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Review article

Advances in clinical application of lipidomics in healthy ageing and healthy longevity medicine

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ABSTRACT

It is imperative to optimise health and healthspan across the lifespan. The accumulation of reactive oxygen species (ROS) has been implicated in the hallmarks of ageing and inhibiting ROS production can potentially delay ageing whilst increasing healthy longevity. Lipids and lipid mediators (derivatives of lipids) are becoming increasingly recognized as central molecule in tissue and cellular function and are susceptible to peroxidation; hence linked with ageing. Lipid classes implicated in the ageing process include sterols, glycerophospholipids, sphingolipids and the oxidation products of polyunsaturated fatty acids but these are not yet translated into the clinic. Further mechanistic studies are required for the understanding of lipid classes in the ageing process. Lipidomics, the system level characterisation of lipid species with respect to metabolism and function, might provide a significant and useful biological age profiling tool through longitudinal studies. Lipid profiles in different ages among healthy individuals could be harnessed as lipid biomarkers of healthy ageing with potential integration for the development of lipid-based ageing clock (lipid clock). The potential of a lipid clock includes the prediction of future morbidity or mortality, which will promote precision and healthy longevity medicine.

1. Introduction

Ageing leads to loss of physical function and chronic diseases (Kudryashova et al., 2020) and therewith a reduced quality of life (Guan et al., 2022). Extending healthspan, the period of life free from chronic diseases and disability, has become a priority for many countries due to the medical and societal impacts of diseases (Carrard et al., 2021). Biological age, an individual's age defined by the level of age-dependent biological changes, is a more accurate predictor of the ageing process and mortality compared with chronological age (Moqri et al., 2023). Biological markers of ageing include DNA methylation, transcriptomics-, proteomics- and metabolomics-based predictors (Erema et al., 2022; Simpson and Chandra, 2021). Lipidomics, a large-scale analysis of lipid species (Zullig et al., 2020) is a branch of metabolomics. Specie -specific lipidome has been linked with longevity in animal kingdom but not in human longevity (Pradas et al., 2022). Lipidomics has been suggested to be a 'turning point' in understanding the processes involved in ageing; mass spectrometry techniques are advancing in this area and promising for translational purposes (Sol et al., 2023). This review provides insight into the potential clinical application of lipidomics in healthy ageing and healthy longevity medicine.

1.1. Lipids and oxidative stress

Lipids have diverse functions, such as cell membrane stability, energy storage, intercellular signalling, control of cell proliferation, metabolism, inflammation, and apoptosis (Yoon et al., 2022). Lipids are

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important players in the ageing process and disruption to major lipid pathways, lipid accumulation, peroxidation and impaired fatty acid (FA) utilization in organs are causal to many age-related diseases (Mir et al., 2022; Tan et al., 2022; Yoon et al., 2022).

Oxidative stress is a main cause of macromolecular damage due to the accumulation of reactive oxygen species (ROS) and therewith accelerated ageing (Sies and Jones, 2020). Of all macromolecules, oxidative damage to lipids is important and emerging in biomedical research, due to the notable biological activities of lipid peroxidation products (Liebisch et al., 2020). Oxidative stress alters the structural features of lipids which compromises the endothelial membrane resulting in changes in biological function and diseases (Danielli et al., 2023). The accumulation of lipid peroxides, if left uncontrolled or a reduced antioxidant environment leads to inflammation and ferroptosis (a regulated iron-dependent cell death) (Danielli et al., 2023; von Krusenstiern et al., 2023). However, the underlying mechanisms of lipid- and oxidised lipid-mediated control of membrane composition and cell fate are yet to be uncovered; the employment of multidisciplinary synergistic approach has been suggested (Egea et al., 2017; von Krusenstiern et al., 2023).

1.2. Deregulated lipid metabolism and the hallmarks of ageing

Deregulated lipid metabolism alters cell physiology, with characteristic accumulation of exosome rich in oxidised lipids, accumulation of senescence associated secretory phenotype, alteration of membrane fluidity, increased lipid uptake and increased intracellular lipid droplets (Sharma and Diwan, 2023). Altered levels of cholesterol has also been reported to be capable of inhibiting Na+,K+-ATPase activity (Garcia et al., 2019). Twelve hallmarks of ageing have been described (Lopez-Otin et al., 2023); ten of which are directly linked with lipid metabolism and oxidation as highlighted in Fig. 1.

