Trends in Analytical Chemistry 191 (2025) 118368

Contents lists available at ScienceDirect

Trends in Analytical Chemistry

journal homepage: www.elsevier.com/locate/trac

Intra- and inter-individual variation of the human lipidome

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ARTICLE INFO

Keywords:
Inter-individual variation
Intra-individual variation
Human lipidome
Lipidomics
Mass spectrometry

ABSTRACT

Lipids play essential roles in cellular functions such as membrane structure, signaling, and energy storage. Lipidomics—global study of lipids in cells and tissues—seeks to identify biomarkers and uncover underlying metabolic pathways. Human lipid concentrations in cells and biofluids can fluctuate at multiple temporal scales, reflecting normal biochemical and physiological variation, or responses to various internal and external stimuli. Understanding both intra- and inter-individual lipid variability is crucial for accurate lipidomics study design and interpretation. This knowledge also supports personalized healthcare, moving beyond static reference ranges. Here, we review key drivers of intra-individual variation, including diet, circadian rhythms, sleep, environmental exposures, and physiological states. We also examine inter-individual factors such as genetics, age, sex, microbiome composition, and medications. Finally, we discuss how these variables interact and influence lipidomics outcomes, aiming to enhance reproducibility and guide future research.

1. Introduction

Lipidomics, the global study of lipids in biological systems, has been one of the fastest growing 'omics' fields over the past decade. Currently there are approximately 14,000 publications resulting in "lipidomics OR lipidome" search terms in PubMed. Advancements in analytical resolution and sensitivity have transformed the field, broadening its scope and increasing the scale of its applications in the studies of human health and disease.

Lipids hold promise as molecular biomarkers, sensitive to early disease-related processes and to onset of overt disease. Lipidomics serves as an important bridge between various other 'omics' levels such as genomics, proteomics, and exposomics, facilitating a deeper understanding of the intricate interplay between genetic variations, environmental exposures, and host metabolism [1,2]. The human lipidome is dynamic, with lipid levels exhibiting significant variability influenced by both internal factors, such as biological differences (*e.g.*, sex, age) and gut microbiome, and external factors such as stress, dietary patterns, environmental exposures, sleep, and medications [3]. Clinical medicine often relies on the so-called "normal ranges" (*e.g.*, total cholesterol level for assessing the risk of cardiovascular disease) to guide clinical decision-making and subsequent diagnostic or treatment strategies. However, as lipidomics enables the accurate and comprehensive

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https://doi.org/10.1016/j.trac.2025.118368
Received 15 April 2025; Received in revised form 19 June 2025; Accepted 11 July 2025
Available online 12 July 2025

Abbreviations

CAR	Acyl carnitines
CE	Cholesterol esters
CL	Cardiolipins
CVD	Cardiovascular disease
DG	Diacylglycerols
DHA	Docosahexaenoic acid
EPA	Eicosapentanoic acid
FA	Fatty acids
FFA	Free fatty acids
HDL(-C)	High Density Lipoprotein (cholesterol)
LCFA	Long chain fatty acid
LDL(-C)	Low Density Lipoprotein (cholesterol)
MCFA	Medium chain fatty acids
OCFA	Odd chain fatty acids
(L)PC	(Lyso)Phosphatidylcholines
(L)PE	(Lyso)Phosphatidylethanolamines
PC(O/P)	Ether PC/Choline plasmalogens
PE(O/P)	Ether PE/Ethanolamine plasmalogens
PL	Phospholipids
PG	Phosphatidylglycerols
PUFA	Polyunsaturated fatty acids
SFA	Saturated fatty acids
SM	Sphingomyelins
SPE	Solid phase extraction
S1P	Sphingosine-1-phosphate
TG	Triacylglycerols
(U)HPLC	(Ultra) high-performance liquid chromatography
VO2	Peak oxygen consumption

analysis of many hundreds of lipids, understanding the sources of variability in lipid measurements and their implications has become increasingly important. One significant source of variability arises from analytical considerations, encompassing pre-analytical factors (*e.g.*, sample collection and storage), and analytical techniques (*e.g.*, instrumental platforms). Another critical source of variability stems from inter- and intra-individual factors, which, although less prominently addressed in the current literature than analytical variability, exert a considerable influence on the dynamic nature of lipid levels (See Table 1). In this review, our main objective is to provide an in-depth understanding of the sources of inter- and intra-individual variability, elucidating their substantial impact on the interpretation of lipidomics study results.

2. Defining and determining the lipidome

The term 'lipidome' refers to the entire collection of small molecules defined as lipids in a biological system. Theoretically, the lipidome comprises the study of all lipid components; however, in practice, the coverage depends on sampling, storage, analytical techniques, and data preprocessing tools used for the analysis. Mass spectrometry (MS)-based methods are primarily used to detect, identify, and quantify the complex composition of lipids in biological matrices, including cells, organelles, or entire organisms. Here, we summarize the diversity of lipids and the key methods applied in lipidomic analyses.

2.1. Diversity of lipids

The LIPID MAPS classification system is derived from the biochemical synthesis of the lipid molecules and consequently their building blocks [4]. There are eight lipid categories in total: fatty acyls, glycerolipids, glycerophospholipids, sphingolipids, saccharolipids and polyketides, which are formed through the condensation of ketoacyl thioesters, and sterol and prenol lipids, which are formed through the condensation of isoprene molecules [5]. Each of these categories is then further classified into a total of 86 classes and 328 subclasses (Fig. 1).

The main functions of lipids include the formation of biological membranes and energy storage, which is then accessible through beta-oxidation. Furthermore, bioactive lipids, also referred to as lipid mediators, play an important role in signal transduction. The lipid function can be class-specific or may even depend on specific lipid molecules. This poses a major challenge for lipidomics analyses, as the selectivity to measure specific lipid species including their exact configuration is hard to achieve and is often conflicting with the aim to measure as many lipids as possible in the same analytical process. This is partly based on the abundance of lipids sharing the same chemical formula including structural isomers that may differ only in the double bond position in fatty acids. Lipids share the same building blocks such as fatty acyl residues, head groups and ring structures with different modifications. The different analytical strategies (further described in the next section) can resolve these substructures to different degrees, resulting in different levels of identification. These differing identification levels are taken into account in the lipidomics shorthand nomenclature [4].

Where there is insufficient mass resolving power in MS analyses, isobaric lipids can further contribute to incomplete structural resolution. Another major challenge in lipidomics is the broad dynamic range of the different lipid species, spanning from pmol/L (leukotrienes and prostanoids) to mmol/L (cholesterol) range [6]. At the same time, the linear dynamic range covered by mass spectrometers does not exceed six orders of magnitude, whereas nuclear magnetic resonance spectroscopy has even lower sensitivity and dynamic range. Hence, several specialized assays are required to cover all lipid classes, making a comprehensive analysis time-consuming and costly.

2.2. Analyzing the lipidome

Due to the high complexity of the lipidome, its comprehensive analysis requires the use of various analytical techniques [7,8]. In this section, we aim to provide an overview of the methodological approaches commonly employed in clinical lipidomics, rather than an exhaustive review of the latest technological advancements. Understanding the strengths and limitations of the applied methodologies is crucial for interpreting the results of lipidomic studies and recognizing potential sources of technical variability. The most commonly employed methods are based on MS and are often coupled with chromatographic separation systems. In particular, the coupling of (ultra) high-performance liquid chromatography ((U)HPLC), electrospray ionization, and high-resolution mass spectrometry and/or tandem mass spectrometry is utilized when a comprehensive analysis of abundant lipids is desired [9]. Both reversed-phase and hydrophilic interaction chromatography are commonly employed in these analyses. Supercritical fluid chromatography is also employed as an alternative to (U)HPLC separation [10,11]. It offers the advantage of high sample throughput with high separation efficiency. However, a significant portion of lipid analysis is also performed using mass spectrometric detection without preceding chromatographic separation [9,12]. This direct infusion (shotgun) analysis of lipids allows for high sample throughput with broad analyte coverage. Yet, limitations of the shotgun approach, such as increased ion suppression or the inability to separate isomeric/isobaric compounds, should be considered [13].

An emerging technique that can be coupled with shotgun and (U)HPLC-MS lipidomics methods is ion mobility [14,15]. It proves particularly useful when isobaric and isomeric molecules cannot be separated, adding an additional dimension to enhance the information content and

Table 1
Summary of the studies reporting intra- and inter-individual variability of human lipidome.

Topic	Study description	Factors	Type of intervention	Sample type	Sample size	Analytical methods	Summary of findings	Refs
Inter-individual	Lipidomic associations with age	Age	N/A	Dried blood spots	24	LC-MS	Age was associated with a stepwise increase in several phospholipids, TG, CE and a reduction of some CAR.	[194]
Inter-individual	Lipidomic associations with age and sex	Age and Sex	N/A	Plasma	10,339 and 4207	LC-MS	Age was positively associated with CAR and Cer in both sexes, PC(O), PC(P) and LPC were negatively associated with age in both sexes. PE(P), LPE(P), and LPI were positively associated with age in females and negatively associated in males. Postmenopausal females had higher TG, DG, PI, and alkyl-diacylglycerol vs. premenopausal females, while postmenopausal females had lower ether and lysophospholipids. Throughout adulthood males displayed higher TG, DG, CE, LPC and lower PC than females.	[205]
Inter-individual	Lipidomic associations with age and sex	Age and sex	N/A	Plasma	7266 and 2045	DI-MS	Age was associated with lower plasma lipids, including several CE, TG, DG, PC, LPC and PC(O) and increase of certain PC and SM in males while in females it was associated with higher levels of several lipids including TG, CE, SM, Cer, PC-O, PE-O. Throughout adulthood males displayed higher TG, DG, CE LPC and lower PC than females.	[206]
Inter-individual	FFA kinetics in males and females	Sex	N/A	Plasma	106	GC-MS	Females displayed higher free fatty acids rates of appearance (FFA-Ra) than males.	[232]
Inter-individual	VLDL kinetics in males and females	Sex	N/A	Plasma	233	GC-MS	Males displayed higher VLDL-TG secretion rates than females.	[223]
Intra-individual	Lipidomic changes across the menstrual cycle	Sex	N/A	Plasma	34	LC-MS	Several plasma phospholipids, including PC, PC-O, LPC, LPE were decreased during the luteal phase relative to the follicular phase.	[236]
Intra-individual	Crossover activity study of post-menopausal women with rheumatoid arthritis	Physiology	Sitting, exercise, light breaks	Plasma	11	Colorimetric enzymatic assay, immunoassay	Effect of active breaks on extended sitting, light breaks alleviate inflammation but do not change lipidome in contrast to acute exercise.	[156]
Inter-individual	Post-exercise multi-level omics profile for peak oxygen consumption	Physiology	Exercise, recovery	Plasma	36	LC-MS	One-hour post-exercise includes distinct recovery phases with lipidomic signatures, uncovers trends for short- and long-term recovery.	[158]
Intra-individual	Crossover analysis of lipidomic and metabolomic analysis of HIIT exercise and VLCHF diet	Diet, Physiology	HIIT exercise, VLCHF diet	Plasma	14	LC-MS	Diet is more important than exercise for the changing of the lipidome.	[38]
Intra-individual	Effect of combined physical exercise training on obese women	Physiology	Exercise	Plasma	14	LC-MS	Exercise affected fat location and lipid class composition in the body.	[161]
Inter-individual	Profiling of ultramarathoners	Physiology	N/A	Plasma	52	LC-MS	Runners had overall higher PC levels, higher choline levels pre-race, but same choline post-race.	[166]
Inter-individual	Recovery profile post-marathon	Physiology	N/A	Serum	31	GC-MS	Better characterization of acute metabolic changes after a marathon.	[167]
Intra-individual	Plasma free fatty acid and adipose tissue activity induced by cold exposure	Physiology	Cold exposure	Brown adipose tissue, plasma	14	LC-MS, PET scan	33 non-esterified FA and 11 oxylipins increased in response to cold exposure.	[357]
Intra-individual	Biomarkers for post-exercise hypotension	Physiology	Exercise	Plasma	10	LC-MS, nanoLC-MS	Post-exercise hypotension can be achieved even after short exercise.	[159]
Inter-individual	Comparison between water polo and football players	Physiology	N/A	Erythrocytes, plasma	34	Targeted Analysis	Intense training affects FA composition in blood, exercise type and/or genetic factors may explain the differences.	[165]
Inter-individual	Fatty acid composition of female football players through three seasons	Physiology	N/A	Erythrocytes	40	GC-MS	Football season (training or tournament) affect erythrocyte PUFA).	[358]
Inter-individual	Lipidomic profile of habitual dietary intake in free-living population	Diet	N/A	Plasma	18	FI-MS, LC-MS	Lipid patterns predictive of dietary intake were observed.	[32]

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Table 1 (*continued*)

Topic	Study description	Factors	Type of intervention	Sample type	Sample size	Analytical methods	Summary of findings	Refs
Intra-individual	Oral lipid tolerance test	Diet	Oral lipid tolerance test, oral glucose tolerance test	Plasma	75	FI-MS, LC-MS	Strongest response seen in PE, LPE, PG and Cer after 120 and 180 min of lipid stress test.	[359]
Inter-individual	Lipidome profiling	Diet	N/A	Serum	754	LC-MS	Three different patterns (with differences in phospholipids and PUFA) were found: animal protein, fried snacks/sweets/high-fat dairy, and fruits/vegetables/nuts/legumes.	[33]
Intra-individual	Cross-sectional analysis of CVD and T2D	Diet	Mediterranean diet	plasma	34	LC-MS	Glycemic index, glycemic load, and carbohydrate quality were associated with specific metabolic profiles of CVD and T2D.	[34]
Inter-individual	Link of chronic disease risk factor with habitual diet	Diet	N/A	serum	120	FI-MS	Serum metabolites in multivariable-adjusted model showed variation in branched PC, SM, PC, LPC, CAR, amino acids and hexose.	[35]
Intra-individual	Diet intervention supplemented with either nuts or olive oil with an interest in CVD risk	Diet	Mediterranean diet	plasma	262	LC-MS	Significant changes in plasma were observed, including TG, DG, PL and CE profiles after one year compared to control group. However, no association with CVD risk was observed.	[36]
Intra-individual	Randomized cross-over study monitoring HDL	Diet	Fast food, Mediterranean diet	plasma	10	LC-MS	HDL lipidome changed in only 4 days after diet change, 41 out of 170 lipid species analyzed showed changes. SFA and OCFA were more abundant in fast food diet, as VLCFA and unsaturated FA were more abundant in Mediterranean diet.	[37]
Intra-individual	Isocaloric diets with SFA in comparison to unsaturated FA diet	Diet	Isoenergetic dietary fat	plasma	113	FI-MS, LC-MS	unsaturated FA in contrast to SFA reduce risk-associated lipids, specifically long-term cardiometabolic risk	[41]
Intra-individual	Crossover study with dietary supplementation vegetable oils	Diet	PUFA	plasma	8	Targeted FI-MS	Vegetable oils resulted in changes of PE and plasmalogen composition, mainly due to stearidonic acid and DHA introduction. Linoleic and alpha-linolenic acid did not lead to the same result.	[360]
Intra-individual	Diabetic patient dietary intervention	Diet	MCFA diet, LCFA diet	plasma	7	LC-MS	Diet rich in MCFA lead to a decrease in biomarkers (Cer, CAR) for diabetic cardiomyopathy, LCFA diet did not yield the same effect.	[42]
Intra-individual	Overweight male fat and sugar intervention for isocaloric diets	Diet	SFA, sugar diet	plasma	16	GC-MS	A diet enriched with sugar resulted in lower total cholesterol, HDL and non-HDL cholesterol compared to fat-diet. Saturated fat-enriched diet lead to increased intrahepatic TG content.	[43]
Intra-individual	Eicosanoids affected by high-cholesterol and high-fat intake	Diet	High dietary cholesterol	plasma	14	LC-MS	Diet lead to dysfunctional HDL evident from elevated total cholesterol andoxidized lipid concentration in HDL particles.	[44]
Intra-individual	Circadian rhythm regulates plasma lipid in healthy individual	Circadian	Lipid measurement every 4 h	Plasma	20	LC-MS	35 of 263 detected lipids showed cardiant variation over 28h. Lipid classes that mainly changed are TG, DG, and PC.	[65]
Intra-individual	Examination of circadian variation of fatty acids in healthy adults	Circadian	FA measurement every 2 h over 24 h	Plasma	21	GC-MS	20 of 21 FA (*e.g.*, EPA, DHA) showed significantly associated to diurnal rhythm.	[74]
Intra-individual	Investigation of human circadian metabolome in healthy male	Circadian	Metabolites monitoring every 4 h over 40-h	Plasma	10	GC-MS, LC-MS	FA (*e.g.*, EPA. DHA) are potentially controlled by circadian rhythm that is independent with sleep and diet.	[75]
Intra-individual	Variability of breastmilk lipids in healthy women	Circadian	Morning versus evening comparison	Milk	20	LC-MS, DI-MS	Milk lipidome is strongly affected by the time of the day, with higher concentration in the evening compared to the morning, particularly PE and TG.	[76]
Intra-individual	Rhythmicity of circulating metabolites in different body mass and T2D individual	Circadian	2 h over 24 h	Plasma	23	LC-MS	LPC and PC present a 24-h rhythmicity in participants that lean body, OB/OW or OB/OW with T2D.	[79]
Intra-individual	Association of lipidome with night-shift disruption	Circadian	Night-shift versus day schedule	Plasma	14	LC-MS	Increase of TG and decrease of PC in night-shift compared to day-shift condition.	[77]
Intra-individual	Association of sleep duration variability with cardiovascular disease	Sleep	Sleep duration parten measurement	Serum	259	Blood lipid test	Sleep duration dispersion is significantly associated with LDL, HDL, and total cholesterol in menstrual women.	[95]

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Table 1 (*continued*)

Topic	Study description	Factors	Type of intervention	Sample type	Sample size	Analytical methods	Summary of findings	Refs
Intra-individual	Lipid alteration in sleep deprivation	Sleep	Sleep deprivation in 40 consecutive hours	Plasma	20	LC-MS	TG with PUFA (*e.g.*, TG 54:6, TG 54:5) and PC (*e.g.*, PC 32:2, PC 34:3) are increased while plasmalogen PC (PC 34:1p, PC 36:2p) are decreased during sleep deprivation.	[96]
Intra-individual	Plasma metabolite biomarkers for	Sleep	Insufficient sleep versus adequate sleep	Plasma	16	LC-MS	Various lipid metabolic pathways are related to insufficient sleep. Cer (*e.g.*, Cer d40:2, Cer d41:2) and SM (*e.g.*, SM 43:2, SM d33:2) were changed during insufficient sleep.	[97]
Intra-individual	Relationship habitual sleep and plasma metabolites	Sleep	Sleep duration and timing	Plasma	277	GC-MS, LC-MS	Late sleep time was associated with plasma levels of bile acids (*e.g.*, TDCA, TCDCA), FFA (*e.g.*, linolenate), CAR (e.g, octanoylcarnitine).	[109]
Inter-individual	Metabolomics biomarkers for stress, anxiety, and depression	Stress	Normal stress versus non-normal stress	Serum	38	LC-MS	Glycerophospholipids (*e.g.*, PE, LPE) and bile acids (*e.g.*, GCA, GDCA) were upregulated in groups having anxiety, depression, or stress compared to normal group.	[121]
Intra-individual	Blood lipid reactivity in acute stress condition	Stress	Montreal Imaging Stress Task (MIST)	Plasma	35	Enzymatic colorimetric	Total cholesterol/HDL-C ratio is significant increased in all participant after the MIST.	[124]
Intra- and inter-individual	Variability of human metabolome after 3 months of personal exposures	Environmental exposure	Serum metabolites monitor over 3 months of personal exposures	Serum	157	LC-MS	Glycerophospholipids (*e.g.*, LPC, LPE, PC) have large proportion of variance between subject and within subjects in the EXPOsOMICS Personal Exposure Monitoring study.	[146]
Inter-individual	Investigation variation of metabolome in the human upper intestinal tract	Gut microbiome	Metabolome comparison of differently intestinal locations and stools	Tissue, stool	15	LC-MS	SCFA, secondary bile acids, sulfonolipids, and FA esters of hydroxy FA (FAHFA and AAHFA) present a strong inter-individual variability in upper intestinal and stool samples.	[264]
Inter-individual	Impact of microbiome, diet, and genetic on human plasma metabolome	Gut microbiome, diet, genetic	Plasma metabolome association with different factors	Plasma	1054	FI-MS	12.8 %, 9.3 %, and 3.3 % variance of plasma metabolome is explained by microbiome, diet, and genetic. Variation of plasma FA, steroids, bile acids, glycerolipids, glycerophospholipids are significantly associated with gut microbial species, food intake, and genetic.	[277]
Inter-individual	The link between genetic-associated human plasma lipidome and risk of CVDs	Genetic variation	Genome-wide association with lipidomics	Plasma	2181	DI-MS	Genetic variants have a strong association with various plasma lipid species, including CE, DG, TG, PC, LPC, PE, LPE, SM, Cer.	[183]
Inter-individual	Genome-wide association studies of human serum metabolites	Genetic variation	Genetic variants associated serum metabolites	Serum	6263	NMR	588 SNP-metabolites are significantly associated with serum metabolites, such as FA.	[361]
Inter-individual	Genetic determinants of individual metabolites and their effects on human health	Genetic variation	Genetic variant determine metabolite individually	Plasma	19,994	LC-MS	206 genomic regions were associated with multiple metabolites, including 241 lipids that belongs to various lipid species, such as FFA, Carnitine, phospholipids, steroids, sphingolipids, and bile acids.	[362]
Inter-individual	Genome-wide characterization of circulating metabolic biomarkers	Genetic variation	Characterization the genome-wide association and the circulating metabolites	Serum, plasma	136,016	NMR	155 genomic regions were significantly associated to lipid traits, including lipid, lipoprotein, FA.	[363]
Inter-individual	Genomic atlas of the plasma metabolome to investigate metabolite related to human disease	Genetic variation	GWAS and metabolite level associations	Plasma	8299	LC-MS	Around 300 lipids reported significantly associated with genetic variant. These lipids primarily belong to FA, steroids, SM, glycerophospholipids (*e.g.*, LPE, PE, PC, LPC) species.	[364]

Abbreviations: CAR, Acyl carnitines, CE: Cholesterol esters, CL: Cardiolipins, DG: Diacylglycerols, DHA: Docosahexaenoic acid, DI-MS: Direct-Infusion Mass Spectrometry, EPA: Eicosapentanoic acid, FA: Fatty acids, FFA: Free fatty acids, FI-MS: Flow-Injection Mass Spectrometry, GC-MS: Gas Chromatography Mass Spectrometry, HDL(-C): High Density Lipoprotein (cholesterol), LCFA: Long chain fatty acid, LDL(-C): Low Density Lipoprotein (cholesterol), LC-MS: Liquid Chromatography Mass Spectrometry, MCFA: Medium chain fatty acids, NMR: Nuclear Magnetic Resonance, N/A: Not available, OCFA: Odd chain fatty acids, (L)PC: (Lyso)Phosphatidylcholines, (L)PE: (Lyso)Phosphatidylethanolamines, PC(O/P): Ether PC/Choline plasmalogens, PE(O/P): Ether PE/Ethanolamine plasmalogens, PL: Phospholipids, PG: Phosphatidylglycerols, PUFA: Polyunsaturated fatty acids, SFA: Saturated fatty acids, SM: Sphingomyelins, SPE: Solid phase extraction, S1P: Sphingosine-1-phosphate, TG: Triacylglycerols.

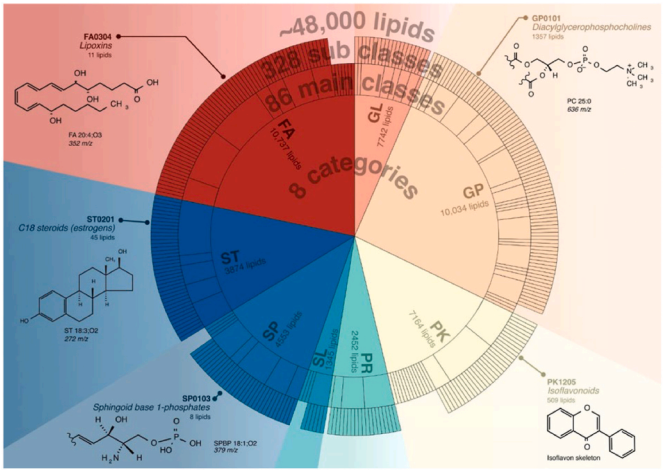

Fig. 1. Diversity of lipids in the human lipidome.

resolution of lipidome analysis. To gain a more comprehensive insight into the lipidome, additional techniques such as the utilization of ozone can be employed for the identification of double bond positions in fatty acids [16,17]. MS-based methods offer a wide range of methodological options that can be utilized depending on the specific research question and problem at hand. The choice of method ultimately depends on the requirement for selectivity, sensitivity or sample throughput, as well as relative or absolute quantification. Ultimately each methodology is a compromise of these factors.

The hitherto described methods for lipidome analysis rely on appropriate sample preparation prior to analysis. For liquid samples such as blood plasma, serum, urine, or saliva, various forms of liquid-liquid extraction are commonly used, including the Folch method, Bligh & Dyer method, or MTBE extraction [7]. In some cases, solid-phase extraction is employed, particularly when targeting specific low concentrated lipid classes. Another option is the single-phase extraction, which is increasingly utilized for lipid analysis, especially when combined with metabolomics analysis [18,19]. These sample preparation approaches can also be applied to tissue or cell samples, although in such cases, a homogenization step is necessary before the actual extraction. However, it should be noted that the homogenization process results in the loss of spatial distribution information of lipids in tissue samples.

Emergence and developments in MS-based imaging (MSI) techniques have enabled studies of spatial heterogeneity of lipids. There are three forms of ionization techniques that are commonly used for imaging lipids with MS: matrix assisted laser desorption ionization (MALDI), desorption electrospray ionization (DESI), and secondary-ion mass spectrometry (SIMS). Technology advances have improved the spatial resolution (transition mode MALDI [20], nanoDESI [21]) and/or sensitivity (MALDI2), allowing imaging down to a single-cell or even sub-cellular levels [22]. Clearly, lipid MSI has a vast range of applications which are outside the scope of this review. However, recent examples have shown how lipid changes spatially correlate with histology findings in both oncology [23] and neurology [24]. There are still some significant barriers for widespread adoption of MSI. The sample throughput is typically low, depending also on the size of the tissue and the spatial resolution desired. Quantification is also difficult due to altering matrix effects that suppress signals of interest by various amounts [25] and due to spatially different adduct formation [26]. However, use of internal standards and use of new image processing tools based on AI are overcoming these challenges.

Apart from the use of MS techniques, there are few other techniques that are relevant for lipidome analysis. One notable technique is nuclear magnetic resonance spectroscopy (NMR spectroscopy), which has been employed in several studies and has recently evolved into a valuable tool for lipidomics [27,28]. The high sample throughput of NMR spectroscopy makes it an attractive non-destructive method, although it may not fully resolve the complexity of the lipidome. The same applies to Raman spectroscopy, which is still in the early stages of establishment as a tool for lipidome analysis compared to the previously mentioned techniques but can serve as an important complement to the existing methods [29].

A lipidomic analysis workflow outlining key analytical factors to consider when conducting a clinical lipidomics study is illustrated in Fig. 2. Regardless of the chosen protocol for lipidome measurement, it is of utmost importance to appropriately document the necessary details of the applied methodology, quality control parameters and identification methodology and make them available in publications related to the studies [30].

3. Factors affecting the intra-individual variability of lipidomes

In general, factors that impact variability of the lipid profiles (the lipidome) in humans, can be classified into four main groups: (i) the intrinsic biological activity of cells, which reflect genetic variation, age, and biological sex; (ii) the influence of environmental factors like stress, diet, lifestyle; (iii) environmental exposure (*e.g.*, environmental toxicants and other xenobiotics); and (iv) the interaction of the microbiome with these factors.

3.1. Diet

Lipid composition varies greatly among food products [31]. Consequently, diet plays a highly significant role in shaping the human lipidome. Lipidomic profiling has been applied to investigate dietary patterns and to identify biomarkers specific to diet. Lipidomic data can be reduced into lipid patterns, potentially showing relationships between these patterns and the diet. For example, specific serum lipid patterns have been shown to correlate with dietary fat intake, fish intake or alcohol consumption [32]. Similarly, general dietary habits linking various foodstuffs and ingredients can be associated with specific lipidomic profiles differing in serum phospholipids (PL) and

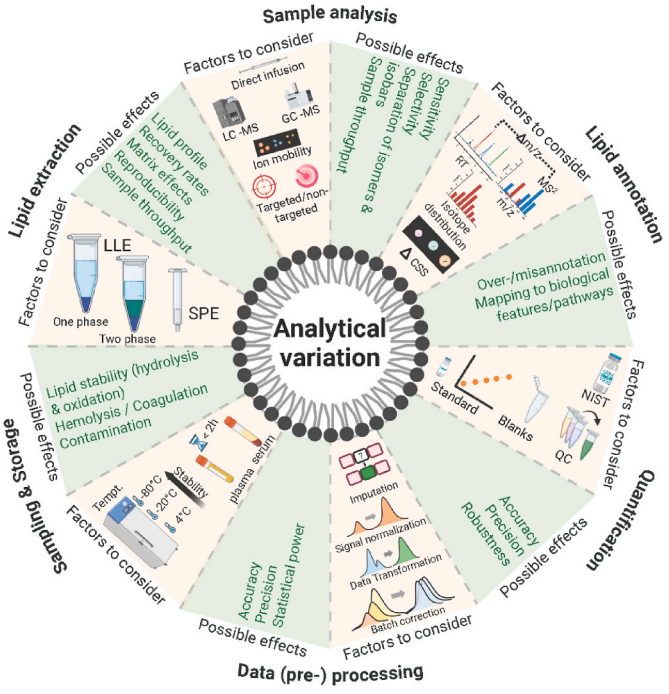

Fig. 2. An overview of the factors contributing to analytical variations in clinical lipidomics studies. LLE: Lipid liquid extraction, SPE: Solid phase extraction, QC: Quality control, RT: Retention time.

polyunsaturated fatty acids (PUFA) [33]. In the Mediterranean population, glycemic index, glycemic load and carbohydrate quality index of the diet were associated (positively or negatively) with numerous molecular species across the lipidome, such as positive association of PC 32:1 and negative association of SM (22:1) and PE (38:6) with glycemic index and glycemic load [34]. Serum variation of phosphatidylcholines (PC), sphingomyelins (SM), and acyl carnitines (CAR), was also found to be highly explainable by the pattern of habitual diet, in a cross-sectional study comprising 2380 participants [35]. Specifically, CAR, acyl-alkyl-PC, and LPC were linked to a dietary pattern characterized by high butter consumption and low margarine intake, while elevated red meat and fish consumption, combined with low intake of whole-grain bread and tea, was associated with PC alterations.

Dietary intervention studies have shown strong modulating effects of dietary components on the human lipidome. A one-year intervention with one group receiving extra virgin olive oil and another group receiving nuts in addition to the Mediterranean diet, resulted in statistically significant changes in the plasma lipidome, including altered triacylglycerol (TG), diacylglycerol (DG), phosphatidylethanolamine (PE), and cholesterol ester (CE) profiles as compared to the control group that was mainly advised to follow a low-fat diet [36]. Dietary changes can rapidly result in significant changes of the lipidome, as evidenced by the differences in 41 out of 170 species in the HDL lipidome just four days after a dietary intervention [37]. A very low carbohydrate and high-fat diet significantly altered plasma lipid profiles, including increased CAR, plasmalogens, fatty acid (FA) esters of hydroxy FAs, SMs, ceramides (Cer), CE and FA. In contrast, total TG and PL levels decreased [38]. Adoption of a healthy Nordic diet resulted in changes in 21 plasma lipids at week 12, particularly by increasing plasmalogen and decreasing ceramide concentrations in participants having metabolic syndrome [39].

Substituting dietary saturated FA with unsaturated FA has been shown to result in plasma lipid profiles associated with reduced CVD risk. SFA-containing glycerolipids and sphingolipids decreased, whereas those inversely associated with CVD risk, such as PUFA-containing CE, LPC and MG, increased [40,41]. An intervention with a diet rich in medium-chain fatty acids (MCFA) for diabetic patients led to decreased plasma lipid levels of biomarkers implicated in diabetic cardiomyopathy, including several SMs, ceramide, and acylcarnitine species. Conversely, a diet rich in long-chain fatty acids (LCFA) and overall higher degree of unsaturation did not yield the same effect [42].

A sugar-rich diet resulted in lower total cholesterol and HDL-C in plasma compared to an isocaloric diet enriched with saturated fat, whereas the latter increased intrahepatic TG content, providing additional insight into the ongoing debate about the impacts of dietary fats and sugars on metabolic health [43]. A high-fat and high-cholesterol diet not only increased total cholesterol but also led to elevated levels of oxidized lipids in HDL particles, indicative of dysfunctional HDL [44].

Driven by sustainable and healthy diet, there is an increasing trend of adopting proteins from alternative sources in the diet. Adopting a whole-food plant-based diet decreased total cholesterol and LDL-C of vegetarian, vegan and non-vegetarian participants [45]. Compared to isocaloric meat-based diet, a vegetarian diet significantly reduced LDL-C, oxidized LDL-C and total cholesterol. Additionally, plasma PC and PE profiles differed between the two diets. These changes were potentially mediated through alterations in the gut microbiota, highlighting the complex interplay between diet, gut health, and lipid metabolism [46]. Microbial proteins represent new sustainable sources of dietary proteins. Replacing meat and fish with dietary mycoprotein reduced serum total cholesterol levels in hypercholesterolemic adults [47]. Plant based food are rich source of phytochemicals as plant secondary metabolites, which have regulating effects on human lipidome. The metabolic effects of dietary phytosterols have been investigated beyond their known cholesterol- and TG-lowering capabilities, showing altered PC and PS profiles of LDL-C fraction after intake of phytosterols, indicating potential impact on inflammation and atherogenesis [48].

Despite the commonly assumed link of the dietary intake of meat and animal fat to increased risk for CVD, a healthy diet (rich in fiber and micronutrients) enriched with cheese, pork, or beef, reduced the total cholesterol and increased HDL particle size in young healthy adults. The pork diet led to an upregulation of unsaturated FA and plasmalogen species, along with a downregulation of TG species. These results suggest that within an otherwise healthy diet, moderate consumption of animal products, especially pork, may not have adverse effects [49]. Simple reductions in total caloric intakes without changing the dietary composition has been shown to reduce the total cholesterol, LDL-C and TG levels [50,51]. The changes in plasma lipidome during a low-caloric dietary intervention can predict long-term outcomes related to weight and glycemic control. The differentially expressed lipids may serve as lipidomic signatures that differentiate metabolic responders from non-responders, with distinct outcomes in weight and glycemic control. Thus, identifying lipidomic signatures could help clinicians tailor interventions to improve metabolic outcomes [52].

Studies of postprandial plasma lipidomes indicate that TG metabolism rates (slow vs. fast) and dietary fat types, such as cream fat versus fish or vegetable oils, influence lipemic responses, with genetic factors also contributing to individual variability [53–55]. The fatty acid (FA) composition and their positional distribution on the glycerol backbone of TG molecules significantly influence lipid metabolism. For instance, unsaturated FAs at the sn-2 position of TGs may mitigate the hypercholesterolemic effects of saturated fats, highlighting their diverse metabolic roles [56]. Human milk, a vital nutrient for infants derived from maternal metabolism, exemplifies these principles. While its FA composition is influenced by maternal diet, the TG regioisomer profile remains stable, with palmitic acid at the sn-2 position playing a key role in fat absorption, infant growth, and overall health [57–59].

Adequate dietary intake of n-3 polyunsaturated FA is important for maintaining health. Specific serum PC can serve as surrogate markers for omega-3 index, as indicators of individual's n-3 status [60]. Omega-3 intake has also been associated with oxylipin profiles in healthy adults [61]. Nutritional supplementation with n-3 PUFA, specifically eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA), can also influence the skin lipidome, reducing skin inflammation [62]. Finally, the intra-individual variability in timing of eating is another factor potentially contributing to the variability of lipidomic profiles [63].

In summary, diet exerts a significant influence on intra-individual lipidome variation, with effects that can be highly specific to different food products, nutrition composition, and supplementation. Given this variability, dietary factors should be carefully considered and reported as part of the design of long-term studies, particularly those investigating lipid metabolism and lipid biomarkers. Standardizing dietary intake, implementing multiple sampling time points or dietary questionnaires are essential to account for dietary fluctuations and minimize their impact on lipidome variability, ensuring more accurate and reproducible findings.

3.2. *Circadian rhythm*

The circadian rhythm orchestrates the daily physiological and activity patterns of mammals in synchronization with the solar system, representing a near-ubiquitous phenomenon in physiology. The suprachiasmatic nucleus (SCN), acting as a pacemaker, or master clock neuron, responds to both light and feeding signals, subsequently governing the biological physiology of clock cells in peripheral organs [64]. Genes associated with lipid biosynthesis and fatty acid oxidation are highly expressed in peripheral tissues. Consequently, the circadian system plays an important role in rhythmically activating and regulating metabolism, including lipid and carbohydrate homeostasis, to ensure the balance of energy expenditure and storage [65]. Indeed, mounting evidence points to the tight interplay between lipid dynamics and circadian clocks, both at systemic and tissue-specific levels [66].

This rhythmic regulation operates at various levels, controlling

cellular physiology to organ function in response to blood nutrient intake. Circadian rhythm is closely linked to the feeding-fasting, sleep-wake, rest-activity cycles, which are coordinated with metabolic, hormonal and neuronal signals. This synchronization enables metabolic organs such as the liver and adipose tissue to adjust to rhythmic food consumption [67]. Altered feeding-fasting cycle closely links with alteration of habitual diet, which obviously cause differences of nutritional intake, degradation in intestine by gut microbiome, bide acids, and absorption into blood, consequently altering circulating lipid levels [68]. Disturbance of sleep-wake cycle or rest-activity cycles, *e.g.*, nighttime work, were reported to associate with metabolic diseases, particularly CVD [69,70]. The circadian system exerts its regulatory influence on lipid pathways through multiple peripheral organs. For instance, liver tightly controls fatty acid synthesis and beta-oxidation through circadian activity involving ATP citrate lyase, acetyl CoA carboxylase, and carnitine palmitoyl transferases 1 and 2 [71]. Additionally, the PPAR family, involved in fatty acid catabolism, is diurnally controlled based on the stages of starvation, feeding, or activity stage [72]. Bile acid synthesis reaches peak concentration during periods of high food consumption, regulated by the circadian system through the circadian expression of 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase (HMGCR) and cholesterol 7α-hydroxylase (CYP7A1) [64]. Human plasma lipid classes regulated by the circadian rhythm include, but are not limited to, fatty acids, sterols, glycerophospholipids, and TGs. In fact, the circadian rhythm of lipid levels has been suggested for a long time. A study involving seven subjects who consumed meals at night revealed higher postprandial serum TG levels, while total cholesterol, LDL-C, HDL-C, and apolipoprotein levels were lower compared to daytime meals [73]. In another study investigating the diurnal variation of 20 fatty acids in healthy subjects, DHA and EPA levels decreased during the overnight period [74]. Furthermore, fatty acids are under circadian control, exhibiting rhythmicity in plasma levels at different times of the day [75]. In a study of 20 healthy individuals, PC, DG, and TG exhibited circadian rhythmicity across four days [65]. Systemic variations were also reported in a study exploring the variation of women's milk lipidome, revealing varying levels of Cer, PL, DG, and TG at different times of the day. This emphasized higher levels of PE and TG in the evening compared to the morning time [76]. Moreover, circadian misalignment, such as shift work, leads to a strongly disrupted skeletal muscle lipidome and is potentially linked to the increased risk of T2D. Dyslipidemia linked to CVD was reported in a simulated night-shift experiment, where participants who underwent a three-day night-shift revealed an increase of TG and decrease of phospholipid levels in blood, suggesting a temporal disruption of lipidemia due to night-shift [77].

Circadian misalignment, either due to the irregular lifestyle or shiftwork, can perturb balance of regular biological lipid process and induced the metabolic dysfunction ultimately, thus increasing risk of metabolic diseases, including obesity, diabetes, liver disease, and cardiovascular diseases. The evidence of blood lipid variability is even clearer when recording the rhythmicity of circulating lipids for 24 h. CAR and PL displayed high magnitude of time-of-day variation, where factors related to circadian rhythm, such as light/dark cycle, sleep/wake, and food intake, were controlled strictly [78]. Phospholipids exhibited daily rhythms during 24-h time series sampling in both healthy, obesity and T2D individuals, emphasizing rhythmicity patterns of lipids is not only different intraday but also behave differently between individuals with metabolic phenotypes [79]. Another reason why circadian rhythm has a strong correlation with human lipidome is its close relationship with other lipid-regulating factors. Factors such as gut microbiome, age, dietary, and sleep are highly coordinated with both systemic and molecular circadian clocks. The interplay between these factors and circadian clocks is complicated, host and gut microbiome interactions, for example, are influenced by the feeding/fasting pattern, light/dark cycle, dietary timing, which indirectly regulate the downstream metabolic processes [80]. Changes in habitual diet due to night work shifts as well as frequent sleep loss in elderly individuals can interact with circadian rhythmicity, contributing to fluctuations in lipid levels in the body [81–83]. Therefore, it is expected that human circadian lipidome will vary throughout the day. Any disturbances or interferences that disrupt the circadian rhythm can induce the variation of intra-subject lipidomes at different times point, and the differences may exhibit extensive discrepancies influenced by other factors along with the circadian system. To minimize variability and improve reproducibility, it is crucial to standardize sampling times, control environmental conditions to the extent possible (*e.g.*, light, temperature, shift), and stratify cohorts by age and sex. Additionally, implementing rigorous analytical practices, such as randomization and quality control, will enhance data reliability, facilitating the accurate translation of findings into human health and disease research.

3.3. Sleep

Alongside the circadian rhythm, sleep stands as a fundamental biological process crucial for maintaining and consolidating integral physiological activities, including cognitive, metabolic, and immune functions [84,85]. The sleep-wake cycle is intricately connected to the circadian clock, mediating various metabolic pathways within the human body. A plethora of epidemiological and clinical studies have explored the correlation between the sleep quality and various physiological functions at both organ and molecular levels [86,87]. The duration of sleep and circadian changes, induced by factors such as shift-work or habitual alterations, can significantly impact metabolic functions, thereby being linked to detrimental consequences, especially in terms of cardiometabolic outcomes [88,89]. 'Omics' studies have provided a valuable opportunity to unravel the interconnection between sleep quality and molecular variations. For instance, in a study by Emma et al., the blood transcriptome of subjects experiencing insufficient sleep was profiled, revealing up to 74 blood mRNA biomarkers that could potentially be used to monitor quality of sleep [90].

Lipidomics research has predominantly focused on the relationship between lipidome with various sleep disorders, such as obstructive sleep apnea (OSA), suggesting diagnosis biomarkers or biological fingerprints linked to disorders. For instance, people with OSA appear to have higher risk of CVD or metabolic disease due to the alterations of lipid profiles. Lipid-related pathways, encompassing glycerophospholipid and bile acid metabolism, were involved in OSA pathogenesis, including in connection with Alzheimer's disease [91,92]. However, the link between the overall physical conditions and various sleep domains, including sleep timing, quality, duration, and intra-individual variability, remains insufficiently investigated and understood. The evidence of sleep disorder-related metabolic health suggests a complex interplay between the metabolic system and sleep patterns. Variable sleep patterns are notably associated with personal work schedule, personality traits, physical conditions, and psychological issues, leading to day-to-day sleep variability [93]. This, in turn, initiates dysregulated dietary practices (*e.g.*, caloric intake), followed by metabolic alterations and eventual adverse cardiometabolic health [94].

Recent studies have made efforts to evaluate the relationship between sleep quality and human lipidome. A study involving 259 young healthy women suggested negative cardiovascular health effects associated with sleep duration dispersion, particularly as linked to total cholesterol, LDL-C, and HDL-C levels [95]. Another study revealed linear trends in plasma lipid levels, including a decrease in TG and PC levels and an increase in choline plasmalogen levels, across 20 subjects undergoing 40 consecutive hours of sleep deprivation [96]. Christopher and colleagues identified changes in phospholipids and sphingolipids during insufficient sleep, proposing a blood lipid biomarker panel for predicting insufficient sleep in humans [97]. In alignment with these findings, CAR, PC, and TG lipids were changed in the group of overweight/obese participants with high sleep variability [98]. Poor sleep quality is particularly common in elderly individuals, which potentially

leads to changes of lipid profile, especially when incorporating the interaction of circadian rhythm [83,99].

In animal experiments, restricted sleep revealed an overall shift in various lipids that were affected by reduced sleep duration, specifically phospholipids and glycerolipids [100]. Indeed, poor sleep quality or prolonged insufficient sleep has been linked with alteration of lipid profiles including total cholesterol, HDL-C, LDL-C, and TGs, and inflammatory markers, potential risk factors for cardiovascular and metabolic diseases [101–103]. Moreover, variability in sleep duration, both long and short sleep, may generate adverse lipid profile through different biological pathways. This was suggested in a GWAS study in long- and short-sleep populations. Most notably, genes associated with short sleep explain around 4 % variance of TG levels in blood [104]. On the other hand, an increase in sleep duration was associated with increases in TC and LDL in a longitudinal study conducted in 503 subjects [105].

Reduction in sleep quality or quantity may increase appetite, thus increasing the risk of metabolic disorders [106–108]. Additionally, differences in habitual sleep have notable effects on human plasma metabolites, including fatty acids, sterols, and bile acids, as reported in a study investigating the association of metabolites with sleep timing [109]. Sleep cycle, habits, and quality can significantly influence the human lipidome, potentially masking baseline levels or altering lipid profiles at the time of sampling. These variations may introduce confounding effects, complicating the interpretation of lipidomics data. To minimize the impact of sleep-related factors in lipidomics studies, one might consider documenting sleep patterns and stratifying study participants based on sleep characteristics.

3.4. Stress

Humans face a myriad of stressful situations during their daily lives, often varying from one day to the next or across months to years. Stress has become an integral part of life and is now well-recognized for its direct and indirect impacts on human health, particularly in relation to cardiometabolic diseases [110,111]. Stressors are associated with various human body reactions, including acceleration of various metabolic and immune dysfunctions. Stress impacts also vary due to additional behavioral risks such as sleep deprivation, depression, and alcohol abuse. Responses to stress are highly individual as they also depend on the life course experiences [112]. Stress can manifest as acute stress, chronic stress, or episodic acute stress, each affecting the body's response in distinct ways. For example, chronic stress might impact energy metabolism by mobilizing the energy storages, which can lead to weight gain , a known risk factor of CVD [113]. Stress is not easy to identify, making it more likely to be an overlooked factor yet it has a marked impact on lipidome [114]. The growing epidemic of stress-related disorders could contribute to the intrinsic variability of human biological responses, ultimately challenging the interpretability and predictability of 'omics' results.

Two key contributors to the body's response to stress or threats are the sympathetic–adrenal–medullary (SAM) system and the hypothalamic–pituitary–adrenal (HPA) axis. The SAM system regulates the release of noradrenaline and adrenaline into the bloodstream, activating internal organs and rapidly and intensively triggering serial responses to deal with threats. These responses include increased heart rate, breathing rate, eye dilation, and blood flow. In addition to the SAM system, the HPA responds to stressful experiences by controlling the release of a series of stress hormones, starting with corticotrophin-releasing factor (CRF) and culminating in the production of the glucocorticoid cortisol. The surge in cortisol facilitates the utilization of energy stored in muscle and liver, increasing protein and fat mobilization [115]. In acute response, cortisol levels can reach peak level in around 20 min after the onset of stress. Chronic stress responses result in long-term exposure to elevated cortisol levels, leading to various negative health outcomes such as obesity [116], metabolic syndrome [117], and mental health issues [118]. This elevated baseline stress can lead to the blunting of the peak cortisol response [119]. An increasing body of empirical evidence is elucidating the relationship between stress-related problems and lipids, a connection that has been examined in many previous studies even before the emergence of 'omics' technologies, primarily through measuring total cholesterol, TG, and lipoprotein cholesterol levels [120]. In a study involving 38 undergraduate students, there was a significant upregulation of glycerophospholipids (LPE, PC, PE, PI, PA, and PS) in participants classified as experiencing stress, anxiety, or depression, as compared to the control group [121]. Significant elevations of SM were found in women who underwent antenatal depression compared to those without antenatal depression [122].

Acute stress responses can occur several times a day whenever the body faces an immediate threat. Stressful experiences can thus alter individual lipidomes at different time points, depending on whether this is a "flight-or-flight" or a chronic stress response, reshaping human physiology, including lipid homeostasis. Acute stress has been shown to interfere with the liver functions of rats and affect the expression of genes associated with lipid metabolism when rats underwent 14 consecutive days of acute stress [123]. Particularly, blood lipid profiles and cortisol levels were found to fluctuate during 60-min repeated measurement after 30-min acute stress therapy in 35 healthy men [124]. A systematic review of 39 studies investigating the association between metabolomics and psychological distress phenotypes presented a wide range of steroids, fatty acyls, and lipid levels between groups comparison [125]. The alteration of lipid in stress response appears to be predictable, as increasing cortisol level (corticosterone in rodents) are closely linked to an increase of metabolic rate *via* promotion of gluconeogenesis, inhibition of insulin production, thereby facilitating the delivery of blood to the muscles and brain. On the other hand, long-term exposure to high levels of cortisol leads to hyperglycemia, promoting the neogenesis of adipocytes, which are now considered producers of hormones and regulatory factors rather than a simple energy storage factory [126]. The interplay of these factors increases appetite, energy intake and expenditure, often observed in individuals with stress-associated issues such as sleep deprivation and depression, leading to disturbances in blood lipidome [127–129].

Lipids play a key role in the regulation of the HPA axis, with endocannabinoids shown to provide a fast feedback mechanism to suppress glucocorticoid production [130]. Another form of stress that contributes to metabolic disorders is socioeconomic disadvantages of childhood experiences. In a prospective study of 3000 individuals (Young Finns cohort), those who were consistently at a socioeconomic disadvantage from a young age (6 years old) had altered lipid profiles (*e.g.*, elevated TG) and were at increased risk of obesity, diabetes, liver disease, and hypertension later in life [131].

In summary, stress can arise in various forms and at different time points, potentially introducing bias and variability into lipidomics data interpretation. Therefore, collecting comprehensive phenotypic data from study participants is crucial for identifying potential stress-related confounders. Recording recent life events or work-related stressors, factors often overlooked, can help account for stress-induced lipidome variations. Additionally, incorporating standardized stress assessment tools and measuring physiological stress markers (*e.g.*, cortisol) can further aid in identifying lipidomic changes associated with stress, ultimately improving the robustness and reliability of research findings.

3.5. Exposure to environmental chemicals

Exposure to environmental chemicals encompasses various exogenous factors, including environmental pollution *via*, *e.g.*, air, water, and soil. The rapidly industrialized landscape of the current era has led to a significant increase in the release of chemicals into the environment. A large number of these chemicals are classified as endocrine disrupting chemicals (EDC), which can act similarly to natural hormones and disrupt homeostasis by binding to hormone receptors. These compounds

include compounds used as plasticizers, flame retardants, pesticides, fragrances, preservatives and huge number of other synthetic chemicals. Consequently, humans are exposed to an ever-growing array of contaminants with exposures starting already before birth, and which can potentially have both short-term and long-term harmful impacts on human health. Indeed, a considerable number of human diseases have increasingly been associated with environmental exposure, spanning autoimmune diseases, diabetes, obesity, metabolic dysfunction associated steatotic liver disease (MASLD), respiratory diseases, and fetal growth issues [132].

EDCs can trigger an array of biological changes, leading to dysregulation of signaling pathways, cell functions, and contributing to pathological development and progression. Several persistent organic pollutants, such as polycyclic aromatic hydrocarbons (PAHs), per- and polyfluoroalkyl substances (PFAS) and polychlorinated biphenyls (PCBs), as well as some heavy metals, have been reported to be associated changes in lipid metabolism [132]. Specific pollutants, including tributyltin, phthalates, bisphenol A, and others, are identified as having obesogenic properties, influencing adipogenesis and lipid accumulation [133,134]. Several of the EDCs can accumulate in the liver and interfere with bile acid, glucose, amino acid and lipid metabolism [135].

One specific class of EDCs that has shown to modulate lipid metabolism is PFAS, a class of compounds that most of the human population is exposed to. For example, recent study reported associations between exposure to PFAS and the sex-specific dysregulation of bile acids, TG, and ceramides in MASLD [136]. Several other studies have also reported links between liver diseases and PFAS exposures [137,138] as well as other metabolic diseases [139]. Given the major rout of EDC exposure is diet, it is not surprising that exposure to EDCs, such as to PFAS, can alter also the gut microbiome, which in turn can also modulate the host metabolism. Particularly, early-life exposure to PFAS may introduce variations in the infant gut microbiome and increase vulnerability to diseases. Indeed, while earlier studies have focused on the direct impacts of exposure on metabolic regulation, *e.g.*, through their interaction with specific receptors, recent studies indicate that several of the effects observed may in fact be mediated through alteration of the gut microbiota, causing alterations in gut microbiota metabolites that can then act as mediators [136,140].

Beyond PFAS, numerous other environmental exposures, encompassing non-persistent and persistent chemicals, plastics, nanoparticles, have all been linked to disturbance in lipid homeostasis and the onset of certain diseases. Commonly altered lipid classes are glycerophospholipids, sphingolipid, and glycerolipids [141]. In model systems, environmental chemicals such as bisphenol A (BPA), perfluorooctanoic acid, triclosan, p,p-dichlorodiphenyl-dichloroethylene, tributyltin chloride and triphenyl phosphate have shown to alter the extracellular lipidome of human white adipocytes, with both compound-specific changes but effects that were common to several tested chemicals, including increases in LPC, glycerophospholipids and Cer and a decrease in FA, with possible implications in inflammation, lipid and glucose uptake [142]. Also other flame retardants and plasticizers have shown to induce concentration-dependent alterations in the lipidome, particularly in TG, DG, PC, and cholesterol ester subclasses [143].

Chronic exposure to environmental chemicals can lead to acute or long-term responses in human metabolism, causing intra-individual time-dependent lipid variation. Individual exposure can vary over time and subject to subject, with variations strongly related to environmental conditions, physical status (age, BMI), and other individual factors [132,144]. With exposure to chemicals that have a short biological half-life, acute or temporal effects might be high, resulting in higher intra-individual variability compared to inter-individual variability [145]. Oxidative stress is one of the initial responses of organisms exposed to toxicants [146] and markers of oxidative stress in human plasma showed high intra-individual variability over time in a study of 206 participants [147]. Environmental exposures can influence human lipids directly by generating stress on exposed organs or indirectly by affecting lipid metabolism and the host gut microbiome [132]. Although the evidence of intra-individual exposure variability is convincing [144], there is still a lack of studies investigating the correlation between intra-individual exposure variability and lipidomics. Such studies could improve the interpretability of exposomics studies, leading to more reliable and causative conclusions regarding the impact of environmental exposure on health outcomes. However, completely eliminating influences of chemical exposures on lipidomes in clinical studies is impossible in practice. Therefore, accurately accounting for lipidome variations driven by environmental exposures requires comprehensive records of these factors to adjust lipidomics results appropriately. Integrating exposomics with lipidomics should be encouraged in future studies, as this approach can help elucidate the extent of variation explained by environmental exposures, ultimately improving the interpretation of research findings. Additional strategies, such as employing covariate-adjusted models, standardizing metadata collection, and performing stratified analyses, can further enhance the reliability and robustness of lipidomics research.

3.6. *Physiological status*

Changes in physiological status such as cold exposure and exercise induce changes in energy and lipid metabolism contribute to inter- and intra-individual variation in human lipidomes. Most research in humans focuses on blood-based lipids (serum, plasma and red blood cells), and only a limited number on human tissues including liver, adipose tissue, muscle and pancreas [148]. Other matrices studied include urine and other polar and dilute liquids such as sweat and saliva [149].

Cold exposure accelerates lipid turnover in adipocytes throughout the cellular process (uptake, catabolism and secretion). Straat et al. report an increased free FA level in blood reaching a maximum concentration after 60 min of mild cold exposure (19 °C) accompanied by decrease in TG concentrations, which started already after 30 min of cold exposure [150]. On the other hand, prolonged cold exposure increased the content of TG rich in PUFA presumably due to increased cell energy demand, leading to inhibition of lipase in the adipose tissue. Cold exposure activates the 12-lectin-like oxidized receptor and EPA pathway, releasing 12-hydroxyeicosapentaenoic acid, an eicosanoid negatively correlated with body mass index. Activation of cytochrome P450 epoxygenase and linoleic acid epoxide hydrolase lead to increased transport of FA to brown adipocytes. During cold exposure, thermogenesis increases CL and PG species in brown adipose tissue to improve proton transport, while oxylipin concentrations increase to enhance glucose and FA transport and uptake by peripheral cells [148]. Furthermore, the formation of plasmalogens induce the cold-response by increasing peroxin levels (Pex3, Pex16, Pex19) in adipocyte peroxisomes, promoting peroxisomal α oxidation of methyl-branched fatty acids and β oxidation of very long chain fatty acids (VLCFAs) [151].

Oxidation of fat is dependent on the heart rate and oxygen intake during exercise, maximum fat oxidation occurring at around 60–80 % of maximum heart rate [152,153]. Lack of exercise and a high-fat diet may lead to TG accumulation as well as shifts in cellular fuel choice of the mitochondria between glycolysis and lipolysis, two modes of oxidation in cell respiration [154]. Thus, fat oxidation is cordially linked to glucose oxidation and insulin-related processes [155].

More profound differences in lipid classes are found in plasma between sitting and exercise than between sitting and light breaks. Pinto et al. report marked changes in the lipid classes in exercise compared to the sedentary and light-intensity break condition of patients with rheumatoid arthritis [156]. FFAs, PS, LPE, sphingosine as well as plasmalogens of PC, PE and LPE were all upregulated during exercise. In contrast, ceramide-1-phoshate and PS were the only lipid subclasses that were downregulated in the light break condition as compared to the sedentary condition.

During exercise, skeletal muscle signals the liver *via* MCFA species,

reflecting increased energy demand [157,158]. Simultaneously, a complex mix of ARA-mediated eicosanoids is released by skeletal muscle to activate counteracting pro-/anti-inflammatory, hypo-/hypertensive and vasoconstrictive/-dilatory responses [149,159]. Similarly, the long chain PUFAs (LC-PUFAs), EPA and DHA, have compensatory inflammation signaling utility post-exercise [160,161]. In general, exercise is associated with a temporary accumulation of CE, PC, DG, Cer and SM species and a decrease in TG in serum [158]. Post-exercise recovery phases can be divided into immediate, early and late recovery, though temporal definitions vary [158,162–164].

Multitude of biomarker studies shed light on what distinguishes a professional athlete's lipidome from the rest [158,165–167]. For instance, Høeg et al. report certain polyunsaturated PC species as highly correlated with a marathon finish time [166]. Endurance running profiles and effects of marathons have been lately covered by Høeg et al. [166] and Stander et al. [167] from different angles. Høeg et al. measured the pre-and post-marathon plasma lipids of marathon runners, finding that runners had overall higher PC levels, higher choline levels pre-race, but same choline levels post-race as controls [166]. Stander et al. focused attention on the enormous strain subjected to the marathon runners. After a marathon, elevated levels of complex lipids, increased content of α-oxidation products, including odd-chain FA, FFA [149], and acylcarnitine-species for less fit marathoners in serum was observed [158]. Skeletal muscle lipid content (especially TG) is relatively high in lean, insulin sensitive endurance trained athletes, likely to facilitate more efficient local FA oxidation and signaling than lipid transport from adipose tissue or liver [168].

Peak oxygen consumption (VO2), typically in a treadmill test, serves as an indicator of fitness. Contrepois et al. observed characteristic lipids in plasma of healthy volunteers after 2–60 min of exercise to be highly predictive of peak VO2 [158]. A positive correlation was found between VO2 and plasma levels of hydroxy-FAs. On the other hand, high levels of TGs and branched-chain amino acids in plasma indicate low VO2, despite the fact that TG and DG variability among healthy volunteers are greatest across lipid species [158].

Temporal fluctuations in physiological status can contribute to lipidome variability, posing a challenge in lipidomics studies. To mitigate this, several strategies can be incorporated into study design to minimize variability and improve data robustness. Continuous monitoring using wearable devices, standardized protocols for physical activity assessment, and stratified analyses can help account for these variations. Additionally, employing covariate-adjusted models can further enhance the reliability of findings.

3.7. Pathological status

Beyond the physiological status, pathological conditions significantly contribute to intra- and inter-individual variability in the lipidome, reflecting dynamic metabolic alterations and systemic responses to disease. Transitions from health to disease, whether due to acute conditions (*e.g.*, inflammation) or chronic disorders (*e.g.*, diabetes), can induce substantial lipidomic transformations, affecting lipid species such as TG, PC, Cer, and CE [169]. The extent of lipid disturbances caused by pathological conditions depends on disease type and progression. In metabolic disorders, lipotoxicity induces endoplasmic reticulum (ER) stress, disrupts lipid signaling, and activates inflammatory kinases, contributing to organ dysfunction, including fatty liver disease, insulin resistance, and dyslipidemia [170]. Similarly, in neurodegenerative diseases, lipid peroxidation, protein aggregation, and neuronal damage can drive lipidomic alterations [365,367]. Notably, the immune system plays a central role in metabolic regulation during pathological states. Sickness metabolism, a complex interplay between immune activation and organ-specific metabolic responses, helps regulate systemic homeostasis. Metabolic reprogramming of the immune system is a critical factor in the pathogenesis of various diseases, including cancer, metabolic disorders, and autoimmune diseases [171,172]. As infection severity increases, different immune cells are activated, each engaging distinct metabolic pathways. Consequently, immune-driven metabolic shifts contribute to intra-individual lipid variability, further complicating the interpretation of lipidomic data [173].

Given the strong link between lipid metabolism and disease, many lipids have been proposed as disease biomarkers, underscoring the profound impact of pathological status on the human lipidome. For example, sphingolipids are implicated in Alzheimer's disease [174], while ceramides serve as biomarkers for cardiovascular diseases [175]. Although lipidomic alterations associated with chronic diseases, such as cancer and liver disease are well-documented [176], the effects of acute pathological conditions on lipid variability, particularly intra- and inter-day fluctuations, remain underrecognized. Acute conditions, such as respiratory viral infections, can induce substantial lipid profile shifts, with PC, phosphatidylethanolamine (PE), and phosphatidylinositol (PI) predominantly altered in the early infection phase, whereas fatty acids (FA), LPC, and CE become more prominent during later and recovery phases [169]. Notably, different respiratory viruses elicit distinct lipidomic responses; for instance, human sputum lipid profiles differ significantly between influenza (H1N1, H3N2) and rhinovirus infections [177]. These findings underscore the need to consider acute pathological events when interpreting lipidomic data.

Beyond acute conditions, long-term cohort studies have demonstrated that greater lipid variability, particularly in total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL), is associated with an increased risk of cardiovascular disease [178,179]. Renal function, assessed *via* estimated glomerular filtration rate (eGFR), has been shown to correlate with blood lipid levels and should be accounted for in longitudinal lipidomics analyses [180]. Other pathological factors, such as inflammation, hormonal fluctuations, and endocrine dysregulation, may also contribute to intra-individual lipid variability.

Fig. 3 summarizes the factors that induce intra-individual variations, and the lipid species associated with these factors that have been reported to change within individuals.

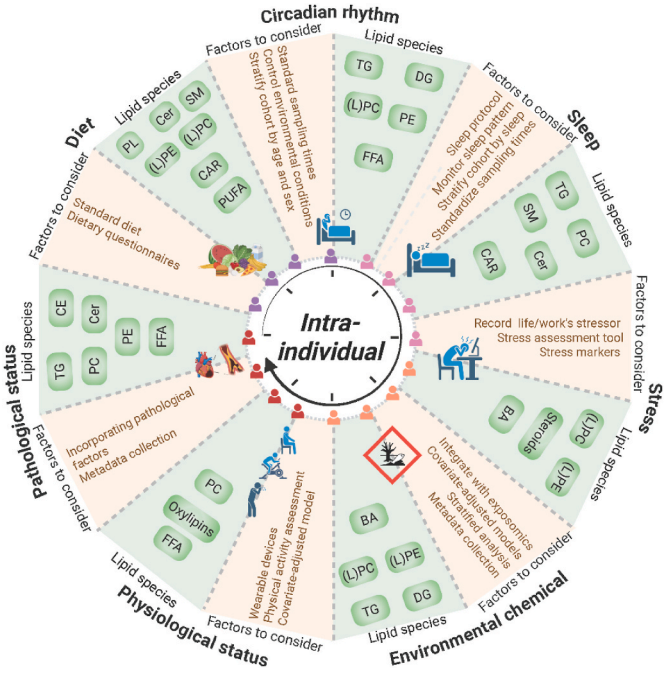

Fig. 3. An overview of factors that induce lipidome intra-individual variations and the lipid species associated with these factors.

4. Factors affecting inter-individual variability of lipidomes

4.1. Genetic variation

Metabolic traits, especially lipid metabolism, are increasingly acknowledged as integral components of genetics research, serving as intermediate phenotypes that bridge the gap between genetic variants and the ultimate biological endpoints of significance. For example, the increase of TG is linked to cardiovascular disease; elevation of liver enzyme might indicate abnormal liver function; high urate level links to gout [181]. Blood lipid levels are now considered in part inheritable from genetic traits, which are highly variant among individuals and ultimately induce lipid-level variability between humans. Genetic factors that induce variance of lipid profile between persons include the allele frequencies, effect sizes and linkage-disequilibrium patterns.

In a GWAS study of plasma lipidome, a well-established association between lipid-associated variants with various disease endpoints, including cardiovascular disease, diabetes, metabolic disorders, and neurological disease, were reported in 7174 Finnish individuals [182]. In another study, 35 lipid-associated loci were explored across 2181 individuals with 25 cardiovascular-related phenotypes and suggested the high heritability and correlativity of PUFA levels with genetic variants [183]. Many other studies provide evidence of how genetic variant architecture affects the human lipidome and link with disease's phenotypes, by identifying co-localization of lipid-loci with coronary artery disease [184]. The inter-individual genetic differences, importantly, affect the lipidome variation between people, with the gene-environment interactions further exacerbating this variation [185,186]. When the association of genetic and lipid metabolism traits were examined in 17 gene polymorphisms within 13 genes, the result showed the APOC3, and APOE-related polymorphisms significantly impacted the lipid traits, such as variation of apolipoprotein, LDL-C, total cholesterol, and TG [187]. Impact of apolipoprotein E genotypes on inter-individual variation of plasma lipids is well recognized, and more substantial variation could be seen when integrating with age, sex, and geography of population [188,189]. The variation of plasma lipids was even found within monozygotic twin pairs, having different genetic mutation [190], indicating considerable variation of human plasma lipidome caused by genetic variation [191]. In a recent study of coronary artery disease, more than 3000 SNP-lipid class associations were reported, of which 737 independent genomic regions connected to lipid metabolism, emphasizing lipidome variation among 4492 individuals. Many of the genetic-associated lipid species, including sphingolipids, glycerophospholipids, and glycerolipids, were linked to incidence of coronary artery disease [184]. Furthermore, other gene-related factors modulate the inter-individual variation of lipid homeostasis *via* epigenetic intermediate, such as DNA methylation, histone modifications, and regulation by RNAs. The blood lipid traits (TG, HDL-C, LDL-C) were found linked to DNA hypomethylation. For instance, methylation of carnitine palmitoyltransferase 1A (*CPTA1*) was strongly associated with fasting TG and VLDL variation, particularly explaining approximately 12 % and 6 % of TG variation in discovery (n = 991) and validation cohorts (n = 1261), respectively [192]. In another European epigenome-wide study, a seven of lipid-related CpGs annotated to *ABCG1, MIR33B/SREBF1*, and *TNIP1* have associated with the HDL-C, TG and LDL in blood lipid or adipose tissue [193]. Variation of inter-individual lipidomics may be explained by the regulation of gene expression by epigenetic variation (*e.g.*, DNA methylation), particularly it's interaction with environmental factors. Altogether, genetic polymorphisms, epigenetic variation might potentially exacerbate the inter-individual lipid level variation, especially, when genetic factors are closely linked with other factors, such as environmental exposures, age, and sex. Integrating multi-omics approaches can help identify associations between heritable lipids (*e.g.*, TG, Cer) and genetic determinants, allowing for the distinction between gene-driven variations and lipid alterations linked to specific outcomes. Furthermore, exploring gene-lipid metabolite network interactions can provide deeper insights into the connections between genetic, epigenetic, and lipid metabolism pathways.

4.2. Age

Throughout the various stages of the human lifespan, most biological processes undergo significant changes, and lipid metabolism is no exception. Several studies have consistently reported how the plasma lipidome is substantially different in children across different age groups [194,195] and adulthood, where a striking sexual dimorphism, as discussed in the sex section, has been reported [196]. Age is a well-established factor contributing to both intra- and inter-individual lipid variability, reflecting the complex biological processes that occur throughout the aging process. As individuals age, their lipidome undergoes systematic changes. Specifically, circulating CAR, FA, and glycerolipids tend to increase, whereas glycerophospholipids generally decline [197]. Both short- and long-term intra-individual lipid variations have been observed in pediatric cohorts [198–201], indicating that lipid fluctuations also occur early in life and persist over time.

With a global population experiencing a constant growth in its elderly fraction, and the understanding that aging is among the biggest risk factor for disease development, considerable efforts have been directed towards a characterization of this complex phenomenon [202]. Several ageing processes are evolutionary conserved, and studies in pre-clinical models have shown that aging is a dynamic and adaptable process [203]. While aging is characterized by a progressive, time-related loss of physiological functions (*e.g.*, loss of female fertility after the menopause and lower muscle to fat mass ratio), it is increasingly recognized that a proportion of the population reach an old age still maintaining a functional ability to enable their wellbeing, a process referred to as healthy ageing [204].

Sleep-wake cycle and circadian rhythms are generally synchronized with age range, but little is known on how these cycles affect the plasma lipidome in healthy old people. A recent study on healthy young and older adults (12 sex-matched volunteers per group) reported that compared to the younger group, elderly participants did not show differences in the prevalence of circadian rhythmicity in the plasma lipidome but displayed advanced phase and attenuated amplitude of circadian-regulated lipid metabolism, highlighting a novel aspect in the chrono-biology of healthy ageing [83].

More broadly, population-based studies have started to unravel the plasma lipidomic signature of aging. In two large Australian cohorts, Beyene and colleagues reported that about 70 % of the analyzed lipids were significantly associated with age, after adjusting for sex, BMI, total cholesterol, HDL-C, and TG [205]. Specifically, age was strikingly positively associated with CAR and Cer in both sexes, PC(O), PC(P) and LPC were negatively associated with age in both sexes, while PE(P), LPE (P), and LPI showed opposing effects (positive in females and negative in males) [205]. Of interest, the authors also investigated the effect of menopause on the circulating lipidome, showing that postmenopausal females displayed higher TG, DG, PI, and alkyl-diacylglycerol *vs*. premenopausal females, while postmenopausal females had lower ether and lysophospholipids [205]. Tabassum and colleagues reported, in two large European cohorts, that in males age was mostly associated with a decrease in plasma lipids, including several CE, TG, DG, PC, LPC and PC (O) and increase in just 10 lipid species including PC, and SM, while in females age was mostly associated with higher levels of several lipid classes including TG, CE, SM, Cer, PC(O), PE(O). Several lipids were concordant between the Australian and European studies, but in the European cohort, the authors did not observe an association between menopause and the plasma lipidome [206]. Dissecting the independent impact of age and menopause status on the plasma lipidome is challenging, as age and menopause status are highly collinear variables, these discrepancies highlight the need for further studies in this field.

There is a general consensus in the literature that total cholesterol

levels increase in plasma in both males and females from the age of about twenty [207,208]. Of the cholesterol metabolites found in plasma, 24S-hydroxycholesterol (24S-HC) is present at much higher concentrations in infants and children than adults, this difference may be as much as five-fold [209]. This is explained by the relative size of the brain, where 24S-HC is synthesized [210], to liver, where 24S-HC is metabolized [211,212]. In infants, the brain is about three times that of the liver, while in the adult the two organs are of similar size. From the age of about twenty the plasma concentration of 24S-HC stays rather constant but in older age the liver is reduced in size to a greater extent than in brain resulting a small but significant rise in plasma 24S-HC after the age of about 65 [213]. The ultimate products of cholesterol metabolism are steroids and bile acids, and these also vary with age and sex. For example, the plasma concentration of dehydroepiandrosterone (DHEA) sulfate is higher in males than females and decreases with age in both sexes [214]. The bile acid composition in humans shows differences between neonatal and adult period with bile acids hydroxylated at 1β, 2β or 6α being produced by neonates but are absent or present at very low concentrations in adults [215].

Overall, the current evidence strongly suggests that plasma lipidome is highly influenced by people's age and that this variable should be considered as a factor of inter-individual variabilities in clinical studies.

4.3. Sex

Human lipid metabolism is significantly influenced by biological sex in an age-associated manner. However, the mechanisms underlying these differences remain unclear. A clear example of this age–sex interaction and inter-individual lipid variation is illustrated in the study by Beyene et al. (Fig. 4), which provides compelling evidence for sex-by-age interactions in lipid metabolism [205]. Notably, 26 out of 36 lipid classes or subclasses exhibited significant sex-dependent age associations. During adulthood and the fertile age, females exhibit a plasma lipid profile associated with a better cardiovascular health compared to males. This includes lower levels of TG, total cholesterol, LDL-C, and higher levels of HDL-C [216]. The widespread adoption of lipidomic technologies is advancing our understanding of how biological sex affects hundreds of different plasma lipids beyond the routine measures [206,217–220]. Indeed, population-based studies have shown that more than 50 % of the plasma lipidome is significantly different between sexes [205,206,218].

Routinely measured total TG and LDL-C (which predominantly reflects total plasma CE) have consistently been reported as lower in females than males from most of adulthood until old age, when these differences tend to diminish [216]. In alignment with clinical data, lipidomic studies also support the lower levels of TG and DG in females compared to males throughout most of adulthood [205,206,218]. Similarly, albeit to a lesser extent, CE have been found to be lower in females than males, consistent with their primary plasma carrier concentrations (LDL) across the lifespan [216]. Tracer studies have provided insights into the sexual dimorphism of TG metabolism. For instance, in the postprandial state, females exhibit lower hepatic *de novo* lipogenesis than males, potentially explaining, at least in part, the lower circulating TG levels in females [221,222]. Mittendorfer and colleagues

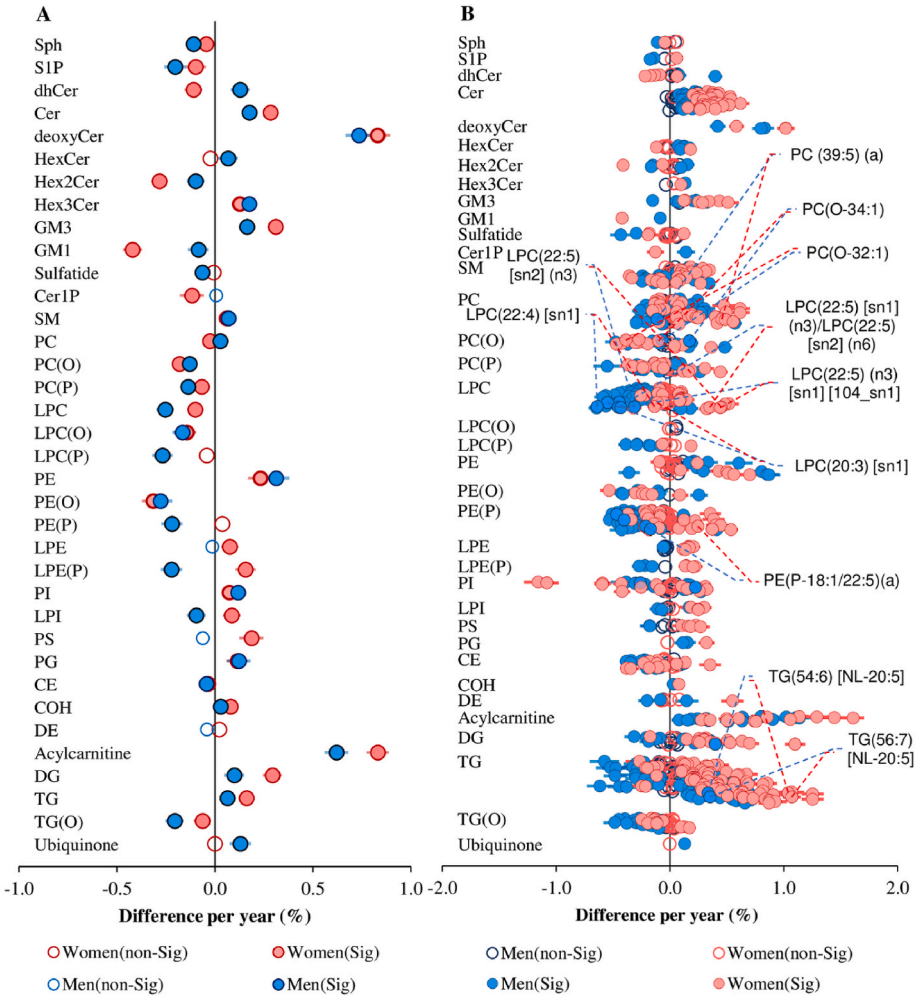

Fig. 4. An example illustrating the variation in lipid classes and lipid species associated with sex and age. Figure adapted from Beyene et al. [205], with permission.

showed a higher plasma VLDL-TG secretion rate in males than females, which could partially explain the differences in circulating TG between sexes [223]. Moreover, they found that while plasma VLDL-TG in males are primarily due to their secretion rates, in females, their concentration is mainly influenced by their clearance rate, which was higher in males than females [223]. Differences in VLDL-TG secretion and clearance rates between sexes are also influenced by body adiposity (abdominal and total obesity) and aging/menopause state [224], adding a further layer of complexity into the generalizability of these findings. Moreover, how different lipid species carried within VLDL are affected by biological sex across the lifespan is still not known.

Plasma PCs are predominantly carried by HDL particles; hence, it is not surprising that their levels have consistently been reported to be higher in females than males [205,206]. Conversely, LPC have consistently been reported to be higher in males than females [205,206,218]. In plasma, LPC can be derived from PC through the action of two enzymes: a) lipoprotein-associated phospholipase A2 (Lp-PLA2), an enzyme with pro- and anti-inflammatory capabilities [225] that catalyzes the hydrolysis of fatty acids at the sn-2 position of phospholipids, generating a fatty acid and an LPC, and (b) lecithin cholesterol acyltransferase (LCAT), a key enzyme in the biogenesis of HDL [226] that transfers fatty acids from PC to unesterified cholesterol, thus generating CE and LPC. Compared to males, females display lower LCAT activity [227], which has been associated with higher PC and lower LPC [228], potentially explaining, at least in part, the higher plasma PC levels in males compared to females. Interestingly, Lp-PLA2 is higher in males than females [229] and could contribute to the higher plasma LPC levels in males. However, the specific contributions of Lp-PLA2 and LCAT activities to circulating PC and LPC in males and females is not known, thus warranting further investigation.

Plasma FFA constitute one of the most abundant circulating lipid classes [6] and have been extensively studied for their role in the onset and progression of obesity-related metabolic disorders [230]. FFA levels have been reported to be higher in females than males [231,232] with tracer studies showing that females display higher rates of appearance of FFA (FFA-Ra) due to higher fat-to-lean mass ratio than males [232–234]. However, higher circulating FFA levels in females do not seem to predispose them to insulin resistance, while it does to males [235].

A source of intra-variability in the plasma lipidome of fertile females, often overlooked in real-life study cohorts, is constituted by the menstrual cycle phases as reported by Draper and colleagues [236]. Other crucial lipids, including SM and Cer, have been reported to exhibit differences between sexes as reviewed in Ref. [196].

With respect to oxysterols (oxidized form of cholesterol), the plasma concentration of 27-hydroxycholesterol (27-HC, systematic name (25R) 26-hydroxycholesterol) measured following alkaline hydrolysis of sterol esters is reported to be about 30 % higher in males than in females [237]. 27-HC is made by most cells in the body and represents the first metabolite in the acidic pathway of bile acid biosynthesis [238]. There are some indications that plasma levels of 24S-HC are higher in females than males, but data interpretation is complicated by variations of 24S-HC with age [209]. 24S-HC is abundant in brain and is made by the neuronal enzyme cholesterol 24-hydroxylase (CYP46A1) [239]. 24S-HC is exported from brain into the circulation across the blood brain barrier and its concentration in plasma can be indicative of the number of functional neurons in brain and a potential marker of neurodegeneration [213]. Interestingly a recent CYP46A1-targeted PET study showed higher expression of CYP46A1 enzyme in women than in men, backing up suggestions that 24S-HC is more abundant in female than male plasma [240].

Major changes of the plasma oxysterol profile are seen during pregnancy. This is most evident for 22R-hydroxycholesterol (22R–HC) and 20R, 22R-dihydroxycholesterol (20R,22R-diHC), two intermediates in the pathway of cholesterol to pregnenolone catalyzed by CYP-11A1 [241]. 22R–HC and 20R, 22R-diHC are usually undetectable in adult male and female plasma [242,243], however, during pregnancy these molecules are present in their free unesterified form at ng/mL levels [244]. Pregnenolone is metabolized further to hormonal steroids and pregnant women have been found to have a special pattern of steroid sulfates in plasma [245–247].

Overall, there is robust evidence demonstrating that biological sex plays a significant role in determining inter- and intra-individual variability in the plasma lipidome.

4.4. Gut microbiome

Growing evidence suggests that the gut microbiome shapes host metabolism and disease outcomes throughout the life course [248,249]. There is an increasing awareness that the microbes themselves do not primarily cause specific health effects but rather mediate them *via* the metabolites they produce, including lipids [250–253]. Lipids constitute a significant portion of the gut microbiome's metabolic content [254]. For instance, the lipid content of *E. coli* constitutes 10 % of the total dry weight of the cell [255]. Recent studies, including our own work, have identified a diverse range of lipids in the human gut, potentially indicative of microbial metabolism, although their origin remains uncertain (whether microbial, host, or dietary) [256–259]. The gut lipid profile closely resembles those present in circulating blood.

The concept of microbiota-dependent lipid metabolism dates back over a century. For instance, it is well established that gut microbes transform primary bile acids into secondary bile acids [260]. Short-chain fatty acids (SCFA) produced by gut commensals through fermentation of non-digestible carbohydrates are also involved in regulating lipid metabolism and promoting lipid storage [261,262]. From a biomass perspective, a substantial portion of the gut microbiome's metabolic content comprises lipids. For instance, major lipid classes found within gut microbial membranes include phospholipids (*e.g.*, PE, PS, PC, PI, and PG), glycerolipids (DG and TG), CL, and saccharolipids (*e.g.*, lipopolysaccharides with diverse head groups) [258,263,264]. Recently, Folz et al. also uncovered over 100 metabolites, primarily lipids, including PE, PI, and PG, that were abundant in stool samples when compared to the upper intestinal samples [264]. These lipids can be attributed to bacterial cell material. Specific lipid classes are characteristic of certain bacterial phyla or taxa, including sphingolipids, plasmalogens, and sulfonolipids. For example, commensal bacteria belonging to the Bacteroidetes phylum can produce specific sphingolipids that impacts host sphingolipid metabolism [265,266]. Lactobacillus and Bifidobacterium species have demonstrated the ability to modulate host cholesterol levels by assimilating cholesterol and, in some cases, reducing its absorption by the host [267,268].

Microbially linked and diet derived metabolites account for short-term of intra-individual and the largest inter-individual differences in the gut [264]. The gut microbiome plays a vital role in lipid absorption and metabolism [269,270]. Diet influences inter- and intra-individual microbiome composition [271], which in turn may influence the specific lipid levels of the host [272]. This variability is supported by data from fecal samples collected from ten healthy individuals over three consecutive days, revealing fluctuations in key gut markers, including short-chain fatty acids (SCFAs), total fungal load, and total bacterial abundance [273]. In the Personalized Responses to Dietary Composition Trial (PREDICT 1) study, which involved 1098 subjects, the associations between diet, microbiome, and blood related markers were most pronounced in relation to circulating lipid levels, which indicates that gut microbes may have a greater impact on circulating lipid levels compared to other metabolic derivatives [274]. The results also emphasized the potential predictability of the host microbiome to postprandial TG concentration [274]. In another longitudinal study with 75 subjects, intra-individual variability accounted for 23 % of gut microbiota variation, potentially impacting the variance of functional pathways, including lipid metabolism [275]. Furthermore, Hornburg et al. characterized the lipidome dynamics (>1500 plasma samples) in 112 human participants followed for up to 9 years and identified that distinct

longitudinal lipid signatures were linked to the specific microbiome species [169], suggesting a potential role of the microbiome in regulating host lipid metabolism.

The gut microbiome is one of the dominant factors predicting the variance of circulating blood metabolites including lipid compounds, as evidenced by a study based on a deeply phenotyped healthy human cohort of 491 individuals [276]. More recently, results from another 1368 extensively phenotyped individuals (including 311 individuals with 4-year follow-up data) from the Lifelines DEEP and Genome of the Netherlands cohorts also suggest that inter-individual metabolome variation can be explained by the gut microbiome [277]. They found that the gut microbiome plays a more dominant role than genetics in explaining inter-individual variability in host metabolism. Here, 85 metabolites, including lipids and lipid-like molecules, were explained by the gut microbiome composition [277]. Further, Chen et al. also reported that the inter-individual variability in the plasma bile acid (lipid metabolites) profile does not primarily reflect bile acid pathways in the liver. Instead, it predominantly corresponds to the processes of transport and metabolism within the enterohepatic circulation. These enterohepatic processes are partly regulated by the gut microbiota mediated *via* bile acid biotransformation [277]. Using an ingestible sampling device, a recent study examined metabolome variation along the gut in 15 participants. The findings suggest that there is inter-individual variability in microbial lipid levels, including sulfolipids, bile acids, and fatty acid esters of hydroxy fatty acids, especially in the upper intestine, particularly among those individuals who used antibiotics [264]. Likewise, in a rodent study, it was found that 24.8 % of fecal lipids decreased by more than tenfold in mice treated with antibiotics [258]. In addition, in a related companion publication authors also suggest that dynamic lipidomic changes occur within the gut biogeographic, including microbial conjugated bile acids [278]. Recently, thousands of novel conjugated lipids (*N-acyl amides*) have been discovered; however, these molecules are yet to be fully identified or characterized in human samples [279].

Taken together, these results imply that gut microbiome drives both inter- and intra-individual differences in host circulatory lipid levels. Based on our understanding, current only few studies have explored the microbiome-lipid co-axis and intra-individual differences. While existing research has primarily focused on the influence of microbiota on the plasma lipidome, studies linking the gut lipidome with the microbial-host-lipid co-axis remain understudied. Integrating metagenomics with lipidomics and other omics levels will enable a more comprehensive characterization of microbiome-lipid associations. Additionally, research on microbial-derived lipids will shed light on the relationship between host microbiota and circulating lipids, helping to account for variations observed in lipidomics results. Insights into microbial enzyme-catalyzed lipid metabolism, such as the conversion of bile acids and short-chain fatty acids, could further enhance our understanding of lipid transformations and their impact on the human lipidome.

4.5. Drugs

The applications of metabolomics and lipidomics in drug discovery have become widespread, facilitating the creation of drug-metabolite/lipid connectivity maps that help elucidate the mechanisms of drug action. Daily medication regimens can impact blood lipidomes in various ways, including the use of non-prescription drugs such as dietary supplements, niacin (vitamin B) [280], plant stanol esters [281], and fish oil [282]. Moreover, commonly used drugs undergo extensive changes involving gut microbiome, indirectly impacting their metabolic potential [283].

Different drug classes have the potential to significantly shift the human lipidome, resulting in alterations in compositions and concentration in both systemic lipidome and exposed organs, such as liver. Lipid-lowering medications, as the name implies, inherently alter lipid composition in the human body. Statins, common lipid-lowering agents prescribed to lower cholesterol levels, visibly reshape lipid levels throughout the entire body. Fibrates, commonly used to lower TG levels and increase HDL-C levels, activate peroxisome proliferator-activated receptors (PPARs), resulting in alterations in lipid metabolism alteration [284]. In the context of dyslipidemia, ezetimibe is employed to lower LDL-C levels by reducing cholesterol absorption in the small intestine, potentially influencing the absorption of other lipid species [285]. Other drugs that can induce variability in lipid levels include bile acid sequestrants [286,287], antipsychotics [288,289], immunosuppressants [290,291], diuretics [292], and oral contraceptives [293–295]. The pharmacokinetics of drugs exhibit intra-day and intra-patient variability in the human body. Pharmacometabolomics and pharmacolipidomics thus offer insights that facilitate the deciphering of biological mechanisms in intra-individual and inter-individual drug efficacy and response. The human body is known for its variability in drug responses among individuals, stemming from intrinsic factors such as genes, age, sex, and disease, as well as extrinsic factors like diet and chemical exposures [296]. Endogenous metabolites and lipid metabolism reflect the intricate interplay between drug pharmacology - covering drug targets, binding, and activation - and the (patho)physiology of the individual, including genetic variation, cell and tissue modulation, and the stage of the disease. For instance, statins, which lower cholesterol by inhibiting HMG-CoA reductase, exhibit inter-individual variation in drug response among patients, possibly explained by genetic polymorphisms of uptake and efflux transporters [297]. This interplay generates differences in drug responses and (patho)biochemical networks between individuals, leading to an evident expectation of variability in inter-individual lipid responses. Variations in drug effects and efficacy could potentially result not only in the variability of cholesterol levels but also in other lipid species in both tissues [298] or blood [299]. Consequently, a lipidomics-based approach has recently been employed to suggest biomarkers associated with drug efficacy [300] and safety [301].

Considering cholesterol synthesis beyond the context of statin drugs, there are a surprising number of prescription drugs that can inhibit the enzyme 7-dehydrocholesterol reductase (DHCR7), the last enzyme in the Kandutsch-Russell pathway and the last but one enzyme in the Bloch pathway of cholesterol biosynthesis [302]. Important studies by Korade and colleagues, including a high-throughput screen of a library of 3697 FDA-approved drugs, showed that of the 200 most prescribed pharmaceuticals in the USA, 27 inhibited cholesterol synthesis at the level of either DHCR7, or 24-dehydrocholesterol reductase (DHCR24, the last enzyme in the Bloch pathway, which also provides up-stream cross-over from the Bloch to Kandustch-Russel pathways) [303]. Importantly, plasma/serum analysis of biobanked samples from patients receiving the psychotropic medications baripiprazole, haloperidol, trazodoneare and cariprazine, which inhibit DHCR7, showed 7-DHC and its enzymatically formed isomer 8-DHC to be elevated [304,305]. Cariprazine is an antipsychotic drug prescribed for the treatment of adults with schizophrenia which results in elevated 7-DHC in circulation, and in mouse studies has been shown to inhibit embryonic brain cholesterol synthesis. This may be particularly important in humans with single allele DHCR7 mutations, suggesting that for women in this genetic group it may not be ideal to take cariprazine during pregnancy [304].

Inhibition of DHCR7 will not only lead to an increase in circulating 7-DHC but also its oxysterol metabolites. The conjugated diene in the B-ring of 7-DHC is particularly sensitive to non-enzymatic oxidation, leading to a wide-range of oxysterol structures [306]. Some of these may have toxic effects, *e.g.* 3β,5α-dihydroxycholest-7-en-6-one (DHCEO) the most stable 7-DHC derived oxysterol, has a major effect on neuronal morphology and neurite outgrowth [307]. 7-DHC is also a substrate for the sterol hydroxylase, CYP7A1, which results in the formation of 7-oxocholesterol (also called 7-ketocholesterol) from 7-DHC [308]. 7-Oxocholesterol can act as a precursor of a myriad of other oxysterols [309,310], including 3β,7β-dihydroxycholestenoic acid which is toxic to neurons [311].

Voriconazole is a prescription medicine used to treat fungal infections. It is a CYP51A inhibitor, CYP51A being a sterol 14-demethylase which mediates ergosterol synthesis in fungi and cholesterol in human. Voriconazole will also inhibit CYP enzymes involved in oxysterol metabolism including oxysterol 7α-hydroxylase (CYP7B1) [312] and cholesterol 24-hydroxylase (CYP46A1) [313]. However, of the CYP46A1 modulators the most well studied is efavirenz, the *anti*-HIV drug [314]. Efavirenz will activate CYP46A1 at low doses but act as an inhibitor at higher concentrations [314]. Efavirenz has received considerable attention as an allosteric activator of CYP46A1 and as a potential treatment for neurodegenerative disease including Alzheimer's and Huntington's diseases [315]. CYP46A1 is expressed in neurons where it converts cholesterol to 24S-HC [239], which can be exported from brain [209], encouraging further brain cholesterol synthesis and cholesterol turn-over [316]. Other prescription drugs have the potential to modulate CYP enzymes important for oxysterol production including CYP27A1 and CYP11A1, the first enzymes in the acidic pathway for bile acid biosynthesis and steroid hormone synthesis, respectively [317, 318].

4.6. Spatial variability of lipidomes

Given the advances in both MS sensitivity and MSI, it is now possible to explore how lipids can change both spatially and temporally in individuals. This allows us to study how lipids form gradients in tissues to perform specific biological signaling or function. Diurnal lipid changes in the nuclei and mitochondria have been shown to be circadian rhythm dependent [319]. Cardiolipin, key lipids involved in mitochondrial functionality, form gradients in the cell wall of the mitochondria [320]. Difference in the spatial localization of these lipids can have a profound impact on mitochondria function [321]. For example, ceramides form gradients in the epidermal layers and are critical in maintaining the skin barrier [322]. The spatial localization of signaling lipids also plays a key role in resolving inflammation [323]. Recent development trend is also combining MSI with other imaging techniques such as positron emission tomography (PET) or magnetic resonance imaging (MRI) [324]. For example, combining contrast MRI imaging which DESI-MS can improve the detection of tumor boundaries in breast tumors [325]. PET imaging has also been combined with both MRI and MSI to investigate how changes in the lipid content of baby milk formula impacts the development of rat brains [326]. Despite the analytical challenges as listed in Section 2.2, spatial lipidomic is increasingly being used in the clinic to assist in decision making. For example, detection lipidomic changes at the boundary of healthy and tumor tissue has been tested in the operating room [327].

Fig. 5 summarizes the factors influencing inter-individual lipidome variations and the lipid species associated with these factors that exhibit inter-individual variability.

5. The impacts of various intra- and inter-individual factors on the studies of lipidomes

The lipidome is subject to dynamic variation influenced by a multitude of factors. Understanding the intricate interplay of the driving factors of intra- and inter-individual variation is essential for the analysis and interpretation of lipidomic studies. Intra-individual factors, such as diet, hormonal fluctuations, sleep pattern and physiological status and associated metabolic processes, contribute to the changing lipidomic profiles within individuals over time. Conversely, inter-individual factors encompass differences between individuals, which may also include diet and lifestyle, but also genetics, further shape lipidomic diversity across populations (Fig. 6). Investigating how these factors intersect and impact lipidomic studies is paramount for elucidating the underlying mechanisms of lipid metabolism, identifying biomarkers, and informing personalized approaches to health and disease management. The following sub-sections set the stage for exploring the intricate relationship between intra- and inter-individual factors and their implications on lipidomic studies.

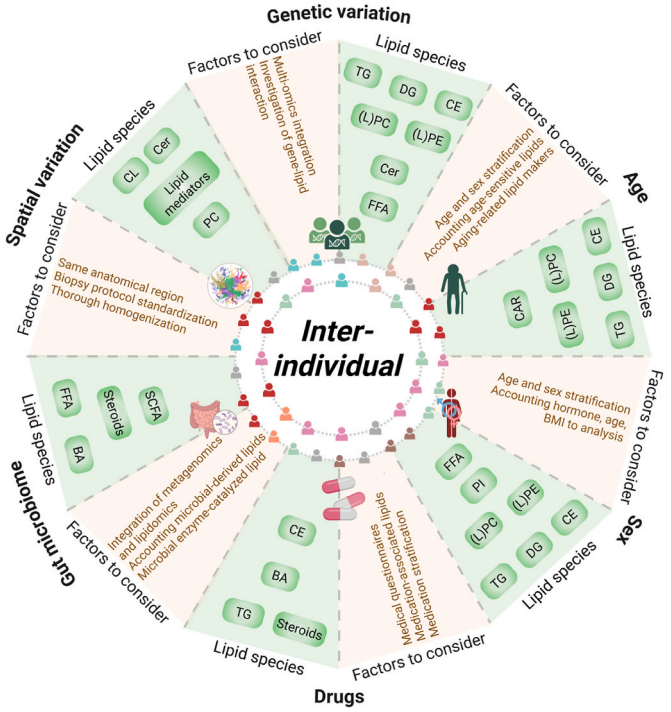

Fig. 5. An overview of factors influencing inter-individual lipidome variations and the lipid species associated with these factors.

5.1. Impact of intra-individual factors on inter-individual variability

As discussed in detail in previous sections, intra-individual factors play a crucial role in shaping inter-individual variability in the lipidome. These factors encompass a range of biological processes and environmental influences that affect lipid metabolism within an individual over time and ultimately contribute to inter-individual variation. Chen et al. have recently elucidated the influence of the microbiome, diet, and genetics on the variation observed in the human plasma metabolome across individuals. Their findings open avenues for designing dietary interventions aimed at modulating the gut microbiome to foster a healthier metabolome [277]. Epigenetic modifications can regulate gene expression patterns related to lipid metabolism, further influencing lipidomic profiles [192]. Hormonal fluctuations, metabolic conditions, and dietary intake can also dynamically impact lipid metabolism within individuals, resulting in temporal variability in lipidomic profiles and contributing to inter-individual variation [169]. Such variation requires specific consideration in study design to address the impact of both intra- and inter-individual variation. This includes strategies for longitudinal data collection to capture temporal fluctuations in lipidomic profiles within individuals, as well as the inclusion of diverse study populations to account for genetic, demographic, and lifestyle-related variability.

5.2. How these factors affect lipidomics-based study

A primary goal of population level lipidomic studies is to capture inter-individual variation in the lipidome and relate this to a range of exposures and outcomes to better understand how we can influence the lipidome (lipid metabolism) and how dysregulation of the same lipid metabolism can lead to adverse outcomes such as cardiovascular disease, metabolic disorders, cancer, or inflammatory conditions [328]. Integration of exposure data, lipidomic profiles, and disease outcomes

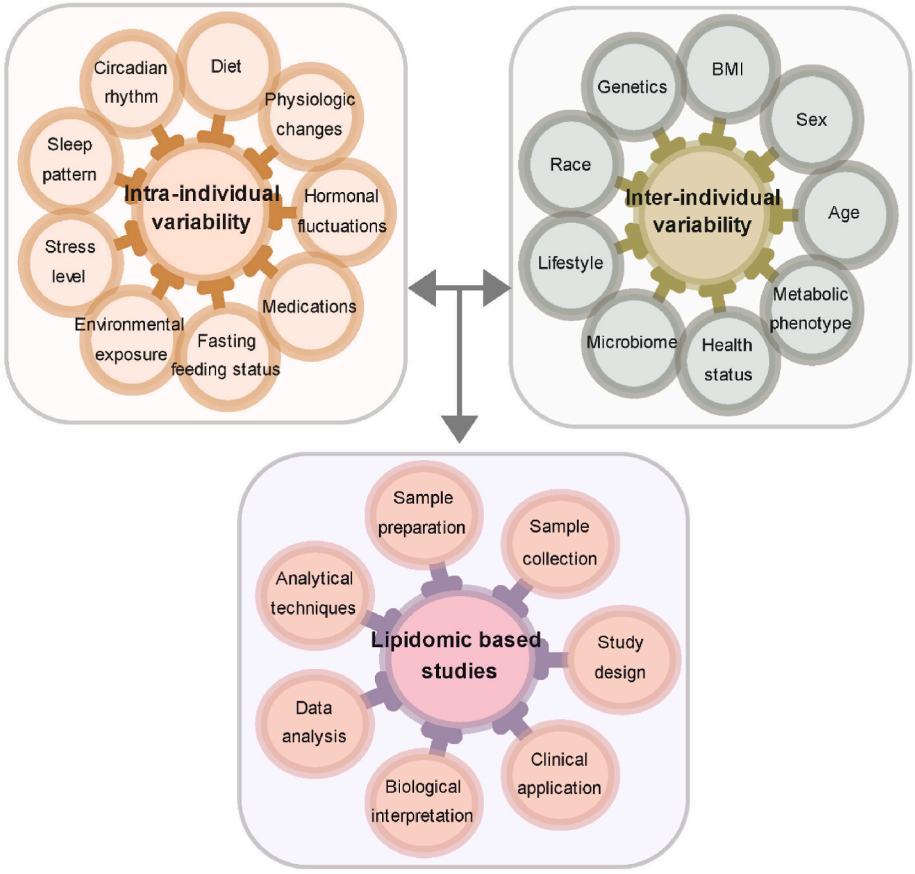

Fig. 6. An overview of the impact of intra-individual variations on inter-individual variability, and how these orchestrate to influence the different stages in lipidome based studies.

allows for the elucidation of the role of lipid variation in disease etiology and pathophysiology, with findings potentially informing clinical practice, public health interventions, and personalized medicine strategies aimed at disease prevention, diagnosis, treatment, or management.

In analyzing associations between lipidomic profiles and various exposures and disease outcomes, several statistical methods are commonly employed. Logistic regression models are frequently used when investigating binary outcomes, such as disease presence or absence, to assess the likelihood of an outcome occurring based on lipidomic variables and other covariates. Linear regression models are utilized when examining continuous outcomes, such as biomarker levels or clinical measures, to quantify the relationship between lipidomic variables and the outcome of interest. Additionally, mediation analyses are conducted to explore potential pathways through which lipidomic profiles may influence disease outcomes, often involving intermediate variables or biomarkers [329].

Intra-individual factors can introduce bias to epidemiological studies in several ways. Temporal variability in lipidomic profiles within an individual due to factors such as diet, medication use, hormonal fluctuations, and physiological changes can confound the association of lipidomic data with longitudinal outcomes [330]. Fasting status can also introduce variance into cross sectional studies [331,332] and so we often collect biological samples in a manner to minimize such intra-individual variation (*i.e.*, fasting plasma collected in the morning). In conventional epidemiological studies, a single sampling is commonly used as an estimate or surrogate for an individual's usual level after controlling several factors, such as fasting condition and common exposures (*e.g.*, smoking, alcohol consumption). This could be a valid option as a number of studies have shown good reproducibility of serum/plasma metabolite measurements [333–336] and a highly conserved and personalized metabolome over time [337]. However, the limitation of using a single sampling as an estimate or surrogate for an individual's usual level in epidemiological studies not only lies in the potential for temporal variability but also measurement error and other dietary and lifestyle changes over time. Lipid metabolism is particularly responsive to changes in diet/lifestyle, and studies have pointed out greater variability over time in lipid metabolic pathways relative to carbohydrate metabolism [338]. Thus, longitudinal sampling and data collection allows for the characterization of temporal fluctuations in lipidomic profiles within individuals, thereby enhancing the reliability of study results. However, this comes at a cost of increased sample numbers and time, in contrast to diverse study populations, that capture genetic and demographic variability as a snapshot in time. Ultimately the study design adopted will depend on the specific questions being addressed and resources available.

Randomized intervention studies present a robust strategy to mitigate the impacts of both inter- and intra-individual variations commonly observed in epidemiological, lipidomic studies. These studies employ controlled interventions to standardize and manipulate factors influencing lipidomic profiles, thereby diminishing confounding effects and augmenting the reliability of study outcomes. For instance, in dietary intervention trials, participants may receive prescribed diets or nutritional supplements for a specified duration, enabling researchers to evaluate the effects of these interventions on lipidomic profiles while controlling for variables such as age, sex, and lifestyle [339].

In contrast to population-based studies, intervention studies typically aim to capture intra-individual variations following interventions such as dietary changes, lifestyle modifications, or medication usage. In such scenarios, inter-individual variation can confound analyses. Age

emerges as a significant contributor to inter-individual variation in metabolic profiles, including lipid levels [169,205,340,341]. Consequently, these studies often focus on homogeneous cohorts, such as males over 45 years with a BMI exceeding 30. While this approach may reduce inter-individual variation and enhance study power, it also diminishes the generalizability of findings to the broader population. To address this issue, many funding bodies now advocate for the inclusion of sex/gender and ethnic diversity in such intervention studies, albeit this may lead to reduced power and/or necessitate larger studies. In such studies, adjustment for confounding variables and stratified analyses can help minimize bias and improve accuracy of association estimates between lipidomic profiles and health outcomes. Employing statistical methods, such as multivariate analysis or mixed-effects models, to adjust for inter-individual and intra-individual variations can help control for confounding factors and improve the accuracy of study findings. Stratifying study populations based on relevant factors, such as age, sex, or metabolic status, can also help account for heterogeneity and identify subgroup-specific associations between lipidomic profiles and outcomes of interest. However, this comes at a cost of reduced power and does not test the significance of any difference between groups. Consequently, interaction analyses are often considered in these situations to maintain power, address the heterogeneity in the study group and define significant differences between groups. Overall, a comprehensive approach integrating various statistical techniques and profiling strategies, and adjustment for confounders, is essential for robustly analyzing associations between lipidomic profiles and relevant factors in human studies. Finally, validation of findings in independent cohorts or populations should be considered and wherever possible incorporated into the study design.

While we recognize many factors that contribute to intra-individual and inter-individual variation in the lipidome, not all factors are obvious. The existence of heterogeneous metabolic (lipidomic) phenotypes with differing cardiometabolic risk profiles has been demonstrated and captured by a metric termed ‘metabolic BMI’ (mBMI), which is derived using lipidomic data [342]. mBMI highlights the presence of unique metabolic health phenotypes that are independent of variations in factors such as BMI, age, and sex. Notably, healthy lifestyle and diet were found to be associated with mBMI, suggesting the potential to modify metabolic health with lifestyle interventions [342,343]. The utilization of mBMI as a metric underscores the importance of considering metabolic factors beyond traditional measures, providing insight into individualized risk assessment and potential interventions targeting metabolic health. Indeed, understanding variations in lipid metabolism and or lipidomic profiles driven by distinct metabolic phenotypes may help improve risk assessment, disease diagnosis, and personalized treatment approaches in clinical practice.

Gene-environment interactions introduce complexity by modulating lipid metabolism pathways, leading to variability in lipidomic profiles among individuals with different genetic backgrounds and environmental exposures [185,344] but also influence obesity, diabetes and CVD risk [344], as well as dietary preferences such as energy and micronutrient intakes [345]. Ultimately, a full understanding of these interactions will be essential for defining intra- and inter-individual variation and for identifying biomarkers, elucidating disease mechanisms, and developing targeted therapies.

5.3. *Interpreting intra- and inter-individual variation in clinical lipidomics*

Both internal (*e.g.*, genetics, metabolism, circadian rhythms) and external factors (*e.g.*, diet, environment, lifestyle) can profoundly impact inter- and inter-individual variation in lipidomic profiles. Currently, there is no universally accepted thresholds defining what constitutes an “acceptable” degree of biological fluctuation in lipidomics for meaningful interpretation. Quantitative metrics such as coefficients of variation (CVs) and intraclass correlation coefficients (ICCs) are commonly used to assess lipidomic variability. Under quality-controlled conditions, intra-individual variability typically presents with CVs below 20 %, as reported in several previous studies, while inter-individual variability is often greater, with CVs ranging from 20 % to 50 %, reflecting normal biological diversity across populations [3,346]. For longitudinal study designs or biomarker discovery, low intra-individual variability is particularly desirable. ICCs serve as a valuable tool to assess temporal stability of lipid species, where values above 0.5 are considered indicative of moderate to good within-individual consistency across repeated measurements [3,346,347]. However, ICCs can differ considerably across lipid species, highlighting the need for lipid-specific thresholds, an area still lacking standardization in lipidomics [169].

To support harmonization and reproducibility in clinical lipidomics, several studies aimed to generate reference values for lipid species using certified standard reference materials [348,349]. For instance, consensus values for four clinically relevant ceramides in NIST SRM 1950 plasma exhibit inter-laboratory CVs below 14 % when isotope-labeled internal standards are used, offering robust benchmarks for method validation and cross-platform comparison. In practice, data filtering protocols often recommend excluding lipid species with CVs greater than 30 % in quality control (QC) samples, with a preference for CVs below 20 % to ensure data robustness [169]. Importantly, lipid class-specific CV thresholds are increasingly utilized. For example, sphingomyelins and phosphatidylcholines typically show lower CVs (<15 %) due to their structural stability, whereas triacylglycerols, particularly those with diverse acyl chain compositions and degrees of saturation, often exhibit wider range of CVs [350].

Discriminating biologically meaningful lipidomic signals from normal physiological variation requires careful study design, analytical rigor, and appropriate statistical processing. In longitudinal studies, it is recommended to report ICCs of individual lipid species and prioritize analysis of those with ICCs >0.5, indicating temporal stability [346, 351]. For lipid species with inherently high intra-individual variability, such as specific triacylglycerols, sufficiently large sample sizes are required in epidemiological studies to detect significant associations despite noise [3]. Biological context is also critical when interpreting lipidomic data. Certain lipid classes, such as sex-dependent sphingolipids or acylcarnitines, can display pronounced biological variation [205]. Adjusting for covariates such as sex, age, BMI, and dietary intake, or conducting stratified analyses, can improve robustness of results. Additionally, class-specific data normalization may help reduce inter-sample variability and enhance the robustness of statistical comparisons [9].

A deeper understanding of lipid structure-function relationships further aids interpretation. For instance, lipid species containing odd-chain fatty acids, although detectable, are rare in endogenous human metabolism and may be more reflective of dietary or microbial influences [352,353]. Similarly, isomeric lipids, such as positional or geometric isomers of phosphatidylcholines (PCs) and triacylglycerols (TGs), can have distinct biological functions despite identical molecular formulas. These isomers often co-elute in conventional LC-MS workflows due to similar retention times and mass spectra, complicating structural resolution. To overcome this, specialized analytical techniques including ozone-induced dissociation (OzID), ultraviolet photodissociation (UVPD), and ion mobility spectrometry (IMS), in combination with targeted MS/MS workflows, are increasingly employed to improve structural annotation and biological insight [354]. Importantly, lipid quantification at the sum-composition level (*e.g.*, PC (34:2)) without specification of sn-positions or double bond locations, may obscure functionally distinct isomers and dilute true biological signals [355,356].

6. Conclusions

In addition to analytical variations, inter and intra-individual variations, if not adequately addressed, can significantly attenuate the power of clinical and epidemiological studies involving lipidomics.

These variations introduce complexities and uncertainties that can obscure true associations between variables of interest and disease outcomes. Failure to properly adjust for these variations may lead to biased estimates and reduced statistical power, thereby compromising the reliability and validity of study findings. Therefore, it is imperative to employ robust methods to account for inter- and intra-individual variations to ensure the accuracy and integrity of epidemiological research. Further research is needed to more fully understand the intra- and inter-individual variation in the lipidome and the impact of various internal and external factors. This knowledge will facilitate study design leading to improved interpretability and reliability of the research results.

CRediT authorship contribution statement

Anh Hoang Nguyen: Writing – review & editing, Writing – original draft, Visualization. **Habtamu B. Beyene:** Writing – review & editing, Writing – original draft, Visualization. **Gabriele Mocciaro:** Writing – review & editing. **Lisa Hahnefeld:** Writing – review & editing, Visualization. **Santosh Lamichhane:** Writing – review & editing. **Mikael Fabritius:** Writing – review & editing. **Henri Avela:** Writing – review & editing. **Yuqin Wang:** Writing – review & editing. **Alex M. Dickens:** Writing – review & editing. **Robert Gurke:** Writing – review & editing. **Baoru Yang:** Writing – review & editing. **William J. Griffiths:** Writing – review & editing. **Tuulia Hyötyläinen:** Writing – review & editing. **Peter J. Meikle:** Writing – review & editing. **Matej Orešič:** Writing – review & editing, Writing – original draft, Conceptualization.

Conflict of interests

The author declares that they have no conflicts of interest with the contents of this article.

Declaration of competing 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.

Acknowledgments

This publication is based upon work from COST Action EpiLipidNET, Pan-European Network in Lipidomics and Epilipidomics (CA19105; https://www.epilipid.net), supported by COST (European Cooperation in Science and Technology). We would like to thank Samuel Rischke for creating Fig. 1. Figures were also created with Biorender.

Data availability

No data was used for the research described in the article.

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