

Lipids as biomarkers of brain disorders

Ghulam Hussain, Haseeb Anwar, Azhar Rasul, Ali Imran, Muhammad Qasim, Shamaila Zafar, Muhammad Imran, Syed Kashif Shahid Kamran, Nimra Aziz, Aroona Razzaq, Waseem Ahmad, Asghar Shabbir, Javed Iqbal, Shahid Mahmood Baig, Muhammad Ali, Jose-Luis Gonzalez de Aguilar, Tao Sun, Atif Muhammad & Arshadム Muhammad Umair

To cite this article: Ghulam Hussain, Haseeb Anwar, Azhar Rasul, Ali Imran, Muhammad Qasim, Shamaila Zafar, Muhammad Imran, Syed Kashif Shahid Kamran, Nimra Aziz, Aroona Razzaq, Waseem Ahmad, Asghar Shabbir, Javed Iqbal, Shahid Mahmood Baig, Muhammad Ali, Jose-Luis Gonzalez de Aguilar, Tao Sun, Atif Muhammad & Arshadム Muhammad Umair (2019): Lipids as biomarkers of brain disorders, Critical Reviews in Food Science and Nutrition

To link to this article: <https://doi.org/10.1080/10408398.2018.1529653>



Published online: 07 Jan 2019.



Submit your article to this journal



View Crossmark data

REVIEW



Lipids as biomarkers of brain disorders

Ghulam Hussain^a , Haseeb Anwar^a, Azhar Rasul^b , Ali Imran^c, Muhammad Qasim^d, Shamaila Zafar^a, Muhammad Imran^e, Syed Kashif Shahid Kamran^a, Nimra Aziz^a, Aroona Razzaq^a, Waseem Ahmad^a, Asghar Shabbir^f, Javed Iqbal^g, Shahid Mahmood Baig^h, Muhammad Ali^b, Jose-Luis Gonzalez de Aguilar^{i,j}, Tao Sun^k, Atif Muhammad^l, and Arshad Muhammad Umair^m

^aDepartment of Physiology Faculty of Life Sciences, Government College University, Faisalabad, Pakistan; ^bDepartment of Zoology Faculty of Life Sciences, Government College University, Faisalabad, Pakistan; ^cInstitute of Home and Food Sciences, Government College University, Faisalabad, Pakistan; ^dDepartment of Bioinformatics and Biotechnology, Government College University, Faisalabad, Pakistan; ^eUniversity Institute of Diet and Nutritional Sciences, Faculty of Allied Health Sciences, The University of Lahore, Lahore, Pakistan; ^fDepartment of Biosciences, COMSATS Institute of Information Technology, Islamabad, Pakistan; ^gDepartment of Neurology, Allied Hospital, Faisalabad, Pakistan; ^hHuman Molecular Genetics Laboratory, Health Biotechnology Division, National Institute for Biotechnology and Genetic Engineering (NIBGE), PIEAS, Faisalabad, Pakistan; ⁱUniversité de Strasbourg, Strasbourg, France; ^jMécanismes Centraux et Périphériques de la Neurodégénérescence, INSERM, Strasbourg, France; ^kCenter for Precision Medicine, School of Medicine and School of Biomedical Sciences, Huazhong University of Science and Technology, Wuhan, China; ^lDepartment of Clinical Laboratory Sciences, College of Applied Medical Sciences, Jouf University, Sakaka, Saudi Arabia; ^mInstitute of Home & Food Sciences, Government College University, Faisalabad

ABSTRACT

Brain is a central and pivotal organ of human body containing the highest lipids content next to adipose tissue. It works as a monitor for the whole body and needs an adequate supply of energy to maintain its physiological activities. This high demand of energy in the brain is chiefly maintained by the lipids along with its reservoirs. Thus, the lipid metabolism is also an important for the proper development and function of the brain. Being a prominent part of the brain, lipids play a vast number of physiological activities within the brain starting from the structural development, impulse conduction, insulation, neurogenesis, synaptogenesis, myelin sheath formation and finally to act as the signaling molecules. Interestingly, lipids bilayer also maintains the structural integrity for the physiological functions of protein. Thus, in light to all of these activities, lipids and its metabolism can be attributed pivotal for brain health and its activities. Decisively, the impaired/ altered metabolism of lipids and its intermediates puts forward a key step in the progression of different brain ailments including neurodegenerative, neurological and neuropsychiatry disorders. Depending on their associated underlying pathways, they serve as the potential biomarkers of these disorders and are considered as necessary diagnostic tools. The present review discusses the role and level of altered lipids metabolism in brain diseases including neurodegenerative diseases, neurological diseases, and neuropsychiatric diseases. Moreover, the possible mechanisms of altered level of lipids and their metabolites have also been discussed in detail.

KEYWORDS

Lipids metabolism; neurodegenerative disorders; fatty acids; neuropsychiatric disorders; brain injuries

Introduction

Lipids are the biomolecules which are characterized by their poor solubility in water and effective solubility in non-polar organic solvents. The brain is a lipid-rich organ comprising 50–60% lipid constituents of its dry weight (Luchtman and Song 2013). There is a diversified group of fatty substances which serves as the energy reservoir with in the living system (Mubarak, Shaija, and Suchithra 2015). In human lipidome, approximately 100,000 lipids species are found which indicate a greater diversity of lipid species (Shevchenko and Simons 2010). The species of lipids can differ based on their head group configuration, nature and numbers of carbon to carbon bonds, molecular weight, and whole structure. Particularly, the overall lipid structure is determined by

the comparative polarity of head group to tails which are hydrophobic in nature. Moreover, a great diversity occurs in single lipid's specie based on the carbon numbers in fatty acid tails, position and the number of double bonds, and diversity in the head group (Brügger 2014).

There is a variety of lipids families that are involved in the specific and complex physiological functions such as energy storage, cellular transportation, and formation of cell membrane. They act as the signaling molecules (Wong et al. 2017), and also play many structural roles like the trans membrane proteins modulators, including ion channels. The variations in the lipid molecules conformation or composition which surround the ion channels may affect their normal functions (Dart 2010).

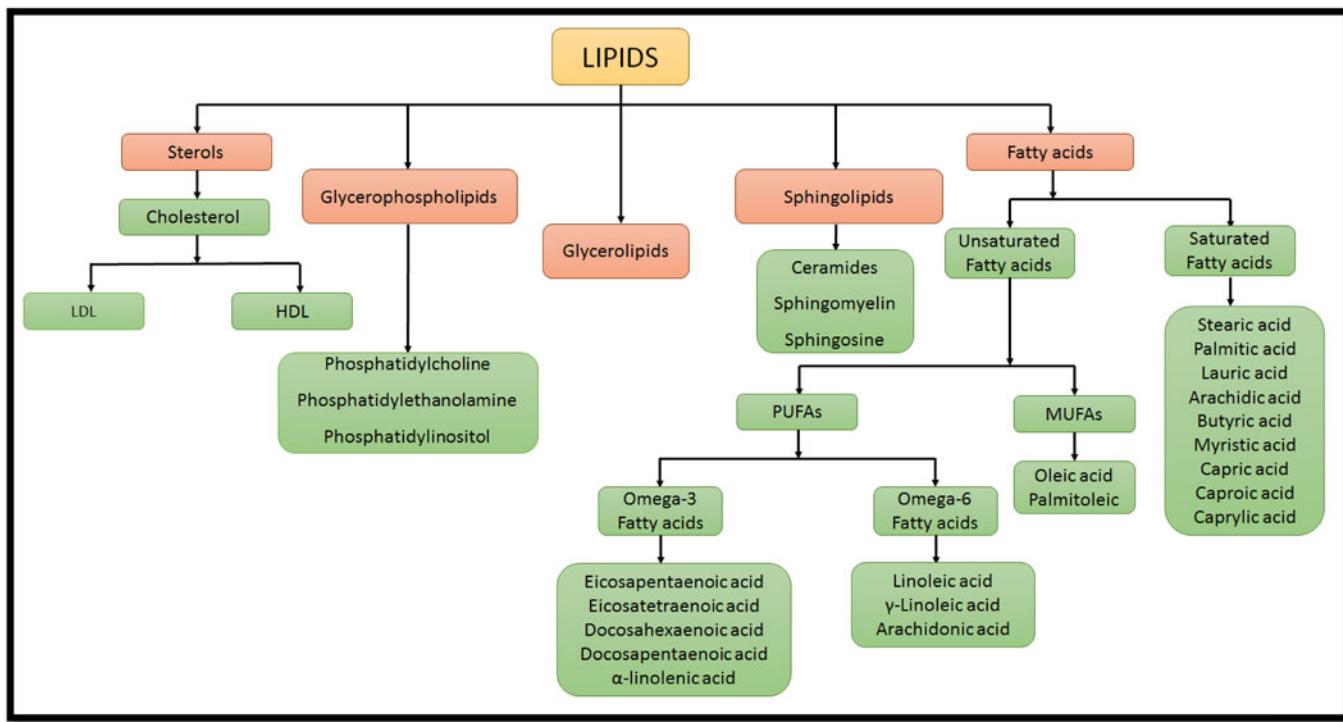


Figure 1. Classification of lipids.

Brain is extremely enriched with lipids where they are important for several key functions such as impulse conduction, insulation, neurogenesis, and synaptogenesis. Lipids are mostly involved in the myelin sheath formation (Cermenati et al. 2015). Any disturbance in the normal functioning of lipids leads to the development of several disorders. In this regard, it is important to notify that brain disorders like neurodegenerative diseases (NDDs), neurological and neuropsychiatric disorders manifest the alteration of lipids metabolism (Schmitt et al. 2014; Hussain, Schmitt, Henriques, et al. 2013; Hussain, Schmitt, Loeffler, et al. 2013). The brain diseases are considerably increasing the rate of morbidity and mortality in the developing as well as developed countries and their prevalence vary from area to area (Hussain, Rasul, et al. 2018; Hussain, Zhang, et al. 2018; Hussain, Rasul, et al. 2017; Hussain, Shahzad, et al. 2017).

This review aims to describe the potential role of different classes of lipids and their metabolism involved in the pathogenesis of brain disorders and diseases. It enlightens the molecular pathways that how lipids can modulate the pathogenesis of different brain disorders and how they can serve as diagnostic biomarkers. Moreover, it provides detailed insights on the up-regulation or down-regulation of lipids involved in the pathology of the diseases. This will build an understanding of researchers regarding the earliest prognosis of diseases. The literature was searched through several e-sites, including Elsevier Science Direct, Scopus, PubMed, Springer Link, and other significant medical journals. The key words used for screening are “Lipids”, “Neurodegenerative Diseases”, “Neurological Diseases”, “Neuropsychiatric Diseases”, and “Brain injuries”. There are several classes of lipids which serve as a hallmark in the development of NDDs.

Classification of lipids

The present era has witnessed a tremendous advancement in research and detailed insights about structure, functions and classes of lipids have been gained by using modern approaches. Due to the better understanding of the multiple biological effects of lipids in pathology, physiology and cell biology, the lipidomics has gained an unparalleled significance in the biological research (Fahy et al. 2011). It is mentioned that lipids perform numerous physiological functions in brain and their metabolic alteration leads to the development of brain disorders (Schmitt et al. 2014). The lipids are a group of fatty substances and their classification is based on head group configuration, molecular weight, presence of carbon to carbon bonds and many other factors. Lipids are classified into five major groups as sterols, glycerophospholipids, glycerolipids, sphingolipids and fatty acids. These groups are further divided into other classes as shown in Fig. 1.

Sterols are the organic molecules which are divided into cholesterol i.e., High-Density Lipoproteins (HDL) and Low-Density Lipoprotein (LDL). Cholesterol is a unique class of lipids containing four hydrocarbon rings in its structure. Both of its classes, LDL and HDL are pivotal to the brain health in regards to the brain function and structural integrity (Orth and Bellosta 2012). Cholesterol is a vital constituent of the neuronal physiology in both early development and adulthood. Thus, its metabolism is needed to be tightly regulated in the brain due to its existence in the Blood-Brain Barrier (BBB) (Zhang and Liu 2015).

Glycerophospholipids are the glycerol-based class of lipids which are the chief component of all biological membranes. These are the prominent molecules involved in the formation of neuronal membranes and, thus, can alter

the functional efficacy to a great extent. They are classified in sub-classes including Phosphatidylcholine, Phosphatidylethanolamine, and Phosphatidylinositol which are also involved in various physiological activities with in the brain at the normal level. Their altered metabolism may also initiate many pathological conditions (Farooqui, Horrocks, and Farooqui 2000).

Glycerolipids are another prominent class of lipids that are synthesized by an assembly of glycerol molecule (mono-glycerides, diglycerides, and triglycerides). The esterification by FAs at the glycerol backbone also exists in their structure. The triglycerides/triacylglycerol are the best form of FA triesters of the glycerol (Ghosh, Strum, and Bell 1997). Three different types of fatty acids esterify each of the 3 hydroxyl groups of glycerol and they serve as the energy stores. The first step in the metabolism of fat is the hydrolysis of triglycerides ester bonds which in turn releases FAs and glycerol from the adipose tissues (Mathews and van Holde 1991).

Sphingolipids contain sphingoid bases and a group of aliphatic amino alcohols which includes sphingosine. In regard to their structural composition, the sphingolipids compound with the functional group of single hydrogen atom is Ceramide but with several other functional groups including phosphocholine results in the formation of Sphingomyelin (SM). They are pivotal for the functional maintenance of the brain as they affect cell recognition and signal transmission (Futerman 2016). Thus, their disturbed metabolism also exhibits a particular influence on the neural tissues.

Fatty Acids (FAs) are one of the most important, prominent and well-known group of lipids. They are divided into sub-classes as Saturated and Unsaturated fatty acids. From these classes, the unsaturated fatty acids includes Monounsaturated Fatty acids (MUFAs) and Polyunsaturated Fatty acids (PUFAs) whereas; the Saturated fatty acids contains Stearic acid, palmitic acid and many others (Haag 2003). They act as key modulators of the brain activity and interact with many neurochemical pathways.

The brain comprises sphingolipids, cholesterol, and glycerophospholipids, which are mainly concentrated in the myelin and neuronal membranes (Wong et al. 2017). Fatty acids particularly ω -3 PUFAs are involved in the brain developments synaptogenesis and neurogenesis (Denis et al. 2013; Igarashi, Santos, and Cohen-Cory 2015).

Metabolism of lipids

Lipids metabolism involves lipids synthesis, up-take, transportation, and finally degradation of lipids molecules. This is a multifaceted process and is carried out by different pathways which regulate the biosynthesis as well as degradation of these molecules. There are different pathways which regulate the same class of lipids in different cells and tissues even under the pathophysiological, therapeutic, and physiological conditions (Huang and Freter 2015). In the living organisms, the metabolic fate of lipids depends on their structure. Their metabolism takes part in the several cellular processes including regulation of cell growth, differentiation,

proliferation, apoptosis, survival, and maintenance of membrane homeostasis (Krycer et al. 2010; Zechner et al. 2012).

Recent studies have shown that almost one hundred enzymes regulate the lipids metabolism inside the cell (Mattes 2005; Lammert and Zee 2016). Moreover, liver X receptors (LXRs) are the essential regulators of lipids homeostasis. They control the gene expression involved in the up taking, transporting, efflux, and excretion of lipids particularly cholesterol (Hong and Tontonoz 2014). Furthermore, hepatic SIRT7 regulates the TAK1/TR4 protein level which is a nuclear receptor involved in the lipids metabolism. This controls the lipids metabolism in liver by regulating the ubiquitin-proteasome pathway (Yoshizawa et al. 2014).

In brain, apolipoprotein (ApoE) plays a crucial role in the lipids metabolism and their homeostasis. It is involved in the distribution of lipids, stability and assembly of cytoskeleton, functional integrity of mitochondria, and function and morphology of dendrites (Huang and Mahley 2014). Alterations in the lipids metabolism lead to change the membrane composition, impaired protein functions and distribution, cellular functions, gene expression and ultimately cause the pathogenesis of many diseases (Santos and Schulze 2012; Wong et al. 2017) particularly brain diseases such as NDDs, brain injuries, and neurological and neuropsychiatric disorders (Lammert and Zee 2016; Hussain, Schmitt, Loeffler, et al. 2013) as illustrated in the Fig. 2.

Impacts of lipids on brain health

Lipids such as cholesterol, fatty acids, sphingolipids, and glycerolipids act as health promoting and structural component of the neuronal cells. Despite all the beneficial roles of lipids in the brain, the disturbed concentration (up-regulation or down-regulation) and altered lipids metabolism lead to the occurrence of several brain diseases (Hussain, Schmitt, Loeffler, et al. 2013). A few examples are briefly discussed in next sessions of the article.

- Cholesterol facilitates the extension of axons, survival of neurons and also promotes the myelin formation (Bruce, Zsombok, and Eckel 2017). Whereas, high cholesterol in membrane causes the integration of A β into membrane in AD and accumulation of α -synuclein in PD which lead to the neuronal death (Abramov et al. 2011; Galvagnion et al. 2015).
- Sphingolipids play an important role in the synaptic transmission and neuronal differentiation and are also associated with the stability of myelin sheath (Olsen and Faergeman 2017). On the other hand, low SM and over-activation of sphingomyelinase lead to the A β accumulation in AD (Horres and Hannun 2012).
- Fatty acids (FAs) participate actively in the development of the nervous system at embryonic and early postnatal stage, and are crucial for its maintenance throughout adulthood (Uauy and Dangour 2006; Rombaldi Bernardi et al. 2012; Chang, Ke, and Chen 2009). While deregulated contents of FAs have been reported in the currently

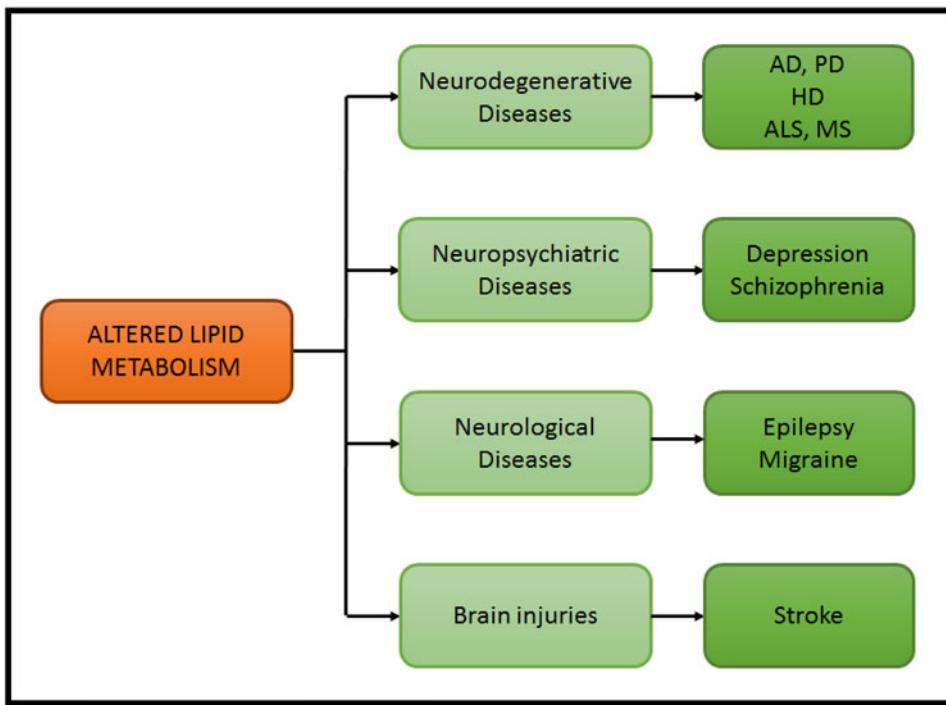


Figure 2. Altered lipids metabolism and associated brain diseases.

incurable pathological conditions of the nervous system (Fernandes, Mutch, and Leri 2017; Henriques, Blasco, et al. 2015; Baierle et al. 2014; Liu and Zhang 2014; Hussain, Schmitt, Loeffler, et al. 2013).

Role of lipids metabolism in neurodegenerative disorders

Lipids have been well recognized as the beneficial molecules for the brain health and functions. They participate in various physiological jobs of the brain required for the maintenance and regulation of its activities. Although they exert many advantageous effects in normal conditions but their altered metabolism results in the development of several neurodegenerative disorders (NDDs).

Alzheimer's disease

The main hallmark in the pathology of Alzheimer's disease (AD) is the aggregation of β -amyloid ($A\beta$) peptides in the brain (Hussain, Rasul, et al. 2018; Hussain, Schmitt, Loeffler, et al. 2013). The neurites and synapses get damaged as a result of plaques formation which also reduces the number of synapses (Hussain et al., 2018). Moreover, gamma secretase enzyme mediates the successive cleavage of the β -secretase (beta-site amyloid precursor protein cleaving enzyme, BACE) and the amyloid precursor proteins (APP) which lead to the formation of $A\beta$ peptides (Nhan, Chiang, and Koo 2015). The impaired lipids metabolism, both up-regulation and down-regulation of numerous lipids acts as the biomarkers of AD.

It is notable that cholesterol plays a critical role in the development of AD. It was demonstrated that the

deregulated membrane cholesterol allows the integration of $A\beta$ plaques into the membranes. It also enhances the level of cytosolic calcium in astrocytes and results in death of neuronal cells (Abramov et al. 2011). The cell death due to necrosis is linked with the calcium overload of the intracellular environment which leads to the alteration of mitochondrial permeability and functional failure (Orrenius, Gogvadze, and Zhivotovsky 2015). Hence, the association between the mitochondria and calcium deregulation is predominantly evident in NDDs (Celsi et al. 2009). The apolipoprotein-E (Apo-E) acts as the cholesterol transporter. It impacts the cholesterol metabolism by binding to the cell surface receptors involved in the cholesterol delivery and allows the production of oxidative products of the cholesterol (oxysterol) (Liu et al. 2013; Gamba et al. 2012). High cholesterol accumulation in lysosomal-endosomal system also results in the alteration of APP processing and lead to the $A\beta$ peptides generation which in turn degenerates neuronal cells (Maulik et al. 2013). Moreover, enhanced level of low density lipoprotein (LDL-C) and reduced level of high-density lipoprotein (HDL-C) have also been linked to Apo-E4 (Reed et al. 2014; Sato and Morishita 2015). Increased LDL-C also enhances the activity of BACE-1, affect the $A\beta$ precursor protein, and impairs the synaptic plasticity (Chen 2014).

The sphingolipids are closely linked with the cholesterol at the site of γ -secretase and BACE-1 expression in the lipid rafts. So, alteration in the sphingolipids metabolism might lead to development of AD (Mielke et al. 2011). The hydrolysis of sphingomyelin can be caused by sphingomyelinase (SMase) for the production of ceramide. Whereas ceramide is produced de novo through anabolism of palmitate and serine. Then ceramidase (AC) can metabolize the Cer to sphingosine which is phosphorylated to

synthesize sphingosine-1-phosphate (Wong et al. 2017). In cases of AD, ceramide induces apoptosis and imbalance in its metabolism may lead to the serious implications (Mullen 2012). It has been demonstrated that in patients of AD, the expression of AC and SMase in the membranes was enhanced which enhanced Cer level and reduced sphingomyelin level by the activation of SMase (He et al. 2010). Moreover, Cer enhances the stability and half-life of BACE-1, leading to the A β production. Interestingly, sphingosine is also enhanced in parallel with AC and sphingosine-1-phosphokinases expression is downregulated (Couttas et al. 2014). Thus, it is worthy to note that imbalanced/altered metabolism of ceramide/SM contributes to the development of AD.

In context of AD, recent studies have demonstrated that metabolism of unsaturated FAs is considerably deregulated in the patients' brain with AD (Snowden et al. 2017). It has been demonstrated that A β peptide's higher secretion is prompted by palmitic acid (16:0), stearic acid (18:0), upstream ω -3 PUFAs, compared to MUFAs and long chain downstream ω -3 PUFAs (Amtul et al. 2011). Moreover, Unsaturated FAs particularly ω -6 PUFAs, such as AA (20:4 ω -6), intensify the pathology of AD by enhancing the production of A β peptides (Amtul et al. 2012). The reduced levels of MUFAs and PUFAs, mainly Oleic acid (18:1n-9) and DHA, respectively, are seen in AD (Martín et al. 2010). It is also important to state that Stearic acid (18:0) levels are condensed remarkably in temporal and frontal cortex, while those of Oleic acid (18:1n-9) are enhanced in the both parts. The levels of Palmitic acid (16:0) is enhanced in the parietal cortex of such patients (Fraser, Tayler, and Love 2010). The reduced level of PUFAs in AD might be due to decreased phospholipase-A2 activity (Schaeffer et al. 2011). In addition, the ratio of MUFAs to SFAs, which is a desaturase activity index, is stated to be negatively associated

with the cognitive performance (Astarita et al. 2011). Furthermore, some FAs variations such as MUFAs, DHA, and plasmalogens support the supposition of peroxisomal dysfunctions or/and of abnormal elongase and desaturase activities (Zarrouk et al. 2017; Henriques, Croixmarie, et al. 2015). It has been reported that low ALA plasma concentration is linked with the increased risk of dementia (Yanai 2017).

The glycerophospholipids (GPs) and its various classes are involved in the maintenance of neuronal membrane. They are involved in the tight integration and vertical positioning of lipid bilayer. They are also significant for the optimal activity of ion channels, membrane bound enzymes and receptors (Frisardi et al. 2011). Many studies have reported that multiple classes of phospholipids including phosphatidylethanolamines (PPEs), phosphatidylinositols (PIs) and phosphatidylcholines (PCs) are remarkably reduced in the neural membrane of AD patients (González-Domínguez, García-Barrera, and Gómez-Ariza 2014; Kosicek and Hecimovic 2013). This decreased concentration is might be due to the stimulation of phospholipase A₂ which not only alters the membrane permeability and fluidity but also changes the ionic homeostasis resulting in the oxidative stress. Many breakdown products of GP activate microglia and inflammatory cytokines which intensify the oxidative stress and inflammation which are involved in the pathogenesis of AD (Frisardi et al. 2011). Experimental studies have revealed that glycerolipids (GL) level is significantly enhanced in the cells treated with A β plaques (Zhang et al. 2012) but more work is need to be done in this context. The altered lipids metabolism in AD has been summarized in the Table 1. In Fig. 3, we have shown the mechanistic approach of AD regarding lipids metabolism.

Table 1. Altered lipid metabolism in AD.

Lipids classification	Lipids alteration	References
Low density lipoprotein	↑	(Chen 2014)
High density lipoprotein	↓	(Reed et al. 2014; Sato and Morishita 2015)
Ceramide	↑	(He et al. 2010)
Sphingomyelin	↓	(He et al. 2010)
Sphingosine	↑	(Couttas et al. 2014)
Phosphatidylcholine	↓	(González-Domínguez, García-Barrera, and Gómez-Ariza 2014; Kosicek and Hecimovic 2013)
Phosphatidylinositol	↓	(González-Domínguez, García-Barrera, and Gómez-Ariza 2014; Kosicek and Hecimovic 2013).
Phosphatidylethanolamine	↓	(González-Domínguez, García-Barrera, and Gómez-Ariza 2014; Kosicek and Hecimovic 2013).
Docosahexaenoic acid	↓	(Martín et al. 2010; Thomas et al. 2015)
α -linolenic acid	↓	(Yanai 2017)
Arachidonic acid	↑	(Thomas et al. 2016)
Palmitic acid	↑	(Fraser, Tayler, and Love 2010)
Stearic acid	↓	(Fraser, Tayler, and Love 2010)
Oleic acid	↓	(Martín et al. 2010)
Oleic acid	↑	(Fraser, Tayler, and Love 2010; Astarita et al. 2011)
Palmitoleic acid	↑	(Astarita et al. 2011; Hussain, Schmitt, Loeffler, et al. 2013)

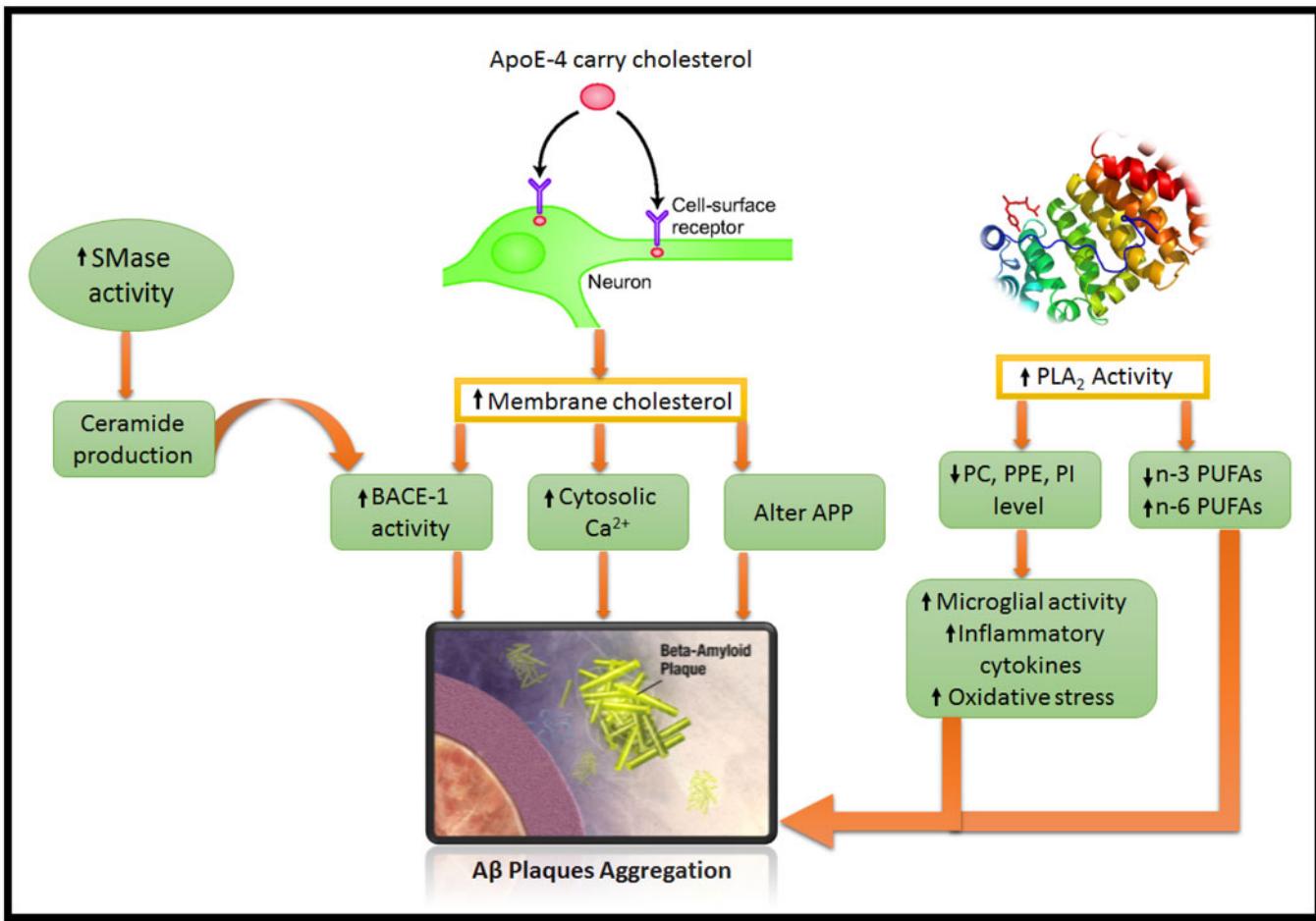


Figure 3. Altered lipids metabolism and Alzheimer's disease.

Parkinson's disease

Parkinson's disease (PD) is characterized by the loss of dopaminergic neurons in substantia nigra (SN). Aggregation and formation of α -synuclein and Lewy bodies occur respectively (Guardia-Laguarta et al. 2015). The early symptoms involve rigidity, shaking, behavioral problems, difficulty in walking, and slothfulness in movement (Sveinbjornsdottir 2016). It was demonstrated that high lipids concentration stimulates the nucleation which leads to the aggregation of α -synuclein (Galvagnion et al. 2015). Most recent data have shown that high level of cholesterol and its oxidized products allow the α -synuclein accumulation (Eriksson et al. 2017) as well as oxidation, inflammation, and dopaminergic neuronal cell death. Surprisingly, some studies have also reported that there is no association between development of PD and cholesterol levels (Doria et al. 2016; Paul, Choudhury, and Borah 2015). Moreover, low levels of total cholesterol (TC), HDL-C and LDL-C have been observed in the PD patients (Guo et al. 2015; Huang et al. 2008).

In context of sphingolipids, the metabolism of ceramide is altered in PD (Posse de Chaves and Sipione 2010; Abbott et al. 2014). The increased level of neutral SMase (nSMase) has been observed in patients of PD. The enhanced nSMase level in turn elevates the level of ceramides, leading to the apoptosis in SN (Posse de Chaves and Sipione 2010).

Sphingosine kinase (Sphk1) plays an important role in the regulation of homeostasis of sphingolipids. Inhibition of Sphks leads to the enhanced secretion of α -synuclein, suppresses PI3K/Akt phosphorylation and triggers the expression of gene encoding pro-apoptotic Bcl-2 proteins (Pyszko and Strosznajder 2014). Hence, it is necessary to elaborate the role of altered sphingolipids metabolism in the PD development.

The lipids bundles collected from the brain cortices of PD patients show significantly reduced levels of ω -6 and ω -3 PUFAs, particularly AA (20:4 ω -6) and DHA. Whereas SFAs, such as stearic acid (18:0) and palmitic acid (16:0) are found to be increased (Fabelo et al. 2011). Similar variations in ω -3 PUFAs such as EPA and DHA, have also been observed (Lin, Huang, and Su 2010). Some investigations indicate that ω -3 PUFAs also adversely influence the pathogenesis of PD. DHA presence attenuates the astrocytosis and neuritic injury in the transgenic mice of PD. Additionally, α -synuclein oligomerization can be triggered by DHA via activation of proliferator-activated receptor- γ 2 (PPAR- γ) and retinoic X receptor (RXR). Its removal from the diet proves beneficial against the harmful influences caused by it facility (Yakunin et al. 2012). Furthermore, conformational and structural alterations in α -synuclein leading to disease symptoms are observed by chronic administration of DHA (Hussain, Schmitt, Loeffler, et al. 2013).

Table 2. Altered lipid metabolism in PD.

Lipids classification	Lipids alteration	References
Low density lipoprotein	↓	(Guo et al. 2015; Huang et al. 2008)
High density lipoprotein	↓	(Guo et al. 2015; Huang et al. 2008)
Ceramide	↑	(Posse de Chaves and Sipione 2010)
Sphingomyelin	↓	(Patel and Witt 2017)
Sphingosine-1-phosphate	↓	(Pyszko and Strosznajder 2014)
Phosphatidylcholine	↓	(Farmer et al. 2015)
Phosphatidylinositol	↓	(Chalimoniuk et al. 2006)
Phosphatidylethanolamine	↓	(Patel and Witt 2017)
Eicosapentaenoic	↓	(Hussain, Schmitt, Loeffler, et al. 2013)
Docosahexaenoic acid	↓	(Hussain, Schmitt, Loeffler, et al. 2013)
Arachidonic acid	↓	(Hussain, Schmitt, Loeffler, et al. 2013)
Palmitic acid	↑	(Fabelo et al. 2011)
Stearic acid	↑	(Fabelo et al. 2011)
Oleic acid	↓	(Schmid et al. 2012)
Palmitoleic acid	↓	(Schmid et al. 2012)
Linoleic acid	↓	(Schmid et al. 2012)

Earlier, it was reported that the expression of Phosphatidylinositol transfer proteins (PI-TP), responsible for transportation of PI and PC from ER to membranes, was found reduced in the brain of PD patients. Oxidative stress was suggested to be the underlying reason of that decreased quantity of PI and PC (Chalimoniuk et al. 2006). It is shown that in PD, α -synuclein encoding gene, SNCA becomes mutated which is linked to the altered levels of cellular PPE. The reduced PPE levels enhance the mitochondrial fragmentation and attenuate the mitochondrial Ca^{2+} accumulation (Calzada, Onguka, and Claypool 2016). Recently, it has been demonstrated that the level of PPE was low in SNc, mid brain, and cerebrospinal fluid of PD patients. The low level might be due to ER stress, inadequate processing of glycosylphosphatidylinositol-anchored proteins (GPI-APs), or impaired autophagy as PPE is linked covalently to Atg8 (trigger formation of autophagosome) (Patel and Witt 2017). The altered lipids metabolism in PD has been summarized in the Table 2.

Huntington's disease

Huntington's disease (HD) is a progressive inherited neurodegenerative condition which is characterized by cognitive, motor and behavioral decline, terminating in death. It is caused by an expanded CAG repeat in the gene known as huntingtin (htt) (Dayalu and Albin 2015). Although, abnormal protein is ubiquitously expressed but cellular deterioration occurs only in the brain, primarily in the cortex and striatum (Gil-Mohapel, Brocardo, and Christie 2014). It has been indicated that oxidative stress is also involved in the pathogenesis of HD. Vulnerable neurons in HD brain might not be able to handle the increased production of Reactive oxygen species (ROS). The main source of ROS are mitochondria and thus, dysfunction of mitochondria is closely

linked with oxidative stress (Gil-Mohapel, Brocardo, and Christie 2014).

The impairment of cholesterol metabolism occurs in HD which is proportional to the CAG repeat length. It is found that cholesterol metabolism attenuated in the progressive stages of HD by measuring the synthetic precursors of cholesterol, its oxidation products, and its metabolites in the five regions of human post mortem brain of HD (Leoni and Caccia 2015; Kreilaus et al. 2016). Furthermore, reduced cholesterol biosynthesis in the brains of mice model of HD and the brain derived cells expressed mutant htt is also found (Hottman et al. 2014). The mechanism by which biosynthesis of cellular cholesterol is compromised in mutant htt is due to the inhibition of SREBPs (sterol regulatory element binding proteins) and attenuated signaling of brain derived neurotrophic factor (Karasinska and Hayden 2011). Moreover, the 24S-hydroxycholesterol level in plasma is reduced in patients of HD (Leoni et al. 2013). Interestingly, natural SIRT1 promotes neuro-protection against HD and increased HDL-C level has been found to be linked with SIRT1 activation. Hence, HDL-C enhancing therapies might alleviate HD (Hottman et al. 2014). This gives the direction that reduced HDL-C is also linked with HD.

The level of cerS1 and sptlc1 is reduced in the patients of HD. The reduction in dihydroCeramide, dihydroSphingosine-1-phosphate and dihydroSphingosine is also observed in HD patients (Pardo et al. 2017). The interrupted metabolism of sphingosine-1-phosphate is notable in the HD patients even at initial stages (Pardo et al. 2017). Moreover, increased SM lead to aggregation of htt in the lipids bilayer (Chaibva et al. 2018). As Cer is metabolized to sphingosine which is phosphorylated to synthesize sphingosine-1-phosphate (Wong et al. 2017), so reduced level of Cer indicates that the level of sphingosine may also be reduced in such cases.

Table 3. Altered lipid metabolism in HD.

Lipids classification	Lipids alteration	References
High density lipoprotein	↓	(Hottman et al. 2014)
24S-hydroxycholesterol	↓	(Leoni et al. 2013)
Ceramide	↓	(Pardo et al. 2017)
Sphingomyelin	↑	(Chaibva et al. 2018)
Sphingosine	↓	(Di Pardo et al. 2017)
Phosphatidylcholine	↓	(Mastrokolas et al. 2016)
Eicosapentaenoic acid	↓	(Block et al. 2010)
Docosahexaenoic acid	↓	(Block et al. 2010)

It is noteworthy to state that supplementation of DHA and EPA is beneficial in HD (Block et al. 2010). Although, this finding put forwards an idea to take the reduced EPA and DHA as a biomarker for the HD and at the same time offers as a therapeutic intervention.

Similarly, the metabolism of PCs is found deregulated in blood of HD patients which is linked with the changes in a particular gene expression (*PLB1*, *MTRR*, *MBOAT1*, and *ALDH1B1*). It has been shown that di-acyl and acyl alkyl PCs are reduced in the blood of HD patients and changes are associated with altered enzymatic pathways and reactions (Mastrokolas et al. 2016). There is dearth of data regarding the lipids metabolism alteration in HD. More data are need to elucidate that lipids are the biomarkers of HD. Altered lipids metabolism in HD has been summerized in the Table 3.

Amyotrophic lateral sclerosis

Amyotrophic Lateral Sclerosis (ALS) is a persistently advancing neurodegenerative ailment which affects the lower and upper motor neurons (MNs) of spinal cord, brain stem, and cerebral cortex, resulting in paralysis, muscle wasting and eventually demise (Liu and Wang 2017; Bruneteau et al. 2015; Henriques, Croixmarie, et al. 2015). An intricate series of causative factors are involved in ALS pathogenesis and lipids metabolism deregulation is one of the prominent features. Both human and animal model of ALS exhibit an altered expression of enzymes involved in the lipids metabolism. Namely, an enzyme, Stearoyl-CoA desaturase-1 (SCD1) which is involved in the saturated fatty acids desaturation is reduced in ALS mouse models and patients at pre-symptomatic stage of disease (Hussain, Schmitt, Henriques, et al. 2013; Hussain, Schmitt, Loeffler, et al. 2013). Primarily, MUFAAs are the basic components of the complex lipids which include phospholipids, triglycerides, diacylglycerols, wax esters, and cholesterol esters (Ntambi et al. 2002), an indicative situation of metabolic phenotype in mice with mutant superoxide dismutase 1 (SOD1), related with the familial ALS (Dupuis et al. 2004). Briefly, ALS is associated with many systemic flaws, like hypermetabolism and dyslipidemia (Hussain, Schmitt, Henriques, et al. 2013). Diet enriched with PUFAs can modify the oxidative reactions and inflammation, therefore, they can also affect the progression and risk of ALS (Fitzgerald et al. 2014).

Moreover, cholesterol metabolism disturbance and sterol along with its metabolites may represent as biomarkers of neurodegenerative conditions, suggesting that an elevated level of cholesterol in CSF is linked to ALS prognosis. The underlying mechanism suggests that as the neurons die in ALS, they release cholesterol and due to poor activity of CYP27A1 enzyme, excess cholesterol is not removed from the CSF (Gray et al. 2015; Abdel-Khalik et al. 2017). Similarly, another study supports that cholesterol level is increased in ALS patients (Vejux et al. 2018). The level of triglycerides reduces in the muscles and plasma and to some extent in the spinal cord also (Henriques, Croixmarie, et al. 2015).

The deregulation of glycosphingolipids (GSLs) metabolism can also serve as disease prognosis in ALS, AD and PD. Evidences suggest that altered metabolism of GSLs in ALS patients has been observed in gray and white matter of spinal cord in cervical region. Both GSLs hydrolysis and their synthesis are up regulated in plasma membrane. The underlying mechanism in this situation is the significant increase in neutral enzymes activities which lead to elevated acidic enzymatic activities of Glucocerebrosidase 1(GBA-1), Glucocerebrosidase 2 (GBA2), galactosylceramidase (GALC), β -galactosidase (β -GAL) and α -galactosidase (α -GAL). Although altered metabolism of GSL serves as a marker of both familial and sporadic ALS but yet it is hard to state whether GSL accretion contributes to the pathogenesis of disease during its terminal phase or it is a part of compensatory response to down regulate the disease progression (Yu et al. 2004; Kori et al. 2016). Among the GSL, SM and glucosylceramides (CerG1) levels of CSF are also up regulated followed by the higher level of Cer and glucosylceramides. In ALS patients, increased level of PC has also been reported (Blasco et al. 2017). Importantly, enhanced level of SM in ALS, mediates death of motor neuron via production of ROS (Schmitt et al. 2014). The altered lipids metabolism in ALS has been summerized in the Table 4.

Multiple sclerosis

Multiple sclerosis (MS) is supposed to be an indecipherable and complex disease with poor etiology (Ransohoff, Hafler, and Lucchinetti 2015). It is a chronic autoimmune and inflammatory ailment of CNS. The myelination of CNS axons is primarily affected at various degrees of damage. Although, the etiology of MS is yet unknown but, it seems to encompass a combination of non-genetic susceptibility and a genetic trigger which lead to the immune assaults on the CNS (Goldenberg 2012). The unimpeded demyelination caused by inflammatory reaction at the early stage of MS, activates a cascade of proceedings that chiefly point out neuro-degeneration through various underlying mechanisms like microglia activation and mitochondrial damage. This cascade results in the neuronal and axonal death. A combination of regenerative, neuro-protective and anti-inflammatory strategies may portray beneficial effects against MS (Mahad, Trapp, and Lassmann 2015).

Table 4. Altered lipid metabolism in ALS.

Lipids classification	Lipids alteration	References
Cholesterol	↑	(Gray et al. 2015; Abdel-Khalik et al. 2017; Vejux et al. 2018)
Triglycerides	↓	(Henriques, Croixmarie, et al. 2015)
Ceramide	↑	(Blasco et al. 2017)
Glucosylceramides	↑	(Blasco et al. 2017; Henriques, Croixmarie, et al. 2015)
Sphingomyelin	↑	(Blasco et al. 2017; Schmitt et al. 2014)
Phosphatidylcholine	↑	(Blasco et al. 2017)
Docosahexaenoic acid	↑	(Schmitt et al. 2014)
Eicosapentaenoic Acid	↑	(Yip et al. 2013)
Arachidonic acid	↑	(Schmitt et al. 2014)
Oleic acid	↑	(Kim et al. 2005)
Linoleic acid	↑	(Kim et al. 2005)

Altered lipids metabolism is involved in the progression of MS and thereby impaired metabolism of FAs could accelerate MS progression (Kong-González et al. 2015). Importantly, MS patients usually share the state of depression and certain ω -6 and ω -3 PUFAs are decreased while levels of SFAs and MUFAs become elevated. The level of dietary FAs intake have not been found to be related with the state of depression in MS patients (Aupperle et al. 2008). Postmortem analyses indicate the activated AA pathway in MS patients. The said up-regulated level of AA is followed by the amplified levels of some members of leukotriene family including LTB4 and LTC4 in the CSF. Overall, AA is enhanced in response to the augmented activity of 5-Lipoxygenase (5-LOX). In fact, one of the studies also attributes the 5-LOX gene as a chief risk factor for MS (Schiss and Calabresi 2016; Neu et al. 2002).

A wide range of FAs including EPA, DHA, stearic acid, Dihomo-gamma-linolenic (dGLA), erucic acid and oleic acid have also been found to be associated with the progression of MS with a poor etiology of underlying mechanisms. Out of the above mentioned FAs, the level of DHA, EPA and dGLA becomes lower while erucic acid, oleic acid, and stearic acid level goes up during the course of disease (Koch et al. 2006; Aupperle et al. 2008). One of the possible mechanisms is the activated production of eicosanoid which causes the depletion of ω -3 and ω -6 FAs from cell membrane. Lipids peroxidation and certain FAs targeting antibodies have been also altered in MS patients. Although, PUFAs exhibit beneficial effects in MS but the chronic supplementation for a period of 2 years can bestow protective effects on neuron degeneration. However, the available data do not provide an adequate knowledge about the beneficial and harmful properties of PUFAs supplementation against MS. Therefore, more research is needed to measure the efficiency of dietary inclusion of PUFAs to treat MS (Farinotti et al. 2012).

Another important class of lipids known as cholesterol is associated with the progression of MS. Triglycerides, TC and LDL levels in serum of MS patients increase (Weinstock-Guttman et al. 2011). Thus, it can be stated that LDL and cholesterol alterations may be designated as

biomarkers to determine the stage and severity of disease. However, the underlying mechanism involved in the cholesterol impairment needs to be explored.

Sphingolipids are distributed in nervous tissue and chiefly GSLs are part and parcel of oligodendrocytes' myelin and plasma membranes. Altered sphingolipids contents in the brains of MS patients were described by Cumings and Goodwin (Halmer, Walter, and Faßbender 2014). In MS lesions, ceramide accumulation and up-regulation of sphingosin-1-phosphate (S1P) receptors 1 and 3 occurs. Moreover, ceramide metabolite ceramide 1-phosphate facilitates the phospholipaseA₂ activation which in turn exhibits a key role in the inflammatory processes (Huwyler et al. 2001). The immune activity has also been detected only in astrocytes of MS patients followed by the up regulated de novo Cer synthesis pathway by serine palmitoyltransferase. The whole process in turn accelerates the demyelinating processes resulting in the progression of MS (Kim et al. 2012; Halmer, Walter, and Faßbender 2014).

The altered metabolism of sphingomyelin-ceramide also mediates the progression of the disease. The levels of dihydroxyphosphatidylethanolamine and sphingosine increase in MS patients. This altered metabolism work through S1P receptors which contribute to the MS pathogenesis and affects neural function, migration and neurogenesis (Ward et al. 2017). Lastly, in order to better elucidate if impaired lipids metabolism can serve as a key biomarker in the pathogenesis of MS, more work is needed. The altered lipids metabolism in MS has been summarized in the Table 5.

In Fig. 4 various factors involved in neurodegeneration followed by the altered lipids metabolism are illustrated.

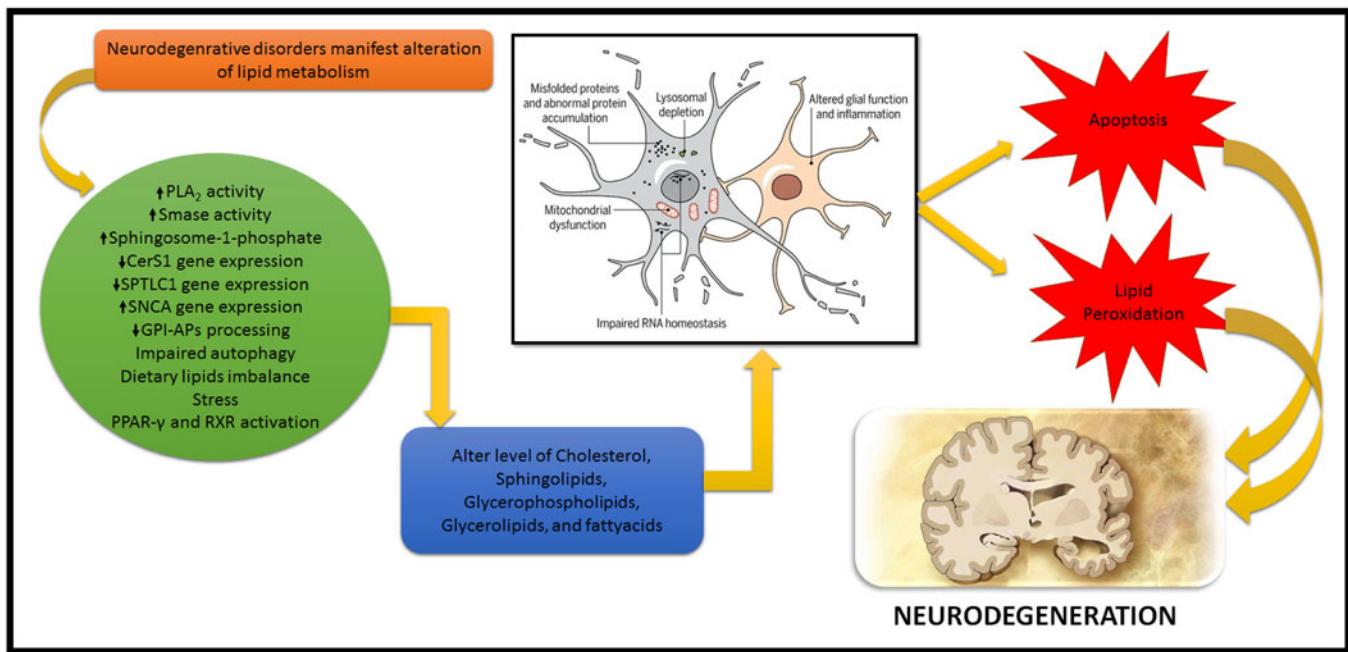
Metabolism of lipids in neuropsychiatry disorders

Depression

Depression is a recurrent, common, and debilitating ailment which has developed as a more prevalent factor from the past many years (Deacon et al. 2017). Anxiety and major depression disorders are often comorbid and their neurobiological bases are not fully clear. These

Table 5. Altered lipid metabolism in MS.

Lipids classification	Lipids alteration	References
Low density lipoproteins	↑	(Weinstock-Guttman et al. 2011)
High density lipoproteins	↓	(Weinstock-Guttman et al. 2011)
Cholesterol	↑	(Weinstock-Guttman et al. 2011)
Triglycerides	↑	(Weinstock-Guttman et al. 2011)
Ceramide	↑	(Halmer, Walter, and Faßbender 2014; Huwiler et al. 2001)
Ceramide 1 Phosphate	↑	(Halmer, Walter, and Faßbender 2014; Huwiler et al. 2001)
Sphingosine	↑	(Ward et al. 2017)
Dihydrosphingosine	↑	(Ward et al. 2017)
Eicosapentaenoic acid	↓	(Koch et al. 2006; Aupperle et al. 2008)
Docosahexaenoic acid	↓	(Koch et al. 2006; Aupperle et al. 2008)
Arachidonic acid	↑	(Aupperle et al. 2008)
Dihomo-gamma-linolenic	↓	(Aupperle et al. 2008)
Oleic acid	↑	(Aupperle et al. 2008)
Erucic acid	↑	(Aupperle et al. 2008)
Stearic acid	↑	(Aupperle et al. 2008)

**Figure 4.** Factors associated with the altered lipids metabolism.

ailments lead to the substantial sufferings to the effected individuals (Hussain, Shahzad, et al. 2017) and about 10% of the depression patients commit suicide (Whiteford et al. 2013). The available treatment fails to exhibit influential outcomes and cannot prove always effective. It is pivotal to elucidate different biomarkers associated with these kinds of disorders to design an effective treatment. Brain lipids including sphingolipids, GP, GL and FAs are considered as vital agents and their deregulation is associated with major depression and anxiety disorders. Brain lipids composition can be altered due to a long-term variation in diet and this may directly affect mood and emotional behavior. Therefore, it is critical to identify reliable

biomarkers, specifically altered lipids which indicate the disease progression (Müller et al. 2015).

Deregulated FAs metabolism is associated with the development of depression and mood disorders (Dyall 2015). It is suggested that ω-3 PUFAs, sphingolipids, glycerophospholipids and glycerolipids play a job in the induction of anxiety and depression (Müller et al. 2015). Both ω-6 and ω-3 PUFAs are not only connected to the depression but also increase the risk factor for depression. Lower level of DHA affects the function of selected areas in brain including striatum, cortex, cerebellum and hippocampus.

Depression is associated with the higher production of pro-inflammatory cytokines. In this aspect, reduced level of

Table 6. Altered lipid metabolism in depression.

Lipids classification	Lipids alteration	References
High-density lipoproteins	↓	(Lehto et al. 2010; Woods et al. 2012)
Low-density lipoproteins	↓	(Lehto et al. 2010; Woods et al. 2012)
Cholesterol	↓	(Lehto et al. 2010; Woods et al. 2012)
High-density lipoproteins	↑	(Sarandol et al. 2006; Woods et al. 2012)
Low-density lipoproteins	↑	(Sarandol et al. 2006; Woods et al. 2012)
Cholesterol	↑	(Sarandol et al. 2006; Woods et al. 2012).
Ceramide	↑	(Gracia-Garcia et al. 2011; Demirkhan et al. 2013; X. Liu et al. 2016)
Sphingomyelin	↓	(Kornhuber et al. 2009; Farooqui 2009; Demirkhan et al. 2013)
Sphingosine 1 phosphate	↑	(Gracia-Garcia et al. 2011; Demirkhan et al. 2013; Liu et al. 2016)
Phosphatidylcholine	↓	(Kornhuber et al. 2009; Farooqui 2009; Demirkhan et al. 2013)
Arachidonic acid	↑	(Mocking et al. 2016; Mocking et al. 2015)
Docosahexaenoic acid	↓	(Martins, Bentsen, and Puri 2012; Grosso et al. 2014)
Eicosapentaenoic acid	↓	(Martins, Bentsen, and Puri 2012; Grosso et al. 2014)
Palmitic acid	↓	(ConkLin, Huang, and Su 2010; Hussain, Schmitt, Loeffler, et al. 2013)
Linoleic acid	↓	(Hussain, Schmitt, Loeffler, et al. 2013; ConkLin, Huang, and Su 2010)
Docosatetraenoic acid	↓	(Hussain, Schmitt, Loeffler, et al. 2013; ConkLin, Huang, and Su 2010)
Oleic acid	↑	(Kei Hamazaki, Hamazaki, and Inadera 2012; Hussain, Schmitt, Loeffler, et al. 2013)
Palmitoleic acid	↓	(Hussain, Schmitt, Loeffler, et al. 2013; ConkLin, Huang, and Su 2010)

ω -3 PUFAs results in the higher expression of pro-inflammatory cytokine IL-6 (Baghai et al. 2011). On the other hand, higher levels of ω -6 PUFAs can be converted in to AA and eicosanoids which exhibit pro-inflammatory action (Mocking et al. 2016; Mocking et al. 2015). Functional impairments of dopamine system are implicated in depression disorders and low levels of dietary ω -3 PUFAs can reduce the dopamine levels, expression of D2 receptors and their mRNA, presynaptic vesicles of dopamine and finally increase the dopamine break down. Moreover, they also decrease the tyrosine hydroxylase resulting in the lower levels of dopamine and thus, elevate the pathogenesis of depression. Finally, it is hypothesized that reduced ω -3 PUFAs (DHA, EPA) and higher levels of ω -6 PUFAs (AA) lower the activity of dopamine (Martins, Bentsen, and Puri 2012; Grosso et al. 2014) and contribute to the depression prognosis. Moreover, the overall altered metabolism of a wide range of FAs is given in the table below. Thus, the entire PUFAs imbalance can be taken as the potential biomarker for the diagnosis of depression and mood behaviors.

Furthermore, altered concentration of sphingolipids, specifically elevated concentration of Cer has been recently reported as the contributing factor in depression (Demirkhan et al. 2013; Gracia-Garcia et al. 2011; Liu et al. 2016). Although, the underlying mechanism is still poorly understood, but it is hypothesized that increased level of sphingosine 1 phosphate (S1P) affects the metabolism of sphingolipids and enhance Cer level. In turn, the increased SM species and Cer level put a step forward in the pathogenesis of depression. Moreover, Gracia-Garcia et al. also reported the elevated level of Cer in individuals with depression and they also enhance the severity of the disease. Most probably, increased Cer level is associated with the severity

of depression (Gracia-Garcia et al. 2011; Demirkhan et al. 2013) by its possible implication in apoptosis. It also is up regulated in the apoptotic cells and thereby mediates the progression of depression. It contributes to the depression associated neurodegeneration by inducing apoptosis. Moreover, increased Cer species can alter the monoamine neurotransmitters re-uptake and initiate a biological cascade which results in the down-regulation of serotonergic neurotransmission, another pathophysiological promise of depression (Liu et al. 2016). Increased activity of SMase results in the over production of Cer and lower SMs level. On the other hand, phosphatidylcholine (PC) levels are also inversely related with the disease progression (Kornhuber et al. 2009; Farooqui 2009; Demirkhan et al. 2013).

Furthermore, in depression, TC level decreases along with a lower LDL and HDL and reduced HDL is associated with the long term symptoms of depression (Lehto et al. 2010; Woods et al. 2012). In contradiction of this study, another study reports that TC level, ApoB, HDL and LDL are significantly higher in such patients (Sarandol et al. 2006; Woods et al. 2012).

Finally, it is noteworthy to state that the altered metabolism of lipids upholds a pivotal role in the progression of depression. So, for the proper diagnosis and treatment, it is crucial to enlighten the role of deregulated lipids metabolism. The altered lipids metabolism in depression has been summarized in the Table 6.

Schizophrenia

Schizophrenia (SZ) is a chronic neuropsychiatric disorder characterized by uncontrolled negative and positive thoughts as well as cognitive impairment (Os and Kapur

Table 7. Altered level of lipids in schizophrenia.

Lipids classification	Lipids alteration	References
Low density lipoprotein	↑	(Wysokiński, Strzelecki, and Kłoszewska 2015)
High density lipoprotein	↓	(Misiak et al. 2017)
Cholesterol	↑	(Wysokiński, Strzelecki, and Kłoszewska 2015)
Ceramide	↑	(Castillo et al. 2016)
Sphingomyelin	↓	(Castillo et al. 2016)
Sphingosine	↑	(Castillo et al. 2016)
Phosphatidylcholine	↓	(Castillo et al. 2016)
Phosphatidylinositol	↓	(Matsumoto et al. 2017)
Phosphatidylethanolamine	↓	(Hamazaki, Choi, and Kim 2010)
Docosahexaenoic acid	↓	(Maekawa et al. 2017)
Docosatetraenoic	↓	(Hussain, Schmitt, Loeffler, et al. 2013)
Docosatetraenoic	↑	(Yang et al. 2017)
Arachidonic acid	↓	(Maekawa et al. 2017)
Palmitic acid	↑	(Yang et al. 2017)
Stearic acid	↑	(Castillo et al. 2016)
Oleic acid	↑	(Yang et al. 2017)
Palmitoleic acid	↑	(Yang et al. 2017)
Linoleic acid	↑	(Yang et al. 2017)

2009). Some of the morphological abnormalities observed in schizophrenia patients' brain include loss of cortical gray matter [29], the reduced hippocampal volume, temporal, the amygdala, frontal lobes and distended ventricular areas [30].

The level of TC and LDL increases while level of HDL becomes lower in the SZ patients (Wysokiński, Strzelecki, and Kłoszewska 2015; Misiak et al. 2017). The level of Cer is significantly higher in patients with SZ while the level of PC is found to be lower in white matter. PC is the choline donor of SM in oligodendrocytes and neurons. The level of Cer is enhanced due to the activation of SMase and SMase is over-activated due to enhanced PS level on left thalamic gray matter of the SZ patients. All these factors promote phagocytosis of the apoptotic cells (Castillo et al. 2016). Moreover, the pro-inflammatory metabolites like Cer level is also enhanced by the activation of SMase due to environmental stress (oxidative stress, psychoactive substances, and cytokines). These factors decrease the myelination and also impairs synaptic transmission (Mühle et al. 2013; Jana, Hogan, and Pahan 2009). Furthermore, reduced level of 16:0/20:4 PI is observed in prefrontal cortex of SZ patients (Matsumoto et al. 2017). A significant reduction in PPE level has also been observed in the frontal cortex of patients (Hamazaki, Choi, and Kim 2010).

It has been proposed that reduction in blood ω-3 PUFAs is involved in cognitive impairment, which ultimately influences the social attitude of patients (Satogami et al. 2017). PUFAs insufficiency tends to increase the risk factor of SZ pathogenesis. Dietary deficiency of two PUFAs including DHA and AA mimics SZ like phenotype in mouse. Moreover, deficiency of PUFAs in the course of early age also portrays prodromal phase of schizophrenia through

nuclear receptor genes epigenetic silencing (Maekawa et al. 2017).

Both in chronic and acute phase of the SZ, a minimized ratio of PUFAs in the cell membrane have been found (Solberg et al. 2016). Moreover, docosatetraenoic acid is also reduced (Hussain, Schmitt, Loeffler, et al. 2013) but recent data indicate that docosatetraenoic acid is enhanced in SZ (Yang et al. 2017). Reduced ω-6 and ω-3 PUFAs are primarily involved in membrane functions abnormalities associated with SZ progression (Reddy, Keshavan, and Yao 2004; Solberg et al. 2016). Reduction in the total membrane PUFAs seen in erythrocytes of young patients with SZ is associated with the grades of demyelination in the white matter of brain (Peters et al. 2009). Level of MUFA (oleic acid, palmitoleic acid) and ω-3 PUFAs (docosatetraenoic acid, arachidonic acid and linoleic acid) is higher in SZ patients as compared to healthy control. This results in enhanced β-oxidation and lipolysis (Yang et al. 2017). The altered lipid metabolism in SZ has been portrayed in the Table 7.

Metabolism of lipids in neurological disorders

Epilepsy

Epilepsy is the most prevalent neurological disorder and an important cause of mortality and disability around the world (Reda et al. 2015). The epileptic state is associated with the initiation of epileptic seizures followed by the abnormal and excessive nerve cells activity in the cortex region of brain (Staley 2015). Epileptic seizures are the most common neurological symptoms in the human being. They are defined as the paroxysmal events of alteration in

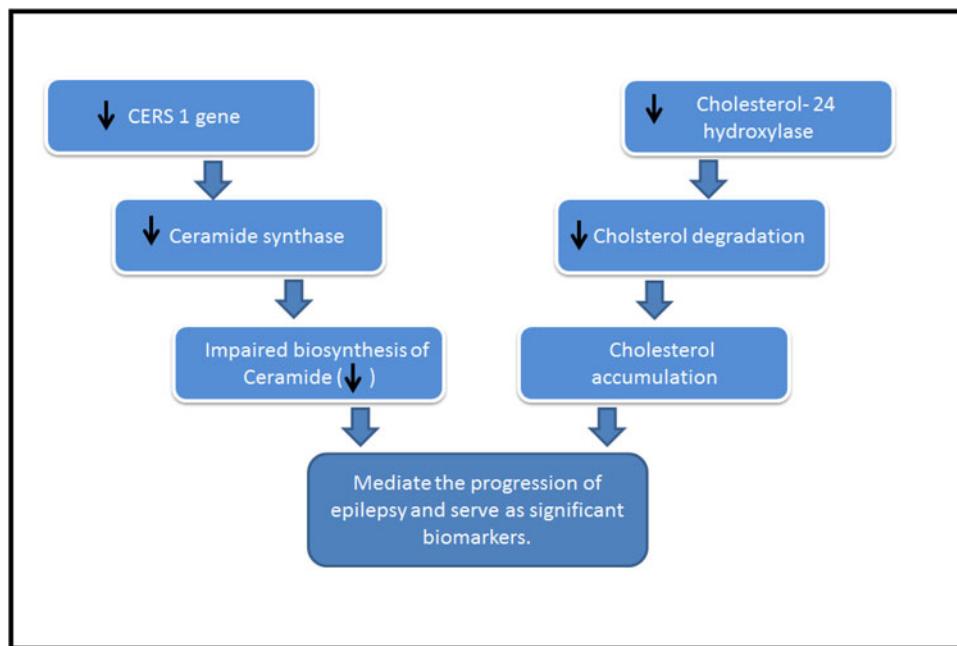


Figure 5. Lipids metabolism mediated epilepsy progression.

consciousness followed by the brain dysfunctions (Chali et al. 2015). A consistent neuronal cell death is evident in the temporal lobe of epileptic brain. According to an epidemiological study, among the NDs, epilepsy is one of the major health ailment (Hussain, Shahzad, et al. 2017).

Elevated cholesterol is involved in the initiation of many neurological as well as neurodegenerative disorders. Cholesterol is degraded by an enzyme named as cholesterol 24-hydroxylase, encoded by CYP46A1 gene. Interestingly, by the inhibition of this catabolic enzyme, cholesterol level in the neurons of hippocampus increases. In turn this increased cholesterol results in the neuronal cell death and deviant hippocampal synchronies (Chali et al. 2015). Thus, it can be stated that altered metabolism of cholesterol can serve as a biomarker of epilepsy.

Many factors are involved in the pathogenesis of epilepsy and may serve as the biomarkers. In this regard, impaired lipids metabolism can a better choice because it modulates the progression of disease by different interplayed mechanisms. Impaired Cer and sphingolipids metabolism is linked with epilepsy. C18 Cer is catalyzed by ceramide synthase-1 (CERS1) and is expressed in healthy brain. In epileptic brain, mutation in CERS-1 gene occurs and is down regulated. Hence, Cer level is also lowered followed by the down regulation of CERS1 gene (Figure 5). Thus, impaired biosynthesis of Cer can be used as a diagnostic measure for epilepsy (Sugiyama et al. 2015).

It is noteworthy that most of the lipids have been used as therapeutic intervention in epilepsy. To date, a few studies have been conducted to explore the new biomarkers of this disease and very few classes of lipids with altered metabolism have been found in epilepsy. Moreover, for elucidation of the exact mechanistic approach of lipids alteration involved in epilepsy pathogenesis, more work is required. The altered lipids metabolism in epilepsy has been summarized in the Table 8.

Table 8. Altered lipid metabolism in epilepsy.

Lipids classification	Lipids alteration	References
Cholesterol	↑	(Chali et al. 2015)
Ceramide	↓	(Sugiyama et al. 2015)

Migraine

Migraine is a neurovascular ailment, which affects 10-15% subjects of the general population (Smitherman et al. 2013). It is characterized by the throbbing, intense, recurrent and unilateral head pain that is often related to vomiting, nausea, phonophobia and photophobia. The exact mechanism underlying the migraine pathogenesis is still incompletely understood. But, it has become evident that neurogenic inflammation and neuropeptide release play pivotal role in pain generation in migraine (Burgos-Vega, Moy, and Dussor 2015).

Along with many other factors involved in pathogenesis, altered lipids metabolism is also noted in the patients. Association of abnormal lipids profile may be associated with severity of migraine (Rist, Tzourio, and Kurth 2011). Serum levels of both TC and total glycerides (TG) also found to be elevated. Whereas, the underlying pathways and mechanistic approaches of elevated cholesterol in pathogenesis has not been explored yet. Moreover, higher level of cholesterol and triglycerides along with the low LDL level is connected with the migraine while level of HDL has no relation (Saberi et al. 2011).

Furthermore, sphingolipids metabolism dysfunction is also an important factor which affects the pathogenesis of migraine. Like altered enzymatic activity of sphingolipids phosphorylation or hydrolysis also contributes to the level of Cer. Importantly, up regulation of ceramidase activity also results in lowering Cer level. This down regulated Cer level is directly linked with the increased pro-inflammatory process, Cer metabolite, and ceramide 1-phosphate (C1P). Whereas, C1P activation is implicated in pathophysiology of migraine, including macrophage chemotaxis, release of AA

Table 9. Altered lipid metabolism in Migraine.

Lipids classification	Lipids alteration	References
Low-density lipoproteins	[↓]	(Rist, Tzourio, and Kurth 2011; Saberi et al. 2011)
Cholesterol	[↑]	(Rist, Tzourio, and Kurth 2011; Saberi et al. 2011)
Triglycerides	[↑]	(Rist, Tzourio, and Kurth 2011; Saberi et al. 2011)
Ceramide	[↓]	(Bikman and Summers 2011; Janoska, Chorążka, and Domitrz 2015)
Ceramide-1 phosphate	[↑]	(Bikman and Summers 2011; Janoska, Chorążka, and Domitrz 2015)
Sphingomyelin	[↑]	(Bikman and Summers 2011; Janoska, Chorążka, and Domitrz 2015)
Arachidonic acid	[↑]	(Bikman and Summers 2011; Janoska, Chorążka, and Domitrz 2015)
Docosahexaenoic acid	[↑]	(Sadeghi et al. 2015)
Eicosapentaenoic	[↑]	(Sadeghi et al. 2015)

Table 10. Altered metabolism of lipids in Stroke.

Lipids classification	Lipids alteration	References
Low-density lipoproteins	[↑]	(Arabadzhieva et al. 2014; Tohidi et al. 2013)
High-density lipoproteins	[↓]	(Arabadzhieva et al. 2014; Tohidi et al. 2013)
Triglycerides	[↓]	(Arabadzhieva et al. 2014; Tohidi et al. 2013)
Ceramide	[↑]	(Borodzicz et al. 2015)
Sphingomyelin	[↓]	(Borodzicz et al. 2015)
Linoleic acid	[↓]	(Iso et al. 2002)
Docosahexaenoic acid	[↑]	(Park et al. 2009)
Eicosapentaenoic acid	[↑]	(Park et al. 2009)
Myristic acid	[↑]	(Yaemsiri et al. 2013)
Palmitic acid	[↑]	(Yaemsiri et al. 2013)
Linoelaidic acid	[↑]	(Yaemsiri et al. 2013)
Oleic acid	[↑]	(Yaemsiri et al. 2013)
Arachidonic acid	[↓]	(Yaemsiri et al. 2013)
α-Linolenic acid	[↓]	(Yaemsiri et al. 2013)
Docosapentaenoic acid	[↓]	(Yaemsiri et al. 2013)
Eicosatetraenoic acid	[↓]	(Yaemsiri et al. 2013).

and prostaglandin E2. To justify the association of altered sphingolipids metabolism with lower Cer level, another possible feature may be the increased activity of sphingomyelin synthase which results in the increased sphingomyelin and lower ceramide levels. Lastly, altered sphingolipids metabolism can also increase the neurogenic inflammation and thus, it may be used as a potential biomarker of migraine (Bikman and Summers 2011; Janoska, Chorążka, and Domitrz 2015).

Among the FAs, up regulated level of linoleic acid is associated with the migraine progression and onset. The mechanism is suggested as increased plasma level of linoleic acid can increase the release of platelet serotonin during the migraine attack and simultaneously, leads to the up regulated synthesis of prostaglandin E1, a powerful vasodilator. Thus, it may serve as a key factor in the progression of migraine attacks. Similarly, ω-3 FAs (EPA and DHA) also affect the frequency of migraine attacks. Several studies have revealed their possible connection with the serotonin level and thus, it may explain the migraine etiology. Lower levels of DHA and EPA result in the higher frequency of migraine (Sadeghi et al. 2015).

Lastly, further research is needed in this aspect to explore the possible mechanism underlying the progression of migraine following the altered lipids metabolism. The altered lipids metabolism in migraine has been summarized in the Table 9.

Metabolism of lipids in brain injuries

Stroke

Stroke is the third principal cause of death which annually troubles almost 780,000 Americans and 150,000 French. After the attack, there is an estimated death rate of 25% during first week and 50% within five years in developed countries. Working capability is negotiated in 70% of victims amongst survivors, while 30% require complete assistance. It leads to reasoning and memory shortfalls, sensory and speech issues, paralysis, functional control impairment and causes post stroke depression, dementia, and long-lasting debility (Blondeau 2011). The stroke among the 85% cases is ischemic which means that the blood vessels are occluded that disrupt the blood flow to a region of the brain. Brain

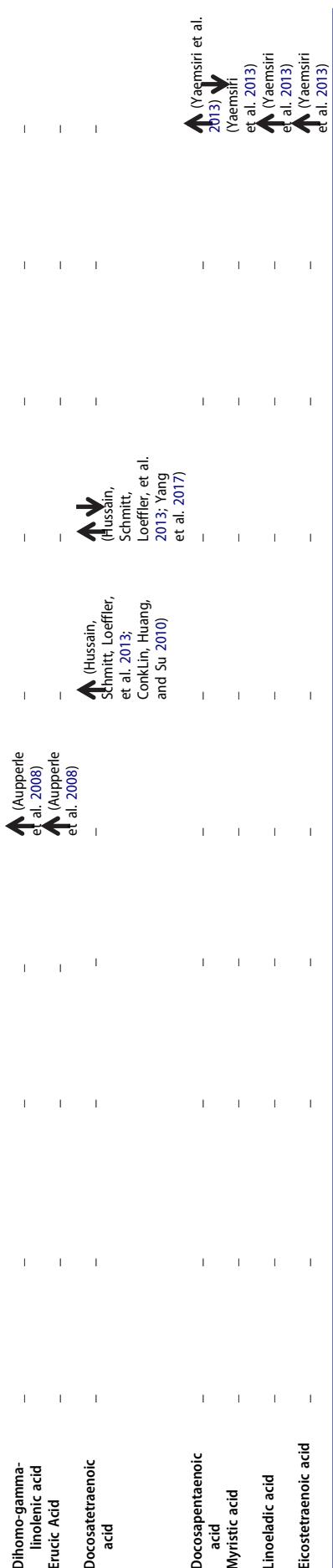
Table 11. Altered lipid metabolism in neurodegenerative, neurological and neuropsychiatry diseases collectively.

Alzheimer's disease	Parkinson's disease	Huntington disease	Amyotrophic lateral sclerosis	Multiple Sclerosis	Depression	Schizophrenia	Epilepsy	Migraine	Stroke
Low density lipoprotein  (Chen 2014)	 (Guo et al. 2015; X. Huang et al. 2008)		 (Weinstock-Guttman et al. 2011)	 (Weinstock-Guttman et al. 2011)	 (Woods et al. 2012; Sarandol et al. 2006; Leito et al. 2010)	 (Woods et al. 2012; Sarandol et al. 2006; Leito et al. 2010)	 (Woods et al. 2012; Sarandol et al. 2006; Leito et al. 2010)	 (Rist, Tzouirio, and Kurth 2011; Saberi et al. 2011)	 (Arabadzhieva et al. 2014; Tohidi et al. 2013)
High density lipoprotein  (Reed et al. 2014; Sato and Morishita 2015)	 (Guo et al. 2015; X. Huang et al. 2008)	 (Hottman et al. 2014)	 (Weinstock-Guttman et al. 2011)	 (Weinstock-Guttman et al. 2011)	 (Misiak et al. 2017)	 (Wysokiński, Strzelecki, and Kłoszewska 2015)	 (Wysokiński, Strzelecki, and Kłoszewska 2015)	 (Rist, Tzouirio, and Kurth 2011; Saberi et al. 2011)	 (Arabadzhieva et al. 2014; Tohidi et al. 2013)
Cholesterol	—	—	 (Gray et al. 2015; Abdel-Khalik et al. 2017; Vejux et al. 2018)	 (Weinstock-Guttman et al. 2011)	 (Weinstock-Guttman et al. 2011)	 (Wysokiński, Strzelecki, and Kłoszewska 2015)	 (Chali et al. 2015)	 (Rist, Tzouirio, and Kurth 2011; Saberi et al. 2011)	 (Arabadzhieva et al. 2014; Tohidi et al. 2013)
S-24 hydrocholesterol Triglycerides	—	—	 (Leoni et al. 2013)	 (Henriques, Croixmarie, et al. 2015)	 (Blasco et al. 2017)	 (Halmer, Walter, and Faßbender 2014; Huwiler et al. 2001)	 (Castillo et al. 2016)	 (Sugiyama et al. 2015)	 (Bikman and Chorążka, and Domitrovic 2015)
Ceramide	 (He et al. 2010)	 (Pose de Chaves and Sipione 2010)	 (Pardo et al. 2017)	 (Blasco et al. 2017; Henriques, Croixmarie, et al. 2015)	 (Halmer, Walter, and Faßbender 2014; Huwiler et al. 2001)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)	 (Bikman and Summers 2011; Janoska, Chorążka, and Domitrovic 2015)	 (Bikman and Summers 2011; Janoska, Chorążka, and Domitrovic 2015)
Glycosylceramides	—	—	—	 (Blasco et al. 2017; Henriques, Croixmarie, et al. 2015)	 (Halmer, Walter, and Faßbender 2014; Huwiler et al. 2001)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)	 (Bikman and Summers 2011; Janoska, Chorążka, and Domitrovic 2015)	 (Bikman and Summers 2011; Janoska, Chorążka, and Domitrovic 2015)
Ceramide-1 phosphate	—	—	—	 (Di Pardo et al. 2017)	 (Ward et al. 2017)	 (Ward et al. 2017)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)
Sphingosine	 (Couttas et al. 2014)	—	 (Di Pardo et al. 2017)	 (Blasco et al. 2017; Schmitt et al. 2014)	 (Komnibuer et al. 2009; Farooqui 2009; Demirkhan et al. 2013)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)	 (Bikman and Summers 2011; Janoska, Chorążka, and Domitrovic 2015)
Dihydro sphingosine	—	—	—	 (Blasco et al. 2017)	 (Komnibuer et al. 2009; Farooqui 2009; Demirkhan et al. 2013)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)	 (Bikman and Summers 2011; Janoska, Chorążka, and Domitrovic 2015)
Sphingomyelin	 (He et al. 2010)	 (Patel and Witt 2017)	 (Pyszko and Stroznajder 2014)	 (Mastrokolias et al. 2016)	 (Blasco et al. 2017)	 (Gracia-Garcia et al. 2011; Demirkhan et al. 2013; X. Liu et al. 2016)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)
Sphingosine-1-phosphate	—	—	 (Pyszko and Stroznajder 2014)	 (Mastrokolias et al. 2016)	 (Blasco et al. 2017)	 (Gracia-Garcia et al. 2011; Demirkhan et al. 2013; X. Liu et al. 2016)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)
Phosphatidylcholine	 (González-Domínguez, García-Barera, and Gómez-Arizta 2014; Kosick and Hecimovic 2013)	 (Farmer et al. 2015)	—	 (Blasco et al. 2017)	 (Kornhuber et al. 2009; Farooqui 2009; Demirkhan et al. 2013)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Castillo et al. 2016)	 (Bikman and Chorążka, and Domitrovic 2015)

(continued)

Table 11. Continued.

	Alzheimer's disease	Parkinson's disease	Huntington disease	Amyotrophic lateral sclerosis	Multiple Sclerosis	Depression	Schizophrenia	Epilepsy	Migraine	Stroke
Phosphatidylinositol	↓(González-Domínguez, García-Barrera, and Gómez-Ariza 2014; Kositek and Hecimović 2013)	↑(Chalmomiruk et al. 2006)	—	—	—	—	↑(Matsumoto et al. 2017)	—	—	—
Phosphatylethanolamine	↑(González-Domínguez, García-Barrera, and Gómez-Ariza 2014; Kosicek and Hecimović 2013)	↑(Patel and Witt 2017)	—	—	—	—	↑(Hamazaki, Choi, and Kim 2010)	—	—	—
Docosahexanoic acid	↑(Martin et al. 2010; J. Thomas et al. 2015)	↑(Hussain, Schmitt, Loeffler, et al. 2013)	↑(Block et al. 2010)	↑(Schmitt et al. 2014)	↑(Koch et al. 2006; Aupperle et al. 2008)	↑(Maekawa, Bentzen, and Puri 2012; Gross et al. 2014)	↑(Maekawa et al. 2017)	—	↑(Sadeghi et al. 2015)	↑(Park et al. 2009)
α-linolenic acid	↑(Yanai 2017)	—	—	—	—	—	—	—	—	↑(Yaeansiri et al. 2013)
Arachidonic acid	↑(Thomas et al. 2016)	↑(Hussain, Schmitt, Loeffler, et al. 2013)	↑(Schmitt et al. 2014)	↑(Aupperle et al. 2008)	↑(R J T Mocking et al. 2016; Mocking et al. 2015)	↑(Mocking et al. 2017)	↑(Maekawa et al. 2017)	—	—	↑(Bikman and Summers 2011; Janoska, Choržáka, and Domitrz 2015)
Palmitic acid	↑(Fraser, Taylor, and Love 2010)	↑(Fabelo et al. 2011)	—	—	—	—	↑(Yang et al. 2017)	—	—	↑(Yaeansiri et al. 2013)
Stearic acid	↑(Fraser, Taylor, and Love 2010)	↑(Fabelo et al. 2011)	—	—	↑(Aupperle et al. 2008)	—	↑(Castillo et al. 2016)	—	—	—
Oleic acid	↑(Fraser, Taylor, and Love 2010; Asturita et al. 2011)	↑(Schmid et al. 2012)	—	↑(Kim et al. 2005)	↑(Aupperle et al. 2008)	↑(Yang et al. 2017)	—	—	—	↑(Yaeansiri et al. 2013)
Palmitoleic acid	↑(Asturita et al. 2010; Martin et al. 2013)	↑(Schmid et al. 2012)	—	—	—	—	↑(Hussain, Schmitt, Loeffler, et al. 2013)	—	—	—
Eicosapentenoic Acid	—	↑(Schmitt, Loeffler, et al. 2013)	↑(Block et al. 2010)	↑(Yip et al. 2013)	↑(Koch et al. 2006; Aupperle et al. 2008)	↑(Martins, Bentzen, and Puri 2012; Gross et al. 2014)	↑(Yang et al. 2017)	—	↑(Sadeghi et al. 2015)	↑(Park et al. 2009)
Linoleic acid	—	↑(Schmid et al. 2012)	—	↑(Kim et al. 2005)	—	—	—	—	—	↑(Iso et al. 2002)



regions which elicit intricate interaction of multiple pathways of cellular signaling become occluded and face deprivation of oxygen and nutrients. This results in the damage of neurovascular entity (endothelial, glial and neuronal cells) of the affected region (Blondeau 2011). There are two main types of stroke: (1) hemorrhagic stroke which occurs due to bleeding and it can be further divided into intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). (2) Ischemic stroke which results from the reduced blood flow can be further divided into transient ischemic attack (TIA) and cerebral infarction (Bu et al. 2016).

Altered cholesterol level is observed in stroke condition. In ischemic stroke (IS), patients' LDL-cholesterol values are higher whereas, HDL-cholesterol and triglycerides levels are reduced. In middle-aged and young individuals the down regulated concentration of HDL- cholesterol acts as an independent risk factor for the development of IS (Arabazhieva et al. 2014; Table 11). A study reports that LDL-cholesterol and HDL-cholesterol are independently related to the increased risk of IS onset in females only (Tohidi et al. 2013; Arabazhieva et al. 2014). The mechanistic approach responsible for this condition is not clear yet.

Apparently, Sphingolipids are also involved in the progression of stroke in which there is an increase in Cer level and the decreased SM level. During ischemia stroke, neuronal apoptosis is mainly followed by the elevated level of Cer. In the brain tissue, the activity of SMase decreases significantly following the ischemic stroke and this can explain the underlying mechanism of altered sphingolipids metabolism (Borodzicz et al. 2015).

Several studies have reported the impaired fatty acids metabolism with the increased risk of disease. Namely, low level of linoleic acid in platelets, erythrocytes, adipose tissue and blood are related with the increased risk of IS and total stroke. In a case study, it was found that FAs alteration is involved in the progression of various subtypes of stroke. Like low level of linoleic acid can accelerate the IS whereas, high levels of serum SFAs and ω -3 PUFAs have been found to be associated with hemorrhagic stroke (Iso et al. 2002).

Higher level of ω -3 PUFAs including EPA and DHA are not only involved in pathogenesis of stroke but they may also increase its risk factor. Both have been found to increase the hemorrhage volume and oxidative stress in a rat model of intracerebral hemorrhagic stroke. They increase the products of lipid peroxidation, lower the activity of protective enzyme SOD and thus, they mediate the stroke progression (Park et al. 2009). Moreover, in ischemia stroke, serum level of myristic acids, palmitic acids and oleic acids have been found to be higher and the serum concentration of AA, DPA, EPA and LA have been found to be lower. This altered FAs level tends to exhibit the higher level of inflammatory markers which are further related to the elevated neurological deterioration (Yaemsiri et al. 2013).

The altered lipids metabolism in stroke has been summarized in the Table 10.

Finally, the following table shows the altered lipids metabolism in neurodegenerative, neurological and neuropsychiatry diseases collectively.

Conclusion and future perspectives

Brain is extremely enriched with lipids where they are important for several key functions such as impulse conduction, insulation, neurogenesis, and synaptogenesis. The metabolism of lipids is very complicated process and is regulated via complex signaling pathways. Although, they carry out a huge number of physiological functions in the brain but, their altered metabolism is also a matter of great interest that adversely affects the brain functions. In fact, the relation behind the altered metabolism of lipids and brain functions rely on the onset of different brain ailments such as neurodegenerative (AD, PD, HD, ALS, MS), neurological (epilepsy, migraine) and neuropsychiatric (depression, SZ) disorders as well as brain injuries such as stroke. In our review, we throw light on the basic classes of lipids including sterols, glycerophospholipids, glycerolipids, sphingolipids and FAs, whose altered metabolism is considered as the biomarkers of these brain ailments. We have enlightened the molecular basis of underlying pathways that how lipids can modulate the pathogenesis of different brain disorders and how they can serve as diagnostic biomarkers. Moreover, it was very interesting to see that in some diseases, the lipids level was augmented whereas in the other disease, the level of same lipids was reduced. We have found the increased level of LDL-C, ceramide, and n-6 PUFAs (AA, palmitic acid) whereas reduced level of HDL-C, sphingomyelin, glycerophospholipids, n-3 PUFAs (EPA, DHA) and stearic acid in case of AD which leads to the aggregation of A β plaques. Unlike AD, the level of HDL-C and AA were found to be attenuated whereas the stearic acid was augmented in PD. Moreover, the level of SM was up-regulated and ceramide was down-regulated in HD which was opposite to as observed in AD, PD and ALS. Interestingly, the n-3 PUFAs (EPA, DHA) were augmented in ALS, migraine, and stroke. About depression, we found the contradictory reports where one said that HDL-C and LDL-C are augmented while other reported them to be reduced. This depicts that the lipids equilibrium is very significant in maintaining the brain health. Moreover, there is very dearth of data regarding lipids alteration in epilepsy which needs to be further investigated. Despite the significant research still there are several lipids whose association with the brain disorders is need be evaluated. As the platforms of lipidomics have become advanced, so it is probably improved and novel analytical and extraction techniques will be available for further estimation. There is a need of encouragement for further research in lipidomics, directed toward the identification of clinically valuable biomarkers for detection of multiple brain disorders at early stages. Moreover, incorporated lipidomics workflow should be developed for optimizing output across several laboratories, and possibly the clinic, would be fundamental to the success of research of lipids biomarkers.

Disclosure statement

The authors declare no conflict of interest.

Abbreviations

AD	Alzheimer's disease
PD	Parkinson's disease
HD	Huntington's disease
ALS	Amyotrophic lateral sclerosis
MS	Multiple sclerosis
SZ	Schizophrenia
NDDs	Neurodegenerative diseases
PUFAs	Polyunsaturated fatty acids
MUFAs	Monounsaturated fatty acids
SFAs	Saturated fatty acids ;
LXR	Liver X receptors
ApoE	Apolipoprotein E
A β	Amyloid beta plaque
APP	Amyloid precursor protein
BACE	Beta site amyloid precursor protein cleavage enzyme
LDL	Low density lipoprotein
HDL	High density lipoprotein
SM	Sphingomyelin
SMase	Sphingomyelinase
PLA ₂	Phospholipase A ₂
GP	Glycerophospholipids
GL	Glycerolipids
GSLs	Glycosphingolipids
PC	Phosphatidylcholine
PI	Phosphatidylinositol
PPE	phosphatidylethanolamine
SN	Substantia nigra
PPAR- γ	Proliferator activator receptor gamma
RXR	Retinoic X receptor
PI-TP	Phosphatidylinositol transfer protein
GPI-Aps	Glycosylphosphatidylinositol anchored proteins
ROS	Reactive oxygen species
SCD	Stearoyl CoA desaturase
GSL	Glycosphingolipids
GBA-1	Glucocerebrosidase 1
GBA2	Glucocerebrosidase 2
GALC	Galactosylceramidase
β -GAL	β galactosidase
α -GAL	α -galactosidase
IL-6	Interleukin-6
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
CERS1	Ceramide synthase-1
C1P	Ceramide-1-phosphate
ICH	Intracerebral hemorrhage
TIA	Transient ischemic attack
IS	Ischemic stroke
TC	Total cholesterol

Funding

This work was supported by the Higher Education Commission of Pakistan (7612/Punjab/NRPU/R&D/HEC/2017) and the National Natural Science Foundation of China.

ORCID

Ghulam Hussain  <http://orcid.org/0000-0001-9090-7789>
Azhar Rasul  <http://orcid.org/0000-0001-9669-7364>

References

- Abbott, S. K., H. Li, S. S. Muñoz, B. Knoch, M. Batterham, K. E. Murphy, G. M. Halliday, and B. Garner. 2014. Altered ceramide acyl chain length and ceramide synthase gene expression in parkinson's disease. *Movement Disorders* 29 (4):518–26. doi:[10.1002/mds.25729](https://doi.org/10.1002/mds.25729).

- Abdel-Khalik, J., E. Yutuc, P. J. Crick, J.-Å. Gustafsson, M. Warner, G. Roman, K. Talbot, E. Gray, W. J. Griffiths, M. R. Turner, et al. 2017. Defective cholesterol metabolism in amyotrophic lateral sclerosis. *Journal of Lipid Research* 58 (1):267–78. doi:[10.1194/jlr.P071639](https://doi.org/10.1194/jlr.P071639).
- Abramov, A. Y., M. Ionov, E. Pavlov, and M. R. Duchen. 2011. Membrane cholesterol content plays a key role in the neurotoxicity of B-Amyloid: Implications for Alzheimer's disease. *Aging Cell* 10(4):595–603. doi: [10.1111/j.1474-9726.2011.00685.x](https://doi.org/10.1111/j.1474-9726.2011.00685.x).
- Amtul, Z., M. Uhrig, R. F. Rozmahel, and K. Beyreuther. 2011. Structural insight into the differential effects of omega-3 and omega-6 fatty acids on the production of abeta peptides and amyloid plaques. *Journal of Biological Chemistry* 286 (8):6100–7. doi: [10.1074/jbc.M110.183608](https://doi.org/10.1074/jbc.M110.183608).
- Amtul, Z., M. Uhrig, L. Wang, R. F. Rozmahel, and K. Beyreuther. 2012. Detrimental effects of arachidonic acid and its metabolites in cellular and mouse models of Alzheimer's disease: Structural insight. *Neurobiology of Aging* 33(4):831.e21. doi: [10.1016/j.neurobiolaging.2011.07.014](https://doi.org/10.1016/j.neurobiolaging.2011.07.014).
- Arabadzhieva, D., Z. Georgieva, A. Kaprelyan, A. Tsukeva, and N. Radeva. 2014. Lipid profile in ischemic stroke patients. *Medicine* IV (1):2012–15.
- Astarita, G., K.-M. Jung, V. Vasilevko, N. V. Dipatrizio, S. K. Martin, D. H. Cribbs, E. Head, C. W. Cotman, and D. Piomelli. 2011. Elevated stearoyl-CoA desaturase in brains of patients with Alzheimer's disease. *PloS One* 6 (10):e24777. doi: [10.1371/journal.pone.0024777](https://doi.org/10.1371/journal.pone.0024777).
- Aupperle, R. L., D. R. Denney, S. G. Lynch, S. E. Carlson, and D. K. Sullivan. 2008. Omega-3 fatty acids and multiple sclerosis: Relationship to depression. *Journal of Behavioral Medicine* 31 (2): 127–35. doi: [10.1007/s10865-007-9139-y](https://doi.org/10.1007/s10865-007-9139-y).
- Baghai, T. C., G. Varallo-Bedarida, C. Born, S. Häfner, C. Schüle, D. Eser, R. Rupprecht, B. Bondy, and C. von Schacky. 2011. Major depressive disorder is associated with cardiovascular risk factors and low omega-3 index. *The Journal of Clinical Psychiatry* 72 (09): 1242–47. doi: [10.4088/JCP.09m05895blu](https://doi.org/10.4088/JCP.09m05895blu).
- Baierle, M., P. Vencato, L. Oldenburg, S. Bordignon, M. Zibetti, C. Trentini, M. Duarte, J. Veit, S. Somacal, T. Emanuelli, et al. 2014. Fatty acid status and its relationship to cognitive decline and homocysteine levels in the elderly. *Nutrients* 6 (9):3624–40. doi: [10.3390/nu6093624](https://doi.org/10.3390/nu6093624).
- Bikman, B. T., and S. A. Summers. 2011. Ceramides as modulators of cellular and whole-body metabolism. *Journal of Clinical Investigation* 121 (11):4222–30. doi: [10.1172/JCI57144](https://doi.org/10.1172/JCI57144).
- Blasco, H., C. Veyrat-Durebex, C. Bocca, F. Patin, P. Vourc'H, J. Kouassi Nzouget, G. Lenaers, C. R. Andres, G. Simard, P. Corcia, and P. Reynier. 2017. Lipidomics reveals Cerebrospinal-Fluid signatures of ALS. *Scientific Reports* 7 (1):17652. doi: [10.1038/s41598-017-17389-9](https://doi.org/10.1038/s41598-017-17389-9).
- Block, R. C., E. Ray Dorsey, A. B. Christopher, J. Thomas Brenna, and I. Shoulson. 2010. Altered cholesterol and fatty acid metabolism in Huntington disease. *Journal of Clinical Lipidology* 4 (1):17–23. doi: [10.1016/j.jacl.2009.11.003](https://doi.org/10.1016/j.jacl.2009.11.003).
- Blondeau, N. 2011. α -Linolenic Omega-3 fatty acid for stroke protection: from brain preconditioning paradigm to nutrition. *Oléagineux, Corps Gras, Lipides* 18 (5):271–78. doi: [10.1684/ocl.2011.0389](https://doi.org/10.1684/ocl.2011.0389).
- Borodzicz, S., K. Czarzasta, M. Kuch, and A. Cudnoch-Jedrzejewska. 2015. Sphingolipids in cardiovascular diseases and metabolic disorders. *Lipids in Health and Disease* 14:55. doi: [10.1186/s12944-015-0053-y](https://doi.org/10.1186/s12944-015-0053-y).
- Bruce, K. D., A. Zsombok, and R. H. Eckel. 2017. Lipid processing in the brain: A key regulator of systemic metabolism. *Frontiers in Endocrinology* 8:60. doi: [10.3389/fendo.2017.00060](https://doi.org/10.3389/fendo.2017.00060).
- Brügger, B. 2014. Lipidomics: Analysis of the lipid composition of cells and subcellular organelles by electrospray ionization mass spectrometry. *Annual Review of Biochemistry* 83 (1):79–98. doi: [10.1146/annurev-biochem-060713-035324](https://doi.org/10.1146/annurev-biochem-060713-035324).
- Bruneteau, G., S. Bauché, J. L. Gonzalez de Aguilar, G. Brochier, N. Mandjee, M.-L. Tanguy, G. Hussain, A. Behin, F. Khiami, E. Sariati, et al. 2015. Endplate denervation correlates with Nogo-A muscle expression in amyotrophic lateral sclerosis patients. *Annals of Clinical and Translational Neurology* 2 (4):362–72. doi: [10.1002/acn3.179](https://doi.org/10.1002/acn3.179).
- Bu, J., Y. Dou, X. Tian, Z. Wang, and G. Chen. 2016. The role of omega-3 polyunsaturated fatty acids in stroke. *Oxidative Medicine and Cellular Longevity* 2016:1. doi: [10.1155/2016/6906712](https://doi.org/10.1155/2016/6906712).
- Burgos-Vega, C., J. Moy, and G. Dussor. 2015. Meningeal afferent signaling and the pathophysiology of migraine. *Progress in Molecular Biology and Translational Science* 131:537–64. doi: [10.1016/bs.pmbts.2015.01.001](https://doi.org/10.1016/bs.pmbts.2015.01.001).
- Calzada, E., O. Onguka, and S. M. Claypool. 2016. Phosphatidylethanolamine metabolism in health and disease. *International Review of Cell and Molecular Biology* 321:29–88. doi: [10.1016/bsircmb.2015.10.001](https://doi.org/10.1016/bsircmb.2015.10.001).
- Castillo, R. I., L. E. Rojo, M. Henriquez-Henriquez, H. Silva, A. Maturana, M. A. Villar, M. Fuentes, and P. A. Gaspar. 2016. From molecules to the clinic: Linking schizophrenia and metabolic syndrome through sphingolipids metabolism. *Frontiers in Neuroscience* 10:488. doi: [10.3389/fnins.2016.00488](https://doi.org/10.3389/fnins.2016.00488).
- Celsi, F., P. Pizzo, M. Brini, S. Leo, C. Fotino, P. Pinton, and R. Rizzuto. 2009. Mitochondria, calcium and cell death: A deadly triad in neurodegeneration. *Biochimica et Biophysica Acta* 1787 (5): 335–44. doi: [10.1016/j.bbabi.2009.02.021](https://doi.org/10.1016/j.bbabi.2009.02.021).
- Cermenati, G., N. Mitro, M. Audano, R. C. Melcangi, M. Crestani, E. De Fabiani, and D. Caruso. 2015. Lipids in the nervous system: From biochemistry and molecular biology to Patho-Physiology. *Biochimica et Biophysica Acta – Molecular and Cell Biology of Lipids* 1851 (1):51–60. doi: [10.1016/j.bbalip.2014.08.011](https://doi.org/10.1016/j.bbalip.2014.08.011).
- Chaibava, M., X. Gao, P. Jain, W. A. Campbell, S. L. Frey, and J. Legleiter. 2018. Sphingomyelin and GM1 influence huntingtin binding to, disruption of, and aggregation on lipid membranes. *ACS Omega* 3 (1):273–85. doi: [10.1021/acsomega.7b01472](https://doi.org/10.1021/acsomega.7b01472).
- Chali, F., F. Djelti, E. Eugene, M. Valderrama, C. Marquer, P. Aubourg, C. Duyckaerts, R. Miles, N. Cartier, and V. Navarro. 2015. Inhibiting cholesterol degradation induces neuronal sclerosis and epileptic activity in mouse hippocampus. *European Journal of Neuroscience* 41 (10):1345–55. doi: [10.1111/ejn.12911](https://doi.org/10.1111/ejn.12911).
- Chalimoniuk, M., G. T. Snoek, A. Adamczyk, A. Małecki, and J. B. Strosznajder. 2006. Phosphatidylinositol transfer protein expression altered by aging and Parkinson disease. *Cellular and Molecular Neurobiology* 26 (7-8):1153–66. doi: [10.1007/s10571-006-9078-0](https://doi.org/10.1007/s10571-006-9078-0).
- Chang, C.-Y., D.-S. Ke, and J.-Y. Chen. 2009. Essential fatty acids and human brain. *Acta Neurologica Taiwanica* 18 (4):231–41. http://www.researchgate.net/profile/Chia_Yu_Chang3/publication/42438067_Essential_fatty_acids_and_human_brain/links/550048aa0cf204d683b3473a.pdf.
- Chen, X. 2014. Role of LDL cholesterol and endolysosomes in amyloidogenesis and Alzheimer's disease. *Journal of Neurology & Neurophysiology* 05 (05):1–15. doi: [10.4172/2155-9562.1000236](https://doi.org/10.4172/2155-9562.1000236).
- Conklin, S. M., C. A. Runyan, S. Leonard, R. D. Reddy, M. F. Muldoon, and J. K. Yao. 2010. Age-Related changes of n-3 and n-6 polyunsaturated fatty acids in the anterior cingulate cortex of individuals with major depressive disorder. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 82 (2-3):111–19. Elsevier: doi: [10.1016/j.plefa.2009.12.002](https://doi.org/10.1016/j.plefa.2009.12.002).
- Couttas, T. A., N. Kain, B. Daniels, X. Y. Lim, C. Shepherd, J. Kril, R. Pickford, H. Li, B. Garner, and S. D. Anthony. 2014. Loss of the neuroprotective factor sphingosine 1-phosphate early in Alzheimer's disease pathogenesis. *Acta Neuropathologica Communications* 2: 9. doi: [10.1186/2051-5960-2-9](https://doi.org/10.1186/2051-5960-2-9).
- Dart, C. 2010. Symposium Review: Lipid microdomains and the regulation of ion channel function. *The Journal of Physiology* 588 (17):3169–78. doi: [10.1113/jphysiol.2010.191585](https://doi.org/10.1113/jphysiol.2010.191585).
- Dayalu, P., and R. L. Albin. 2015. Huntington disease: Pathogenesis and treatment. *Neurologic Clinics* 33 (1):101–14. doi: [10.1016/j.ncl.2014.09.003](https://doi.org/10.1016/j.ncl.2014.09.003).
- Deacon, G., C. Kettle, D. Hayes, C. Dennis, and J. Tucci. 2017. Omega 3 polyunsaturated fatty acids and the treatment of depression. *Critical Reviews in Food Science and Nutrition* 57(1):212–23. Taylor & Francis: doi: [10.1080/10408398.2013.876959](https://doi.org/10.1080/10408398.2013.876959).

- Demirkan, A., A. Isaacs, P. Ugocsai, G. Liebisch, M. Struchalin, I. Rudan, J. F. Wilson, P. P. Pramstaller, U. Gyllensten, H. Campbell, et al. 2013. Plasma phosphatidylcholine and sphingomyelin concentrations are associated with depression and anxiety symptoms in a Dutch Family-Based lipidomics study. *Journal of Psychiatric Research* 47 (3):357–62. doi:10.1016/j.jpsychires.2012.11.001.
- Denis, I., B. Potier, S. Vancassel, C. Heberden, and M. Lavialle. 2013. Omega-3 fatty acids and brain resistance to ageing and stress: Body of evidence and possible mechanisms. *Ageing Research Reviews* 12 (2):579–94. doi:10.1016/j.arr.2013.01.007.
- Doria, M., L. Maugest, T. Moreau, G. Lizard, and A. Vejux. 2016. Contribution of cholesterol and oxysterols to the pathophysiology of Parkinson's disease. *Free Radical Biology and Medicine* 101:393–400. Elsevier: doi:10.1016/j.freeradbiomed.2016.10.008.
- Dupuis, L., H. Oudart, F. Rene, J.-L. G. de Aguilar, and J.-P. Loeffler. 2004. Evidence for defective energy homeostasis in amyotrophic lateral sclerosis: Benefit of a high-energy diet in a transgenic mouse model. *Proceedings of the National Academy of Sciences* 101 (30): 11159–64. doi:10.1073/pnas.0402026101.
- Dyall, S. C. 2015. Long-chain omega-3 fatty acids and the brain: A review of the independent and shared effects of EPA, DPA and DHA. *Frontiers in Aging Neuroscience* 7:52. doi:10.3389/fnagi.2015.00052.
- Eriksson, I., S. Nath, P. Bornefall, A. M. V. Giraldo, and K. Öllinger. 2017. Impact of high cholesterol in a Parkinson's disease model: Prevention of lysosomal leakage versus stimulation of α -synuclein aggregation. *European Journal of Cell Biology* 96(2):99–109. doi: 10.1016/j.ejcb.2017.01.002.
- Fabelo, N., V. Martín, G. Santpere, R. Marín, L. Torrent, I. Ferrer, and M. Díaz. 2011. Severe alterations in lipid composition of frontal cortex lipid rafts from Parkinson's disease and incidental Parkinson's disease. *Molecular Medicine (Cambridge, Mass.)* 17 (9–10):1107–18. doi:10.2119/molmed.2011.00119.
- Fahy, E., D. