches and model systems. *Journal of Cellular and Molecular Medicine, 14*(4), 840–860. https://doi.org/10.1111/j.1582-4934.2009.00897.x

Lu, Y., Gentiluomo, M., Lorenzo-Bermejo, J., Morelli, L., Obazee, O., Campa, D., & Canzian, F. (2020). Mendelian randomisation study of the effects of known and putative risk factors on pancreatic cancer. *Journal of Medical Genetics, 57*(12), 820–828. https://doi.org/10.1136/JMEDGENET-2019-106200

Luque de Castro, M. D., & Quiles-Zafra, R. (2020). Lipidomics: An omics discipline with a key role in nutrition. *Talanta, 219*, 121197. https://doi.org/10.1016/j.talanta.2020.121197

Luu, M., Sabo, E., de la Monte, S. M., Greaves, W., Wang, J. Y., Tavares, R., Simao, L., Wands, J. R., Resnick, M. B., & Wang, L. J. (2009). Prognostic value of aspartyl (asparaginyl)-β-hydroxylase/humbug expression in non–small cell lung carcinoma. *Human Pathology, 40*(5), 639–644. https://doi.org/10.1016/J.HUMPATH.2008.11.001

Madnani, R. S. (2023). AD: A mini-review for the clinician. *Frontiers in Neurology*, *14*. https://doi.org/10.3389/fneur.2023.1178588

Mahajan, U. M., Alnatsha, A., Li, Q., Oehrle, B., Weiss, F. U., Sendler, M., Distler, M., Uhl, W., Fahlbusch, T., Goni, E., Beyer, G., Chromik, A., Bahra, M., Klein, F., Pilarsky, C., Grützmann, R., Lerch, M. M., Lauber, K., Christiansen, N., et al. (2021). Plasma metabolome profiling identifies metabolic subtypes of pancreatic ductal adenocarcinoma. *Cells, 10*(7), 1821. https://doi.org/10.3390/CELLS10071821

Mallick, R., Bhowmik, P., & Duttaroy, A. K. (2023). Targeting fatty acid uptake and metabolism in cancer cells: A promising strategy for cancer treatment. *Biomedicine & Pharmacotherapy, 167*, 115591. https://doi.org/10.1016/J.BIOPHA.2023.115591

Mandik, F., & Vos, M. (2021). Neurodegenerative disorders: Spotlight on sphingolipids. *International Journal of Molecular Sciences, 22*(21), 11998. https://doi.org/10.3390/ijms222111998

Manfreda, L., Rampazzo, E., Persano, L., Viola, G., & Bortolozzi, R. (2023). Surviving the hunger games: Metabolic reprogramming in medulloblastoma. *Biochemical Pharmacology, 215*, 115697. https://doi.org/10.1016/j.bcp.2023.115697

Markowski, A. R., Błachnio-Zabielska, A. U., Pogodzińska, K., Markowska, A. J., & Zabielski, P. (2023). Diverse sphingolipid profiles in rectal and colon cancer. *International Journal of Molecular Sciences, 24*(13), 10867. https://doi.org/10.3390/IJMS241310867

McDonald, J. G., Ejsing, C. S., Kopczynski, D., Holčapek, M., Aoki, J., Arita, M., Arita, M., Baker, E. S., Bertrand-Michel, J., Bowden, J. A., Brügger, B., Ellis, S. R., Fedorova, M., Griffiths, W. J., Han, X., Hartler, J., Hoffmann, N., Koelmel, J. P., Köfeler, H. C., et al. (2022). Introducing the lipidomics minimal reporting checklist. *Nature Metabolism, 4*(9), 1086–1088. https://doi.org/10.1038/s42255-022-00628-3

McFadden, W. C., Walsh, H., Richter, F., Soudant, C., Bryce, C. H., Hof, P. R., Fowkes, M., Crary, J. F., & McKenzie, A. T. (2019). Perfusion fixation in brain banking: A systematic review. *Acta Neuropathologica Communications, 7*(1), 146. https://doi.org/10.1186/s40478-019-0799-y

Meikle, T. G., Huynh, K., Giles, C., & Meikle, P. J. (2021). Clinical lipidomics: Realizing the potential of lipid profiling. *Journal of Lipid Research, 62*, 100127. https://doi.org/10.1016/j.jlr.2021.100127

Melo, H. M., Santos, L. E., & Ferreira, S. T. (2019). Diet-derived fatty acids, brain inflammation, and mental health. *Frontiers in Neuroscience*, *13*. https://doi.org/10.3389/fnins.2019.00265

Meriaux, C., Franck, J., Wisztorski, M., Salzet, M., & Fournier, I. (2010). Liquid ionic matrixes for MALDI mass spectrometry imaging of lipids. *Journal of Proteomics, 73*(6), 1204–1218. https://doi.org/10.1016/J.JPROT.2010.02.010

Michalik, L., Auwerx, J., Berger, J. P., Chatterjee, V. K., Glass, C. K., Gonzalez, F. J., Grimaldi, P. A., Kadowaki, T., Lazar, M. A., O'Rahilly, S., Palmer, C. N. A., Plutzky, J., Reddy, J. K., Spiegelman, B. M., Staels, B., & Wahli, W. (2006). International union of pharmacology. LXI. Peroxisome Proliferator-Activated Receptors. *Pharmacological Reviews, 58*(4), 726–741. https://doi.org/10.1124/PR.58.4.5

Michel, C. I., Holley, C. L., Scruggs, B. S., Sidhu, R., Brookheart, R. T., Listenberger, L. L., Behlke, M. A., Ory, D. S., & Schaffer,

J. E. (2011). Small nucleolar RNAs U32a, U33, and U35a are critical mediators of metabolic stress. *Cell Metabolism, 14*(1), 33–44. https://doi.org/10.1016/j.cmet.2011.04.009

Mishra, B. H., Mishra, P. P., Mononen, N., Hilvo, M., Sievänen, H., Juonala, M., Laaksonen, M., Hutri-Kähönen, N., Viikari, J., Kähönen, M., Raitakari, O. T., Laaksonen, R., & Lehtimäki, T. (2020). Lipidomic architecture shared by subclinical markers of osteoporosis and atherosclerosis: The Cardiovascular Risk in Young Finns Study. *Bone, 131*, 115160. https://doi.org/10.1016/j.bone.2019.115160

Mundra, P. A., Barlow, C. K., Nestel, P. J., Barnes, E. H., Kirby, A., Thompson, P., Sullivan, D. R., Alshehry, Z. H., Mellett, N. A., Huynh, K., Jayawardana, K. S., Giles, C., McConville, M. J., Zoungas, S., Hillis, G. S., Chalmers, J., Woodward, M., Wong, G., Kingwell, B. A., et al. (2018). Large-scale plasma lipidomic profiling identifies lipids that predict cardiovascular events in secondary prevention. *JCI Insight, 3*(17), e121326. https://doi.org/10.1172/jci.insight.121326

Neag, M.-A., Mitre, A.-O., Catinean, A., & Mitre, C.-I. (2020). An overview on the mechanisms of neuroprotection and neurotoxicity of isoflurane and sevoflurane in experimental studies. *Brain Research Bulletin, 165*, 281–289. https://doi.org/10.1016/j.brainresbull.2020.10.011

Nichols, E., Steinmetz, J. D., Vollset, S. E., Fukutaki, K., Chalek, J., Abd-Allah, F., Abdoli, A., Abualhasan, A., Abu-Gharbieh, E., Akram, T. T., Al Hamad, H., Alahdab, F., Alanezi, F. M., Alipour, V., Almustanyir, S., Amu, H., Ansari, I., Arabloo, J., Ashraf, T., et al. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: An analysis for the Global Burden of Disease Study 2019. *The Lancet Public Health, 7*(2), e105–e125. https://doi.org/10.1016/S2468-2667(21)00249-8

Ning, Z., Guo, X., Liu, X., Lu, C., Wang, A., Wang, X., Wang, W., Chen, H., Qin, W., Liu, X., Zhou, L., Ma, C., Du, J., Lin, Z., Luo, H., Otkur, W., Qi, H., Chen, D., Xia, T., et al. (2022). USP22 regulates lipidome accumulation by stabilizing PPARγ in hepatocellular carcinoma. *Nature Communications, 13*(1), 1–18. https://doi.org/10.1038/s41467-022-29846-9

Noreldeen, H. A. A., Du, L., Li, W., Liu, X., Wang, Y., & Xu, G. (2020). Serum lipidomic biomarkers for non-small cell lung cancer in nonsmoking female patients. *Journal of Pharmaceutical and Biomedical Analysis, 185*, 113220. https://doi.org/10.1016/J.JPBA.2020.113220

Nurmohamed, N. S., Kraaijenhof, J. M., Mayr, M., Nicholls, S. J., Koenig, W., Catapano, A. L., & Stroes, E. S. G. (2023). Proteomics and lipidomics in atherosclerotic cardiovascular disease risk prediction. *European Heart Journal, 44*(18), 1594–1607. https://doi.org/10.1093/eurheartj/ehad161

O'Donnell, V. B., Ekroos, K., Liebisch, G., & Wakelam, M. (2020). Lipidomics: Current state of the art in a fast moving field. *WIREs Systems Biology and Medicine*, *12*(1). https://doi.org/10.1002/wsbm.1466

Paglia, G., Kliman, M., Claude, E., Geromanos, S., & Astarita, G. (2015). Applications of ion-mobility mass spectrometry for lipid analysis. *Analytical and Bioanalytical Chemistry, 407*(17), 4995–5007. https://doi.org/10.1007/s00216-015-8664-8

Pakiet, A., Jędrzejewska, A., Duzowska, K., Wacławska, A., Jabłońska, P., Zieliński, J., Mika, A., Śledziński, T., & Słomińska, E. (2023). Serum fatty acid profiles in breast cancer patients following treatment. *BMC Cancer, 23*(1), 433. https://doi.org/10.1186/S12885-023-10914-2

Pan, M., Qin, C., & Han, X. (2021). *Lipid metabolism and lipidomics applications in cancer research* (pp. 1–24). https://doi.org/10.1007/978-981-33-6785-2_1

Pang, Z., Chong, J., Zhou, G., de Lima Morais, D. A., Chang, L., Barrette, M., Gauthier, C., Jacques, P. -É., Li, S., & Xia, J. (2021). MetaboAnalyst 5.0: Narrowing the gap between raw spectra and functional insights. *Nucleic Acids Research, 49*(W1), W388–W396. https://doi.org/10.1093/nar/gkab382

Park, J., Oh, H. J., Han, D., Wang, J. I., Park, I. A., Ryu, H. S., & Kim, Y. (2020). Parallel reaction monitoring-mass spectrometry (PRM-MS)-based targeted proteomic surrogates for intrinsic subtypes in breast cancer: Comparative analysis with immunohistochemical phenotypes. *Journal of Proteome Research, 19*(7), 2643–2653. https://doi.org/10.1021/acs.jproteome.9b00490

Phinney, K. W., Ballihaut, G., Bedner, M., Benford, B. S., Camara, J. E., Christopher, S. J., Davis, W. C., Dodder, N. G., Eppe, G., Lang, B. E., Long, S. E., Lowenthal, M. S., McGaw, E. A., Murphy, K. E., Nelson, B. C., Prendergast, J. L., Reiner, J. L., Rimmer, C. A., Sander, L. C., et al. (2013). Development of a standard reference material for metabolomics research. *Analytical Chemistry, 85*(24), 11732–11738. https://doi.org/10.1021/ac402689t

Pih, G. Y., Gong, E. J., Choi, J. Y., Kim, M. J., Ahn, J. Y., Choe, J., Bae, S. E., Chang, H. S., Na, H. K., Lee, J. H., Jung, K. W., Kim, D. H., Choi, K. D., Song, H. J., Lee, G. H., & Jung, H. Y. (2020). Associations of serum lipid level with gastric cancer risk, pathology, and prognosis. *Cancer Research and Treatment, 53*(2), 445–456. https://doi.org/10.4143/CRT.2020.599

Pluskal, T., Castillo, S., Villar-Briones, A., & Orešič, M. (2010). MZmine 2: Modular framework for processing, visualizing, and analyzing mass spectrometry-based molecular profile data. *BMC Bioinformatics, 11*(1), 395. https://doi.org/10.1186/1471-2105-11-395

Puolitaival, S. M., Burnum, K. E., Cornett, D. S., & Caprioli, R. M. (2008). Solvent-free matrix dry-coating for MALDI imaging of phospholipids. *Journal of the American Society for Mass Spectrometry, 19*(6), 882–886. https://doi.org/10.1016/j.jasms.2008.02.013

Raghu, P. (2020). Functional diversity in a lipidome. *Proceedings of the National Academy of Sciences, 117*(21), 11191–11193. https://doi.org/10.1073/pnas.2004764117

Rampler, E., Coman, C., Hermann, G., Sickmann, A., Ahrends, R., & Koellensperger, G. (2017). LILY-lipidome isotope labeling of yeast: In vivo synthesis of ^{13}C labeled reference lipids for quantification by mass spectrometry. *The Analyst, 142*(11), 1891–1899. https://doi.org/10.1039/C7AN00107J

Ranjbarvaziri, S., Kooiker, K. B., Ellenberger, M., Fajardo, G., Zhao, M., Vander Roest, A. S., Woldeyes, R. A., Koyano, T. T., Fong, R., Ma, N., Tian, L., Traber, G. M., Chan, F., Perrino, J., Reddy, S., Chiu, W., Wu, J. C., Woo, J. Y., Ruppel, K. M., et al. (2021). Altered cardiac energetics and mitochondrial dysfunction in hypertrophic cardiomyopathy. *Circulation, 144*(21), 1714–1731. https://doi.org/10.1161/CIRCULATIONAHA.121.053575

Rawla, P., Sunkara, T., Muralidharan, P., & Raj, J. P. (2018). Update in global trends and aetiology of hepatocellular carcinoma. *Contemporary Oncology (poznan, Poland), 22*(3), 141–150. https://doi.org/10.5114/WO.2018.78941

Reichl, B., Eichelberg, N., Freytag, M., Gojo, J., Peyrl, A., & Buchberger, W. (2020). Evaluation and optimization of common lipid extraction methods in cerebrospinal fluid samples. *Journal of Chromatography B, 1153*, 122271. https://doi.org/10.1016/j.jchromb.2020.122271

Reveglia, P., Paolillo, C., Angiolillo, A., Ferretti, G., Angelico, R., Sirabella, R., Corso, G., Matrone, C., & Di Costanzo, A. (2023). A targeted mass spectrometry approach to identify peripheral changes in metabolic pathways of patients with AD. *International Journal of Molecular Sciences, 24*(11), 9736. https://doi.org/10.3390/ijms24119736

Riekkinen, P., Rinne, U. K., Pelliniemi, T. T., & Sonninen, V. (1975). Interaction between dopamine and phospholipids: Studies of the substantia nigra in parkinson disease patients. *Archives of*

Neurology, 32(1), 25–27. https://doi.org/10.1001/ARCHNEUR.1975.00490430047006

Rosini Silva, A. A., Cardoso, M. R., Resende, L. M., Lin, J. Q., Guimaraes, F., Paiva Silva, G. R., Murgu, M., Priolli, D. G., Eberlin, M. N., Tata, A., Eberlin, L. S., Derchain, S. F. M., & Porcari, A. M. (2020). Multiplatform investigation of plasma and tissue lipid signatures of breast cancer using mass spectrometry tools. *International Journal of Molecular Sciences, 21*(10), 3611. https://doi.org/10.3390/IJMS21103611

Rozeveld, C. N., Johnson, K. M., Zhang, L., & Razidlo, G. L. (2020). KRAS controls pancreatic cancer cell lipid metabolism and invasive potential through the lipase HSL. *Cancer Research, 80*(22), 4332–4345. https://doi.org/10.1158/0008-5472.CAN-20-1255/654658/AM/KRAS-CONTROLS-PANCREATIC-CANCER-CELL-LIPID

Sääksjärvi, K., Knekt, P., Männistö, S., Lyytinen, J., & Heliövaara, M. (2015). Prospective study on the components of metabolic syndrome and the incidence of Parkinson's disease. *Parkinsonism and Related Disorders, 21*(10), 1148–1155. https://doi.org/10.1016/J.PARKRELDIS.2015.07.017

Sah, R. P., Sharma, A., Nagpal, S., Patlolla, S. H., Sharma, A., Kandlakunta, H., Anani, V., Angom, R. S., Kamboj, A. K., Ahmed, N., Mohapatra, S., Vivekanandhan, S., Philbrick, K. A., Weston, A., Takahashi, N., Kirkland, J., Javeed, N., Matveyenko, A., Levy, M. J., et al. (2019). Phases of metabolic and soft tissue changes in months preceding a diagnosis of pancreatic ductal adenocarcinoma. *Gastroenterology, 156*(6), 1742–1752. https://doi.org/10.1053/j.gastro.2019.01.039

Saiki, S., Hatano, T., Fujimaki, M., Ishikawa, K. I., Mori, A., Oji, Y., Okuzumi, A., Fukuhara, T., Koinuma, T., Imamichi, Y., Nagumo, M., Furuya, N., Nojiri, S., Amo, T., Yamashiro, K., & Hattori, N. (2017). Decreased long-chain acylcarnitines from insufficient β-oxidation as potential early diagnostic markers for Parkinson's disease. *Scientific Reports, 7*(1), 1–15. https://doi.org/10.1038/s41598-017-06767-y

Saito, K., Arai, E., Maekawa, K., Ishikawa, M., Fujimoto, H., Taguchi, R., Matsumoto, K., Kanai, Y., & Saito, Y. (2016). Lipidomic signatures and associated transcriptomic profiles of clear cell renal cell carcinoma. *Scientific Reports, 6*(1), 1–12. https://doi.org/10.1038/srep28932

Sáiz-Vazquez, O., Puente-Martínez, A., Ubillos-Landa, S., Pacheco-Bonrostro, J., & Santabárbara, J. (2020). Cholesterol and AD risk: A meta-meta-analysis. *Brain Sciences, 10*(6), 386. https://doi.org/10.3390/brainsci10060386

Samouillan, V., de Lejarza, M., Samper, I. M., Benitez Amaro, A., Vilades, D., Dandurand, J., Casas, J., Jorge, E., de Gonzalo Calvo, D., Gallardo, A., Lerma, E., Guerra, J. M., Carreras, F., Leta, R., & Llorente Cortes, V. (2020). Biophysical and lipidomic biomarkers of cardiac remodeling post-myocardial infarction in humans. *Biomolecules, 10*(11), 1471. https://doi.org/10.3390/biom10111471

Sarafian, M. H., Gaudin, M., Lewis, M. R., Martin, F.-P., Holmes, E., Nicholson, J. K., & Dumas, M.-E. (2014). Objective set of criteria for optimization of sample preparation procedures for ultra-high throughput untargeted blood plasma lipid profiling by ultra performance liquid chromatography-mass spectrometry. *Analytical Chemistry, 86*(12), 5766–5774. https://doi.org/10.1021/ac500317c

Schiliro, C., & Firestein, B. L. (2021). *Cells mechanisms of metabolic reprogramming in cancer cells supporting enhanced growth and proliferation*. https://doi.org/10.3390/cells10051056

Schmid, R., Heuckeroth, S., Korf, A., Smirnov, A., Myers, O., Dyrlund, T. S., Bushuiev, R., Murray, K. J., Hoffmann, N., Lu, M., Sarvepalli, A., Zhang, Z., Fleischauer, M., Dührkop, K., Wesner, M., Hoogstra, S. J., Rudt, E., Mokshyna, O., Brungs, C., et al. (2023). Integrative analysis of multimodal mass spectrometry data in MZmine 3. *Nature Biotechnology, 41*(4), 447–449. https://doi.org/10.1038/s41587-023-01690-2

Schmidt, D., & MacKinnon, R. (2008). Voltage-dependent K+ channel gating and voltage sensor toxin sensitivity depend on the mechanical state of the lipid membrane. *Proceedings of the National Academy of Sciences of the United States of America, 105*(49), 19276–19281. https://doi.org/10.1073/PNAS.0810187105

Scott, D. A., Casadonte, R., Cardinali, B., Spruill, L., Mehta, A. S., Carli, F., Simone, N., Kriegsmann, M., Mastro, L. D., Kriegsmann, J., & Drake, R. R. (2019). Increases in Tumor N-glycan polylactosamines associated with advanced HER2-positive and triple-negative breast cancer tissues HHS public access. *Proteomics. Clinical Applications, 13*(1), 1800014. https://doi.org/10.1002/prca.201800014

Seet, R. C. S., Lee, C.-Y.J., Lim, E. C. H., Tan, J. J. H., Quek, A. M. L., Chong, W.-L., Looi, W.-F., Huang, S.-H., Wang, H., & Chan, Y.-H. (2010). Oxidative damage in Parkinson disease: Measurement using accurate biomarkers. *Free Radical Biology and Medicine, 48*(4), 560–566. https://doi.org/10.1016/j.freeradbiomed.2009.11.026

Serhan, C. N. (2017). Treating inflammation and infection in the 21st century: New hints from decoding resolution mediators and mechanisms. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology, 31*(4), 1273–1288. https://doi.org/10.1096/fj.201601222R

Seyfried, T. N., Choi, H., Chevalier, A., Hogan, D., Akgoc, Z., & Schneider, J. S. (2018). Sex-related abnormalities in substantia nigra lipids in Parkinson's disease. *ASN Neuro, 10*, 175909141878188. https://doi.org/10.1177/1759091418781889

Shang, X., Zhang, C., Kong, R., Zhao, C., & Wang, H. (2023). Construction of a diagnostic model for small cell lung cancer combining metabolomics and integrated machine learning. *The Oncologist*. https://doi.org/10.1093/ONCOLO/OYAD261

Shanta, S. R., Zhou, L. H., Park, Y. S., Kim, Y. H., Kim, Y., & Kim, K. P. (2011). Binary matrix for MALDI imaging mass spectrometry of phospholipids in both ion modes. *Analytical Chemistry, 83*(4), 1252–1259. https://doi.org/10.1021/AC1029659

Sharma, A., Bandyopadhayaya, S., Chowdhury, K., Sharma, T., Maheshwari, R., Das, A., Chakrabarti, G., Kumar, V., & Mandal, C. C. (2019). Metformin exhibited anticancer activity by lowering cellular cholesterol content in breast cancer cells. *PLoS ONE, 14*(1), e0209435. https://doi.org/10.1371/JOURNAL.PONE.0209435

Sharma, U., & Jagannathan, N. R. (2022). Magnetic resonance imaging (MRI) and MR spectroscopic methods in understanding breast cancer biology and metabolism. *Metabolites, 12*(4), 295. https://doi.org/10.3390/metabo12040295

Shimma, S., Sugiura, Y., Hayasaka, T., Hoshikawa, Y., Noda, T., & Setou, M. (2007). MALDI-based imaging mass spectrometry revealed abnormal distribution of phospholipids in colon cancer liver metastasis. *Journal of Chromatography B, 855*(1), 98–103. https://doi.org/10.1016/j.jchromb.2007.02.037

Shrivas, K., Hayasaka, T., Goto-Inoue, N., Sugiura, Y., Zaima, N., & Setou, M. (2010). Ionic matrix for enhanced MALDI imaging mass spectrometry for identification of phospholipids in mouse liver and cerebellum tissue sections. *Analytical Chemistry, 82*(21), 8800–8806. https://doi.org/10.1021/AC102422B

Sinclair, A. J. (2019). Docosahexaenoic acid and the brain- what is its role? *Asia Pacific Journal of Clinical Nutrition, 28*(4), 675–688. https://doi.org/10.6133/apjcn.201912_28(4).0002

Sinclair, E., Trivedi, D. K., Sarkar, D., Walton-Doyle, C., Milne, J., Kunath, T., Rijs, A. M., de Bie, R. M. A., Goodacre, R., Silverdale, M., & Barran, P. (2021). Metabolomics of sebum reveals lipid dysregulation in Parkinson's disease. *Nature Communications, 12*(1), 1592. https://doi.org/10.1038/s41467-021-21669-4

Sjöbeck, M., Haglund, M., Persson, A., Sturesson, K., & Englund, E. (2003). Brain tissue microarrays in dementia research: White matter microvascular pathology in AD. *Neuropathology, 23*(4), 290–295. https://doi.org/10.1046/j.1440-1789.2003.00515.x

Skoura, A., & Hla, T. (2009). Lysophospholipid receptors in vertebrate development, physiology, and pathology. *Journal of Lipid Research*, *50*(SUPPL.). https://doi.org/10.1194/JLR.R800047-JLR200

Smirnov, D., Mazin, P., Osetrova, M., Stekolshchikova, E., & Khrameeva, E. (2021). The Hitchhiker's guide to untargeted lipidomics analysis: Practical guidelines. *Metabolites, 11*(11), 713. https://doi.org/10.3390/metabo11110713

Southam, A. D., Haglington, L. D., Najdekr, L., Jankevics, A., Weber, R. J. M., & Dunn, W. B. (2020). Assessment of human plasma and urine sample preparation for reproducible and high-throughput UHPLC-MS clinical metabolic phenotyping. *The Analyst, 145*(20), 6511–6523. https://doi.org/10.1039/D0AN01319F

Southam, A. D., Pursell, H., Frigerio, G., Jankevics, A., Weber, R. J. M., & Dunn, W. B. (2021). Characterization of monophasic solvent-based tissue extractions for the detection of polar metabolites and lipids applying ultrahigh-performance liquid chromatography-mass spectrometry clinical metabolic phenotyping assays. *Journal of Proteome Research, 20*(1), 831–840. https://doi.org/10.1021/acs.jproteome.0c00660

Spill, F., Reynolds, D. S., Kamm, R. D., & Zaman, M. H. (2019). *Impact of the physical microenvironment on tumor progression and metastasis*. https://www.elsevier.com/open-access/userlicense/1.0/

Šrámek, J., Němcová-Fürstová, V., & Kovář, J. (2021). Molecular mechanisms of apoptosis induction and its regulation by fatty acids in pancreatic β-cells. *International Journal of Molecular Sciences, 22*(8), 4285. https://doi.org/10.3390/ijms22084285

Stromberg, L. R., Lilley, L. M., & Mukundan, H. (2020). Advances in lipidomics for cancer biomarker discovery. In *Proteomic and metabolomic approaches to biomarker discovery* (pp. 421–436). Elsevier. https://doi.org/10.1016/B978-0-12-818607-7.00025-6

Sugiura, Y., & Setou, M. (2009). Selective imaging of positively charged polar and nonpolar lipids by optimizing matrix solution composition. *Rapid Communications in Mass Spectrometry : RCM, 23*(20), 3269–3278. https://doi.org/10.1002/RCM.4242

Sun, C., Wang, A., Zhou, Y., Chen, P., Wang, X., Huang, J., Gao, J., Wang, X., Shu, L., Lu, J., Dai, W., Bu, Z., Ji, J., & He, J. (2023). Spatially resolved multi-omics highlights cell-specific metabolic remodeling and interactions in gastric cancer. *Nature Communications, 14*(1), 1–14. https://doi.org/10.1038/s41467-023-38360-5

Sun, Q., Yu, X., Peng, C., Liu, N., Chen, W., Xu, H., Wei, H., Fang, K., Dong, Z., Fu, C., Xu, Y., & Lu, W. (2020). Activation of SREBP-1c alters lipogenesis and promotes tumor growth and metastasis in gastric cancer. *Biomedicine & Pharmacotherapy, 128*, 110274. https://doi.org/10.1016/J.BIOPHA.2020.110274

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, *71*(3), 209–249. https://doi.org/10.3322/CAAC.21660

Tabassum, R., & Ripatti, S. (2021). Integrating lipidomics and genomics: Emerging tools to understand cardiovascular diseases. *Cellular and Molecular Life Sciences, 78*(6), 2565–2584. https://doi.org/10.1007/s00018-020-03715-4

Tague, E. D., Woodall, B. M., Harp, J. R., Farmer, A. T., Fozo, E. M., & Campagna, S. R. (2019). Expanding lipidomics coverage: Effective ultra performance liquid chromatography-high resolution mass spectrometer methods for detection and quantitation of cardiolipin, phosphatidylglycerol, and lysyl-phosphatidylglycerol. *Metabolomics, 15*(4), 53. https://doi.org/10.1007/s11306-019-1512-7

Tarasov, K., Ekroos, K., Suoniemi, M., Kauhanen, D., Sylvänne, T., Hurme, R., Gouni-Berthold, I., Berthold, H. K., Kleber, M. E., Laaksonen, R., & März, W. (2014). Molecular lipids identify cardiovascular risk and are efficiently lowered by simvastatin and PCSK9 deficiency. *The Journal of Clinical Endocrinology and Metabolism*, *99*(1). https://doi.org/10.1210/JC.2013-2559

Tata, A., Zheng, J., Ginsberg, H. J., Jaffray, D. A., Ifa, D. R., & Zarrine-Afsar, A. (2015). Contrast agent mass spectrometry imaging reveals tumor heterogeneity. *Analytical Chemistry, 87*(15), 7683–7689. https://doi.org/10.1021/acs.analchem.5b01992

Thomas, D., Wu, M., Nakauchi, Y., Zheng, M., Thompson-Peach, C. A. L., Lim, K., Landberg, N., Köhnke, T., Robinson, N., Kaur, S., Kutyna, M., Stafford, M., Hiwase, D., Reinisch, A., Peltz, G., & Majeti, R. (2023). Dysregulated lipid synthesis by oncogenic IDH1 mutation is a targetable synthetic lethal vulnerability. *Cancer Discovery, 13*(2), 496–515. https://doi.org/10.1158/2159-8290.CD-21-0218

Triebl, A., Burla, B., Selvalatchmanan, J., Oh, J., Tan, S. H., Chan, M. Y., Mellet, N. A., Meikle, P. J., Torta, F., & Wenk, M. R. (2020). Shared reference materials harmonize lipidomics across MS-based detection platforms and laboratories. *Journal of Lipid Research, 61*(1), 105–115. https://doi.org/10.1194/jlr.D119000393

Tsao, C. W., Aday, A. W., Almarzooq, Z. I., Anderson, C. A. M., Arora, P., Avery, C. L., Baker-Smith, C. M., Beaton, A. Z., Boehme, A. K., Buxton, A. E., Commodore-Mensah, Y., Elkind, M. S. V., Evenson, K. R., Eze-Nliam, C., Fugar, S., Generoso, G., Heard, D. G., Hiremath, S., Ho, J. E., et al. (2023). Heart disease and stroke statistics—2023 update: A report from the American Heart Association. *Circulation, 147*(8), e93. https://doi.org/10.1161/CIR.0000000000001123

Tsugawa, H., Ikeda, K., Takahashi, M., Satoh, A., Mori, Y., Uchino, H., Okahashi, N., Yamada, Y., Tada, I., Bonini, P., Higashi, Y., Okazaki, Y., Zhou, Z., Zhu, Z.-J., Koelmel, J., Cajka, T., Fiehn, O., Saito, K., Arita, M., & Arita, M. (2020). A lipidome atlas in MS-DIAL 4. *Nature Biotechnology, 38*(10), 1159–1163. https://doi.org/10.1038/s41587-020-0531-2

Ulmer, C. Z., Koelmel, J. P., Jones, C. M., Garrett, T. J., Aristizabal-Henao, J. J., Vesper, H. W., & Bowden, J. A. (2021). A review of efforts to improve lipid stability during sample preparation and standardization efforts to ensure accuracy in the reporting of lipid measurements. *Lipids, 56*(1), 3–16. https://doi.org/10.1002/lipd.12263

Vale, G., Martin, S. A., Mitsche, M. A., Thompson, B. M., Eckert, K. M., & McDonald, J. G. (2019). Three-phase liquid extraction: A simple and fast method for lipidomic workflows. *Journal of Lipid Research, 60*(3), 694–706. https://doi.org/10.1194/jlr.D090795

van Bentum, M., & Selbach, M. (2021). An introduction to advanced targeted acquisition methods. *Molecular & Cellular Proteomics, 20*, 100165. https://doi.org/10.1016/j.mcpro.2021.100165

van Dyck, C. H., Swanson, C. J., Aisen, P., Bateman, R. J., Chen, C., Gee, M., Kanekiyo, M., Li, D., Reyderman, L., Cohen, S., Froelich, L., Katayama, S., Sabbagh, M., Vellas, B., Watson, D., Dhadda, S., Irizarry, M., Kramer, L. D., & Iwatsubo, T. (2023). Lecanemab in early AD. *New England Journal of Medicine, 388*(1), 9–21. https://doi.org/10.1056/NEJMoa2212948

Vegiopoulos, A., Müller-Decker, K., Strzoda, D., Schmitt, I., Chichelnitskiy, E., Ostertag, A., Diaz, M. B., Rozman, J., De Angelis, M. H., Nüsing, R. M., Meyer, C. W., Wahli, W., Klingenspor, M., & Herzig, S. (2010). Cyclooxygenase-2 controls energy homeostasis in mice by de novo recruitment of brown adipocytes. *Science, 328*(5982), 1158–1161. https://doi.org/10.1126/SCIENCE.1186034

Wang, M., & Han, X. (2016). *Advanced shotgun lipidomics for characterization of altered lipid patterns in neurodegenerative diseases and brain injury* (pp. 405–422). https://doi.org/10.1007/978-1-4939-2627-5_24

Wang, G., Qiu, M., Xing, X., Zhou, J., Yao, H., Li, M., Yin, R., Hou, Y., Li, Y., Pan, S., Huang, Y., Yang, F., Bai, F., Nie, H., Di, S., Guo, L., Meng, Z., Wang, J., & Yin, Y. (2022). Lung cancer scRNA-seq and lipidomics reveal aberrant lipid metabolism for early-stage diagnosis. *Science Translational Medicine*, *14*(630). https://doi.org/10.1126/SCITRANSLMED.ABK2756

Wang, J., Zhao, S., Sun, J., Wang, X., Guan, M., Yin, J., & Tang, B. (2023a). Oncogenic role and potential regulatory mechanism of fatty acid binding protein 5 based on a pan-cancer analysis. *Scientific Reports*, *13*(1). https://doi.org/10.1038/S41598-023-30695-9

Wang, M., Wang, C., & Han, X. (2017). Selection of internal standards for accurate quantification of complex lipid species in biological extracts by electrospray ionization mass spectrometry—What, how and why? *Mass Spectrometry Reviews, 36*(6), 693–714. https://doi.org/10.1002/mas.21492

Wang, Q., Hoene, M., Hu, C., Fritsche, L., Ahrends, R., Liebisch, G., Ekroos, K., Fritsche, A., Birkenfeld, A. L., Liu, X., Zhao, X., Li, Q., Su, B., Peter, A., Xu, G., & Lehmann, R. (2023b). Ex vivo instability of lipids in whole blood: Preanalytical recommendations for clinical lipidomics studies. *Journal of Lipid Research, 64*(6), 100378. https://doi.org/10.1016/j.jlr.2023.100378

Wang, X., Bui, H., Vemuri, P., Graff-Radford, J., Jack, C. R., Jr., Petersen, R. C., & Mielke, M. M. (2021). Lipidomic network of mild cognitive impairment from the mayo clinic study of aging. *Journal of AD, 81*(2), 533–543. https://doi.org/10.3233/JAD-201347

Wei, Z., Li, X., Li, X., Liu, Q., & Cheng, Y. (2018). Oxidative stress in Parkinson's disease: A systematic review and meta-analysis. *Frontiers in Molecular Neuroscience*, *11*. https://doi.org/10.3389/FNMOL.2018.00236/FULL

Wei, Q., Wang, H., Tian, Y., Xu, F., Chen, X., & One, K. W. (2013). Reduced serum levels of triglyceride, very low density lipoprotein cholesterol and apolipoprotein B in PD patients. *PLoS One, 8*(9), e75743. https://doi.org/10.1371/journal.pone.0075743

Wenk, M. R. (2005). The emerging field of lipidomics. *Nature Reviews Drug Discovery, 4*(7), 594–610. https://doi.org/10.1038/nrd1776

Williams, C., Mbuyane, L. L., Bauer, F. F., Mokwena, L., Divol, B., & Buica, A. (2021). A gas chromatography-mass spectrometry method for the determination of fatty acids and sterols in yeast and grape juice. *Applied Sciences, 11*(11), 5152. https://doi.org/10.3390/app11115152

Wolrab, D., Chocholoušková, M., Jirásko, R., Peterka, O., Mužáková, V., Študentová, H., Melichar, B., & Holčapek, M. (2020). Determination of one year stability of lipid plasma profile and comparison of blood collection tubes using UHPSFC/MS and HILIC-UHPLC/MS. *Analytica Chimica Acta, 1137*, 74–84. https://doi.org/10.1016/j.aca.2020.08.061

Wolrab, D., Jirásko, R., Chocholoušková, M., Peterka, O., & Holčapek, M. (2019). Oncolipidomics: Mass spectrometric quantitation of lipids in cancer research. *TrAC Trends in Analytical Chemistry, 120*, 115480. https://doi.org/10.1016/J.TRAC.2019.04.012

Wolrab, D., Jirásko, R., Cífková, E., Höring, M., Mei, D., Chocholoušková, M., Peterka, O., Idkowiak, J., Hrnčiarová, T., Kuchař, L., Ahrends, R., Brumarová, R., Friedecký, D., Vivo-Truyols, G., Škrha, P., Škrha, J., Kučera, R., Melichar, B., Liebisch, G., et al. (2022). Lipidomic profiling of human serum enables detection of pancreatic cancer. *Nature Communications, 13*(1), 124. https://doi.org/10.1038/s41467-021-27765-9

Wong, M. W., Braidy, N., Poljak, A., Pickford, R., Thambisetty, M., & Sachdev, P. S. (2017). Dysregulation of lipids in AD and their role as potential biomarkers. *Alzheimer's & Dementia, 13*(7), 810–827. https://doi.org/10.1016/j.jalz.2017.01.008

Wood, P., Tippireddy, S., Feriante, J., & One, R. (2018). Augmented frontal cortex diacylglycerol levels in PD and Lewy body disease. *PLoS One, 13*(3), e0191815. https://doi.org/10.1371/journal.pone.0191815

Wu, Y., & Li, L. (2016). Sample normalization methods in quantitative metabolomics. *Journal of Chromatography A, 1430*, 80–95. https://doi.org/10.1016/j.chroma.2015.12.007

Wu, Y., Wang, Z., Jia, X., Zhang, H., Zhang, H., Li, J., & Zhang, K. (2019). Prediction of AD with serum lipid levels in Asian individuals: A meta-analysis. *Biomarkers, 24*(4), 341–351. https://doi.org/10.1080/1354750X.2019.1571633

Xiao, Y., Ma, D., Yang, Y. S., Yang, F., Ding, J. H., Gong, Y., Jiang, L., Ge, L. P., Wu, S. Y., Yu, Q., Zhang, Q., Bertucci, F., Sun, Q., Hu, X., Li, D. Q., Shao, Z. M., & Jiang, Y. Z. (2022). Comprehensive metabolomics expands precision medicine for triple-negative breast cancer. *Cell Research, 32*(5), 477–490. https://doi.org/10.1038/S41422-022-00614-0

Xie, Y., Wang, B., Zhao, Y., Tao, Z., Wang, Y., Chen, G., & Hu, X. (2022). Mammary adipocytes protect triple-negative breast cancer cells from ferroptosis. *Journal of Hematology and Oncology, 15*(1), 1–5. https://doi.org/10.1186/S13045-022-01297-1/FIGURES/2

Xu, T., Hu, C., Xuan, Q., & Xu, G. (2020). Recent advances in analytical strategies for mass spectrometry-based lipidomics. *Analytica Chimica Acta, 1137*, 156–169. https://doi.org/10.1016/j.aca.2020.09.060

Xue, J., Guijas, C., Benton, H. P., Warth, B., & Siuzdak, G. (2020). METLIN MS2 molecular standards database: A broad chemical and biological resource. *Nature Methods, 17*(10), 953–954. https://doi.org/10.1038/s41592-020-0942-5

Yadav, M., Chaudhary, P. P., D'Souza, B. N., Spathies, J., & Myles, I. A. (2022). Impact of Skin tissue collection method on downstream MALDI-imaging. *Metabolites, 12*(6), 497. https://doi.org/10.3390/metabo12060497

Yandim, M. K., & Bilgin, M. (2022). Shotgun lipidomics elucidates the lipidome alterations of the Mcl-1 inhibitor S63845 in AML cell lines with a focus on sphingolipids. *Experimed*, *12*(3), 209–223. https://doi.org/10.26650/experimed.1196117

Yoo, H. C., Yu, Y. C., Sung, Y., & Han, J. M. (2020). Glutamine reliance in cell metabolism. *Experimental & Molecular Medicine, 52*(9), 1496–1516. https://doi.org/10.1038/s12276-020-00504-8

Yoon, J. H., Seo, Y., Jo, Y. S., Lee, S., Cho, E., Cazenave-Gassiot, A., Shin, Y.-S., Moon, M. H., An, H. J., Wenk, M. R., & Suh, P.-G. (2022). Brain lipidomics: From functional landscape to clinical significance. *Science Advances*, *8*(37). https://doi.org/10.1126/sciadv.adc9317

Yu, D., Rupasinghe, T. W. T., Boughton, B. A., Natera, S. H. A., Hill, C. B., Tarazona, P., Feussner, I., & Roessner, U. (2018). A high-resolution HPLC-QqTOF platform using parallel reaction monitoring for in-depth lipid discovery and rapid profiling. *Analytica Chimica Acta, 1026*, 87–100. https://doi.org/10.1016/j.aca.2018.03.062

Zeng, J., Tan, H., Huang, B., Zhou, Q., Ke, Q., Dai, Y., Tang, J., Xu, B., Feng, J., & Yu, L. (2022). Lipid metabolism characterization in gastric cancer identifies signatures to predict prognostic and therapeutic responses. *Frontiers in Genetics, 13*, 959170. https://doi.org/10.3389/FGENE.2022.959170/BIBTEX

Zhang, J., Zhang, X., Wang, L., & Yang, C. (2017). High Performance liquid chromatography-mass spectrometry (LC-MS) based quantitative lipidomics study of ganglioside-NANA-3 plasma to establish its association with PD patients. *Medical Science Monitor*, *23*, 5345–5353. https://doi.org/10.12659/MSM.904399

Zhang, L., Wang, X., Wang, M., Sterling, N. W., Du, G., Lewis, M. M., Yao, T., Mailman, R. B., Li, R., & Huang, X. (2017). Circulating cholesterol levels may link to the factors influencing Parkinson's

risk. *Frontiers in Neurology*, *8*(SEP). https://doi.org/10.3389/FNEUR.2017.00501/FULL

Zhang, H. L., Hu, B. X., Li, Z. L., Du, T., Shan, J. L., Ye, Z. P., Peng, X. D., Li, X., Huang, Y., Zhu, X. Y., Chen, Y. H., Feng, G. K., Yang, D., Deng, R., & Zhu, X. F. (2022a). PKCβII phosphorylates ACSL4 to amplify lipid peroxidation to induce ferroptosis. *Nature Cell Biology, 24*(1), 88–98. https://doi.org/10.1038/s41556-021-00818-3

Zhang, M., Mileykovskaya, E., & Dowhan, W. (2002). Gluing the respiratory chain together: Cardiolipin is required for supercomplex formation in the inner mitochondrial membrane. *Journal of Biological Chemistry, 277*(46), 43553–43556. https://doi.org/10.1074/JBC.C200551200

Zhang, T., Trauger, S. A., Vidoudez, C., Doane, K. P., Pluimer, B. R., & Peterson, R. T. (2019). Parallel reaction monitoring reveals structure-specific ceramide alterations in the zebrafish. *Scientific Reports, 9*(1), 19939. https://doi.org/10.1038/s41598-019-56466-z

Zhang, W., Jian, R., Zhao, J., Liu, Y., & Xia, Y. (2022b). Deep-lipidotyping by mass spectrometry: Recent technical advances and applications. *Journal of Lipid Research, 63*(7), 100219. https://doi.org/10.1016/j.jlr.2022.100219

Zhao, H., Wang, C., Zhao, N., Li, W., Yang, Z., Liu, X., Le, W., & Zhang, X. (2018). Potential biomarkers of PD revealed by plasma metabolic profiling. *Journal of Chromatography B, 1081–1082*, 101–108. https://doi.org/10.1016/J.JCHROMB.2018.01.025

Zhou, Z., Liang, Y., Zhang, X., Xu, J., Lin, J., Zhang, R., Kang, K., Liu, C., Zhao, C., & Zhao, M. (2020). Low-density lipoprotein cholesterol and ad: A systematic review and meta-analysis. *Frontiers in Aging Neuroscience*, *12*. https://doi.org/10.3389/fnagi.2020.00005

Zhou, J., Liu, C., Si, D., Jia, B., Zhong, L., & Yin, Y. (2017). Workflow development for targeted lipidomic quantification using parallel reaction monitoring on a quadrupole-time of flight mass spectrometry. *Analytica Chimica Acta, 972*, 62–72. https://doi.org/10.1016/j.aca.2017.04.008

Zhou, J., Liu, H., Liu, Y., Liu, J., Zhao, X., & Yin, Y. (2016). Development and evaluation of a parallel reaction monitoring strategy for large-scale targeted metabolomics quantification. *Analytical Chemistry, 88*(8), 4478–4486. https://doi.org/10.1021/acs.analchem.6b00355

Zhou, J., Zhao, J., & Su, C. (2021). Role of aberrant lipid metabolism of cancer stem cells in cancer progression. *Current Cancer Drug Targets, 21*(8), 631–639. https://doi.org/10.2174/1568009619666210316112333

Züllig, T., & Köfeler, H. C. (2021). High resolution mass spectrometry in lipidomics. *Mass Spectrometry Reviews, 40*(3), 162–176. https://doi.org/10.1002/mas.21627

Züllig, T., Trötzmüller, M., & Köfeler, H. C. (2020). Lipidomics from sample preparation to data analysis: A primer. *Analytical and Bioanalytical Chemistry, 412*(10), 2191–2209. https://doi.org/10.1007/s00216-019-02241-y