Telomere attrition, which is the shortening of the telomere length has been linked to dyslipidemia and implicated in age-related diseases (Lorenzo et al., 2023; Subedi et al., 2023). Epigenetic alterations, including histone modification and chromatin remodeling has been reported to be linked with dysfunctional lipid metabolism (Gomez-Alonso et al., 2021; Li et al., 2022). During autophagy, molecules are engulfed in lipid vesicles and transported to lysosomes for degradation. Hence, autophagy is key for cellular homeostasis. Disabled macroautophagy, has been linked to dysfunctional lipid signalling and this affects cellular function (Soto-Avellaneda and Morrison, 2020). Cellular lipid processes including lipid synthesis, degradation and modification have been linked to the relay of nutritional information and fatty acid oxidation is associated with deregulated nutrient-sensing pathways such as insulin-like growth factor1 (IGF-1), signaling mammalian target of rapamycin (mTOR), 5' adenosine monophosphate-activated protein kinase (AMPK), insulin and sirtuin 1 (SIRT1) pathways (Flores and Gao, 2023; Lorenzo et al., 2023). Mitochondrial dysfunction, another hallmark of ageing has been reported to be linked to impaired lipid oxidation and has been implicated in neurodegenerative diseases (Angelova et al., 2021; von Krusenstiern et al., 2023). Cellular senescence, a state of cellular growth arrest has been linked to disruption in lipid homeostasis that affects the physiological state of cells. Some lipids have been reported to be capable of contributing to low-grade inflammation associated with senescence secretory phenotype and some proteins that regulates senescence have been associated with lipid metabolism (Hamsanathan and Gurkar, 2022; Lorenzo et al., 2023). Lipid metabolism impacts stem cell behaviour (Senos Demarco et al., 2020). Stem cell self-renewing and/ or differentiating capability is compromised during ageing and stem cell exhaustion, a hallmark of ageing has been linked with deregulation in membrane lipid homeostasis and fatty acid oxidation (Clemot et al., 2020; Senos Demarco et al., 2020). Lipids are important in cell signalling and implicated in altered intercellular communication (Galkina et al., 2023; Wang et al., 2020). In addition to these, lipid metabolism and especially lipid oxidation is involved in inflammatory and insulin-signalling pathways associated with chronic inflammation (Casado et al., 2023). Dysbiosis is a disruption to the

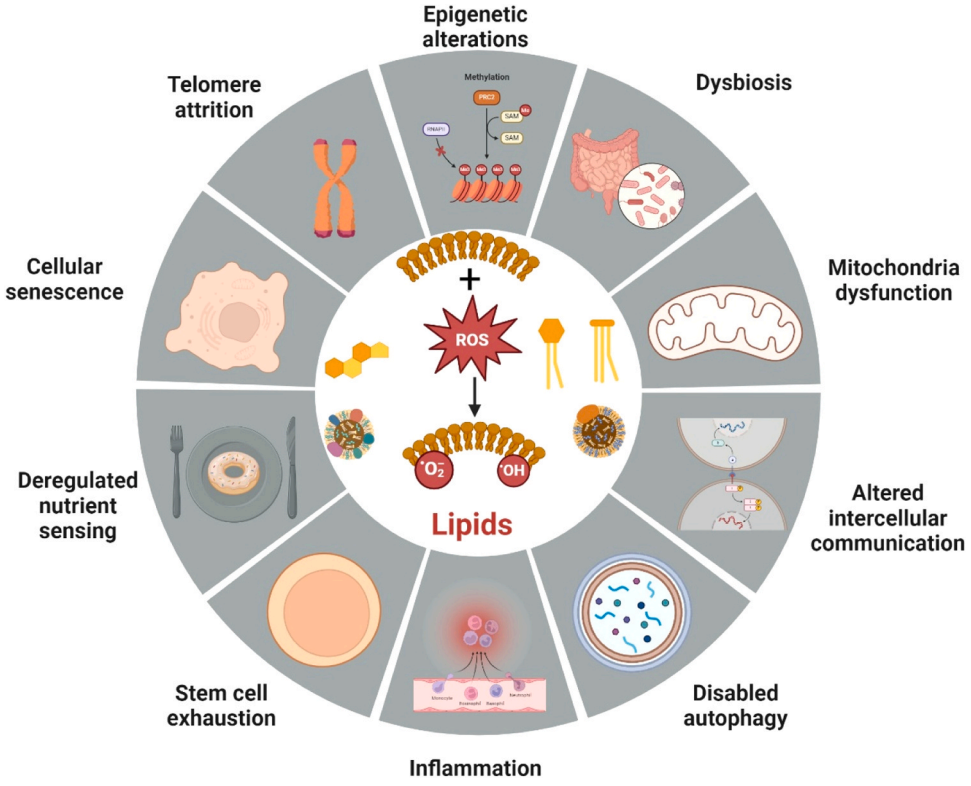

Fig. 1. The hallmarks of ageing associated with deregulated lipid metabolism and lipid peroxidation. Hallmarks and style are based on Lopez-Otin et al.(Lopez-Otin et al., 2023) *(Illustration created with BioRender.com)*.

microbiome. The gut microbiota-produced lipids enter the circulatory system to control several phenotypic functions and a disruption to this is associated with ageing and metabolic disorders (Carneiro et al., 2022; Egea et al., 2017).

2. Healthy longevity and lipidomic opportunities for clinical translation

Healthy longevity medicine aims to optimize health by targeting the aging process across the lifespan, by identifying biological age and targeting ageing mechanism to extend healthspan (Bischof et al., 2022). Lipidomics has been instrumental in lipid biomarker development, drug development and validation (Tan et al., 2022). However, lipidomics is not in clinical use in healthy longevity medicine. Novel roles of lipids in modulating organismal ageing are being identified (Sharma and Diwan, 2023). Fig. 2 shows the lipid classes that are in clinical use and lipids that still have lipidomic potentials for translation to the clinic.

Variation in structure, contributes to the functional diversity seen in lipids (Zhang et al., 2022). A typical lipid profile for clinical use includes plasma measurements of cholesterol and triglyceride (TG) and a more detailed profile might measure the concentrations of major lipoproteins (Tan et al., 2022). However, lipid profiles could be harnessed to more than these.

Lipid classes identified for clinical translation in healthy longevity medicine includes glycerophospholipid, sphingolipids, their derivatives as well as oxidised / modified lipids. It is important to investigate these groups for better understanding of their importance and to establish protocols for accurate identification and quantification of lipid species within these groups. **Glycerophospholipids** include phospholipids (phosphatidylcholine, phosphatidylserine, phosphatidylinositol etc.) which are important constituents of the cell membrane lipid bilayer (Pradas et al., 2022; Sol et al., 2023); ether lipids (plasmenyls - with enyl /ether bonds and plasmanyl - with alkyl /ether bonds) which play a role in antioxidant defence system (Jove et al., 2023) and cardiolipins which are mitochondrial phospholipids, essential for mitochondrial function and dynamics, in particular oxidative phosphorylation and apoptosis (Ji et al., 2022; Paradies et al., 2019). **Sphingolipids** are ubiquitous, have diverse roles in biological processes and are structural component of the plasma membrane (Lessi et al., 2020; Sol et al., 2023). Ceramides (CER) and sphingomyelin (SM) are the most common sphingolipids and have been reported to be potential biomarkers of longevity (Pradas et al., 2022).

Lipid peroxidation involves the addition of oxygen to lipid structure and subsequent fragmentation close to the site of oxidative damage which often result to the formation of reactive ketones, aldehydes as well as α, β-unsaturated compounds that could form covalent adducts with DNA, proteins or nucleophilic headgroups of phospholipids (Chatfield et al., 2022; Tan et al., 2022) but these have not been investigated in longevity medicine. **Oxylipins** are bioactive lipids that could be generated through non-enzymatic and enzymatic oxidation of ω-3 and ω-6 poly unsaturated fatty acid (PUFA) (Biagini et al., 2022; Cruciani et al., 2019). Abnormal oxylipin signalling has been linked to cardiovascular diseases, including hyperlipidemia, hypertension, thrombosis, haemostasis, diabetes and COVID-19 (Biagini et al., 2022; Pawelzik et al., 2023). Examples of oxylipins are eicosanoids (leukotrienes, eoxins, lipoxins, prostaglandins prostacyclin, thromboxanes and resolvins (Gonzalez-Covarrubias, 2013). **Oxidised lipids** including oxidised triglycerides, oxidised ceramides, oxysterols and oxidised phospholipids (OxPLs) are produced enzymatically or non-enzymatically and have been implicated in different age related diseases; (Ademowo et al., 2020; Dakterzada et al., 2023; Leyane et al., 2022; Villase et al., 2021). OxPLs are produced as a result of different types of oxidative stress and do not accumulate under normal conditions in vivo as they are rapidly removed from normal cells / tissues (Mauerhofer et al., 2016). OxPLs have pleiotropic effects as they could exhibit multiple phenotypic expressions (Bochkov et al., 2016); hence could have protective or deleterious effects on tissues depending on their structure and concentration (Mauerhofer et al., 2016).

3. Emerging lipid biomarkers of healthy longevity

Lipid profiles are specific to age and gender **(**Fig. 3 **and** Fig. 4**)** and targeting lipids could contribute to healthspan extension strategies and inform precision medicine in order to manage the ageing population (Almeida et al., 2021; Beyene et al., 2020; Carrard et al., 2021; Sol et al., 2023). Changes in the plasma metabolome induced by ageing includes changes in the bioenergetics that reflects a decrease in mitochondrial β-oxidation, an accumulation of acylcarnitines and unsaturated FA which could be the cause of the increased oxidative damage and inflammation observed during ageing (Sol et al., 2023). A lipid profile resistant to oxidative damage has been linked to lifespan in animals (Pradas et al., 2019).

Lipid species that represent healthy profiles such as ether PC, tend to decrease with age (Fig. 3**)** but the results are inconclusive in humans

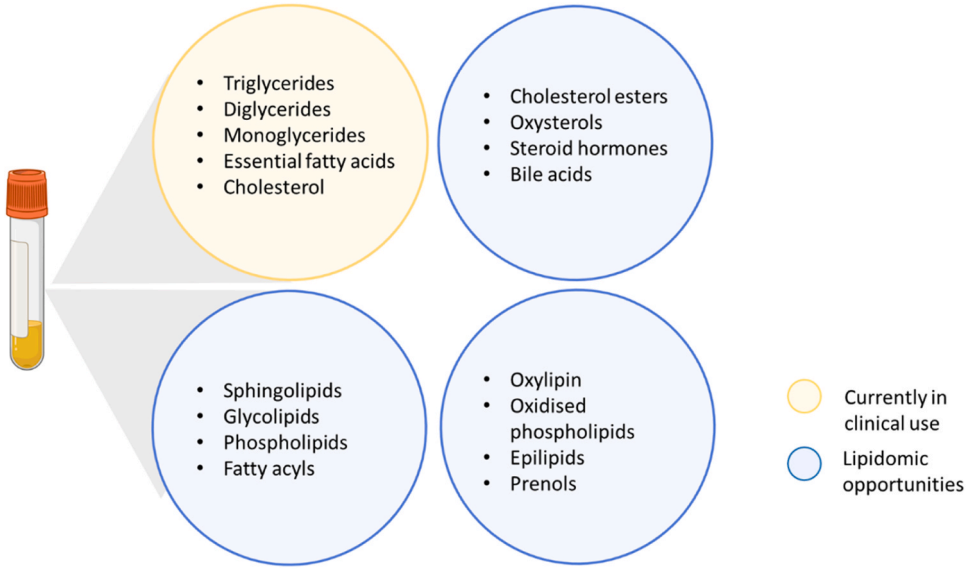

Fig. 2. Classification of lipids based on clinical utilisation and / or lipidomic potential. *(Illustration created with BioRender.com).*

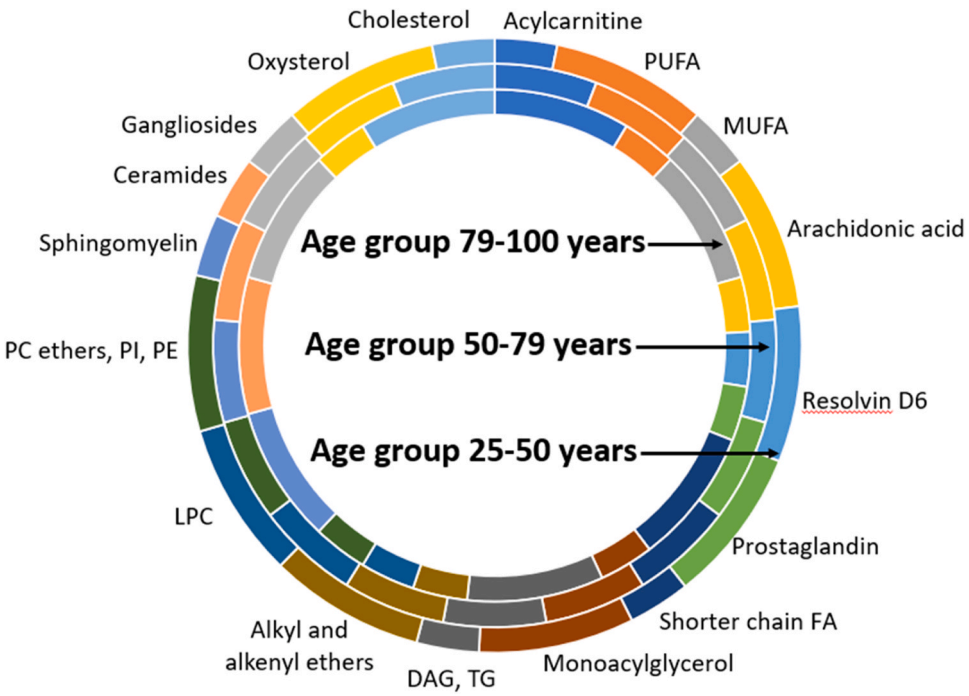

Fig. 3. Relative abundance of lipids in different age groups of healthy individuals. Age groups 25–50, 50–79 and 79–100 years showed proportionate levels of lipid classes. The sizes of the bars depict the abundance of respective lipids in each age category.

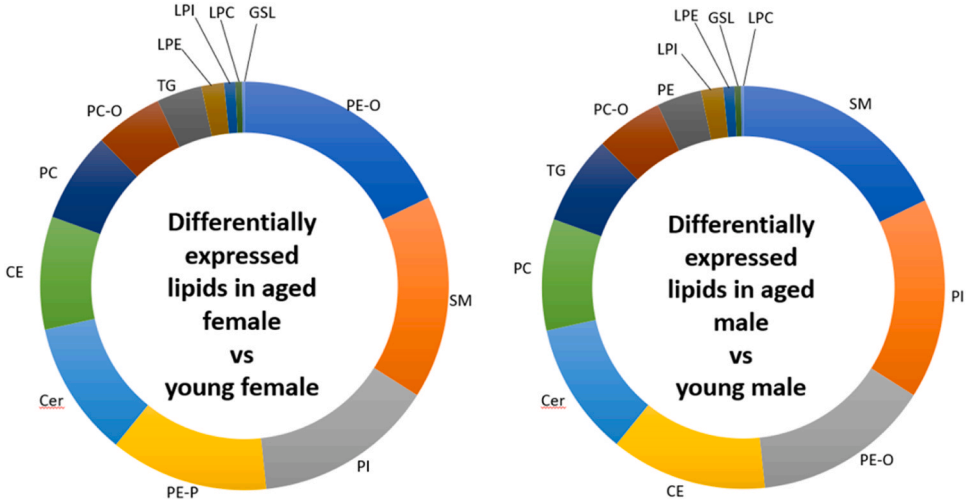

Fig. 4. Most abundant gender related differential lipid profile with age in healthy individuals. The sizes of the bars depict the abundance of respective lipids in each age category. DG: diglycerides, TG: triglycerides, CE: cholesterol esters, PI: glycerophosphoinositols, LPC: lyso-glycerophosphocholines, SM: sphingomyelins, PC: glycerophosphocholines, PC-O: alkyl-glycerophosphocholines, LPE: lyso-glycerophosphoethanolamines, LPE-O:lyso-alkyl-glycerophosphoethanolamines, PE: glycerophospoethanolamines, PE-O: alkyl-glycerophosphoethanolamines, PE-P: alkenyl-glycerophosphoethanolamines, LPI: lyso-glycerophosphoinositols, Cer: ceramides, GSL: glycosphingolipids, MUFA: monounsaturated fatty acid, PUFA: polyunsaturated fatty acids, HbA1c = glycated haemoglobin, GSL: glycosphingolipids.

(Pradas et al., 2019). While lipid species that are associated with age related diseases, such as TG tend to increase with age (Kelly et al., 2015). Specific lipid examples and their trend in ageing are shown in Fig. 3. The observation of the role of ether PC could be linked in parts to its antioxidant capacity. SM on the other hand tend to increase with age and are strongly gender-biased (Carrard et al., 2021; Pradas et al., 2022; Slade et al., 2021; Sol et al., 2023). Comparison in lipid profiles of young adults (20–50 years), middle age, (50–79 years) and old age (79–100 years) healthy individuals (Fig. 3) showed variances in their CER, diglycerides, (DG), TG, phospholipids (PL), SM, cholesterol esters (CE), ganglioside (GM), ether -PC (O-PC) and acylcarnitines levels. (Gonzalez-Covarrubias, 2013; Kelly et al., 2015; Pradas et al., 2022). Higher levels of Cer (d18:1/20:0), Cer (d18:1/23:0), Cer (40:2), cholesterol, and phosphatidylcholine (PC) (14:0/20:4) have been reported in frail older adults compared with robust older adults at hospital admission (Ramirez-Velez et al., 2022)'.

Studies that compared lipid profiles in centenarians with adults, reported higher GM3 (d18:1/24:1), GM3 (d18:2/24:1), Cer (d18:1/24:1) and lower Cer(d16:1/24:0), Cer (d18:0/22:0) and Cer (d18:0/24:0) while GM (d18:1 /16:1), Cer (d18:0/24:0), SM (44:3), (SM (d18:0/22:0), SM (d18:1/22:0), SM (d16:1/24:0) were lower in centenarians (Pradas et al., 2022).

As these are cross sectional studies, there is a need to conduct these investigations longitudinally. Higher levels of monounsaturated fatty

acid (MUFA) compared with PUFA was observed in individuals from older age groups (Ali et al., 2023). The ratio of MUFA to PUFA has been implicated in the regulation of lipid metabolism and lipid oxidation (Mauerhofer et al., 2016). As these are results from healthy groups, low levels of PUFA, low levels of oxidised sterols and high level of MUFA is associated with longevity (group 79–100) (Almeida et al., 2021).

Age and gender specific lipids were measured in clinically healthy human serum: 18–87 years (Slade et al., 2021); 50–98 years (Sol et al., 2023) and those in their 20 s and 70 s (Carrard et al., 2021). Gender specific lipid profiles are shown in Fig. 4**.** While Table 1 shows the lipid species that are cardiometabolically favourable (linked with advanced age without any excluding medical conditions) or deleterious (linked with age-related metabolic imbalance) in both genders (Carrard et al., 2021). SM is the most discriminating lipid between aged and young males while alkyl-glycerophosphoethanolamines are the most discriminating lipid between aged and young females. Interestingly, SM, PI, PE-O, CE. PC and Cer are highly discriminating between aged and young in both genders **(**Fig. 4**).** High SM and Cer as well as high MUFA/PUFA ratio are favourable for longevity in both male and female (Table 1).

Increase in the lipid species from Table 1 has been found to contribute to the attribute on their respective columns (Carrard et al., 2021).

Although we have identified different lipid species for healthy longevity, the mechanisms are not clear and there is a knowledge gap in the precise characterisation of these lipid biomarkers. Lipid markers could be site- or pathology-specific (von Krusenstiern et al., 2023) and precise lipid phenotyping has the potential to capture metabolic individuality (Carrard et al., 2021). There is a need to investigate cell, tissue and /or organ specificity of these biomarkers. Site specific biomarkers have a potential for the development of novel, more precise and informative health-risk profiles beyond genetics which will be important to guide the targeting of preventive interventions. Mass spectrometry is promising in achieving this.

4. Clinical translations of lipids and oxidised lipids in healthy longevity medicine

To date, lipidomic studies on healthy ageing and human healthy longevity are limited and results inconclusive. Challenges in comparing biomarker results across decades includes the changes in diet, physical activities, classification of disease groups, variance in reported data, level of medication in ageing cohort including neuropsychiatric drugs, vitamins, statins and /or anti-hypertensive agents which may affect biomarker levels (Ademowo and Dias, 2022). The use of lipids as biomarkers is therefore complex and needs careful analysis and modelling to find predictive trends. Advances in lipidomics have been leveraged within two research paths including the ability to quantitate lipid flux to understand human physiology and targeted / untargeted analyses of human samples, (blood or tissue) from time points to identify lipidomic patterns (Salvador et al., 2022). These leverage and research applications have been successful in obesity, neurodegenerative diseases, pre-eclampsia, cancer, sepsis, wound healing and cardiovascular diseases (Stephenson et al., 2017).

For effective translation of research findings from bench side to bedside, trials and experiments should be designed by healthy longevity physicians (who are aiming to reduce and predict biological age) (Bischof et al., 2021) and researchers together. Lipid research is recently being recognised as a potential for clinical studies in Healthy Longevity medicine and preliminary results are currently being acquired. The success and time for lipid phenotyping on smaller well clinically defined participants for healthy longevity longitudinal research followed by validation on large sample cohorts and progression to clinical trial cannot be estimated but the research field is emerging and gaining more attention and interest.

Sample profiling to confirm which type of sample is appropriate to answer specific questions is very important. Standardisation of references, patient, and population assay to consider age, gender and ethnicity will also be important for effective translation of research and / or to inform clinical decisions. On the part of the researchers, standardisation, guidelines, controls, optimised methods including specificity and sensitivity are key to accuracy and reproducibility. Guide /choice of informatic tool for lipidomics is also very important (Lipidomics Standards Initiative, 2019; Ni et al., 2023).

Table 1
Summary table for cardiometabolically favourable and deleterious lipids common to aged male and female.

Favourable in both aged male and female	Deleterious in both aged male and female
SM (18:1;2/24:0)	Cer (18:1;2/16:0)
Cer (18:1;2/24:0)	Cer (18:1;2/24:1)
Cer (18:2;2/24:0)	PC (16:0_16:0)
PC (16:0_22:5)	PI (34:1)
PC36:6	PI (36:2)
LPC16:0	PI (36:4)
Low degree of FA unsaturation (Lower MUFA/PUFA)	High degree of FA unsaturation (Higher MUFA/PUFA)
Absence of significantly different PC/PE ratio	Increased / decreased PC/PE ratio

5. Future directions in healthy longevity medicine

To facilitate healthy longevity medicine, there is a need to understand and establish lipid markers that can predict healthy ageing trajectories. Age and gender-dependent lipid metabolism has been highlighted in health and disease, hence gender-stratification will be important for lipid biomarker discovery and development. As ageing is a complex and multifactorial process, the possibility of linking potential lipid biomarkers to a specific hallmark of the ageing (by inducing the hallmark and analysing the potential lipid biomarkers against the control) could also be explored for mechanistic understanding. This approach has been previously suggested (Lopez-Otin et al., 2023) for the development of geroprotective medicines. The evaluation of antioxidants and geroprotectors with avoidance on subjects on lipid-lowering medications is also very important. We suggest longitudinal studies, comparing healthy individuals at young to middle age rather than cross sectional studies and or older individuals. Efforts should be made to identify lipids or modified lipids that serve as biomarkers of aging which are sensitive to change to geroprotective interventions.

Emerging technologies that have been utilised in proteomics such as ex vivo and in vivo Mass Spectrometry Imaging (MSI) (Denti et al., 2022; Ogrinc et al., 2021), and Rapid Evaporative Ionization Mass Spectrometry (REIMS) (Barlow et al., 2021; Davies et al., 2022), bring invaluable information for clinical and biological applications and have potential in lipidomics. Although protein detection and identification ex vivo on tissue sections and in vivo MSI by coupling with SpiderMass technology - an in vivo minimally invasive imaging analysis (Ogrinc et al., 2021; Zirem et al., 2024) have been reported in cancer biomarker discovery, the detection of lipids by these have not been explored in humans. MSI lipid analyses in plants (Lu et al., 2018; Xie et al., 2023) and in animal models (Lam et al., 2022; Ogrinc et al., 2021; Slijkhuis et al., 2024) have been reported as having the potential to broaden the detection range and improve the accuracy of lipidomic analysis which may provide better insights to metabolic processes. MSI has been used for different tissue sections in plants revealing tissue-specific heterogeneity of lipid metabolism (Lu et al., 2018) but the cell/tissue /organ specificity of potential lipid biomarkers of healthy longevity in humans are not yet explored. REIMS has also been used for point of care testing in acute aortic dissection surgeries for the accurate detection of tissue integrity to inform surgical intraoperative decisions (Davies et al., 2022); used in profiling lipids in colorectal lesions for risk stratification and tissue recognition (Mason et al., 2023). REIMS analyses tissue metabolites and

can be applied intraoperatively in real time (Plekhova et al., 2021). These could be explored for translational purposes in longevity medicine.

Emerging mass spectrometry technologies that are promising for the future of lipidomics in healthy longevity medicine include spatial lipidomics which maintain the spatial relationship of those lipid molecules within a complex cellular network (Denti et al., 2022). Spatial lipidomics is capable of mapping lipids within their native spatial context, and spatial lipidomics on formalin-fixed paraffin-embedded (FFPE) tissues may increase the molecular characterization of pathological states, aiding future precision health (Denti et al., 2022; Salvador et al., 2022). However, the application of this in longevity medicine needs careful thoughts for future clinical studies. Confirming and validating potential longevity markers summarised here, in an independent and well-defined cohort using the targeted label free mass spectrometry that has been used as proof of principle could be the next step to explore. It will also be interesting to explore more sophisticated and better translational detection methods for lipids.

Asides from mass spectrometry approaches listed here, there are two computer-based techniques that will significantly influence the future of lipid research, including artificial intelligence (AI), that enables computers to mimic human decision-making process, and machine learning (ML), that utilises automated data analysis and analytical model building (Salvador et al., 2022). Mass spectrometry software have been improved by these techniques through the detection of chromatographic peaks by improvements in noise filtration (Melnikov et al., 2020). In the field of medicine, ML of lipidomic data is proposed to improve the diagnosis of fatty liver disease (Salvador et al., 2022) and this can be explored in longevity medicine in the future.

6. Conclusions

Circulating lipids are distinct according to health status, gender, and age. Molecular phenotyping approaches to stratify health status or define biological age using the potential markers of the ageing process reported here will be crucial in healthy longevity medicine. Understanding the mechanisms of function of the potential markers and their role or association to the hallmarks and pillars of ageing will be instrumental to healthy ageing. It will also be important to continue to explore the potential of epilipidomes (modified lipids) including aspects of reversibility and enzyme interactions.

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CRediT authorship contribution statement

Opeyemi Stella Ademowo: Conceptualization, Writing- Original draft preparation, Writing- Reviewing and Editing. **Markus R Wenk:** Conceptualization, Writing- Reviewing and Editing. **Andrea B Maier:** Conceptualization, Writing- Reviewing and Editing.

Declaration of Competing Interest

None

Data availability

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

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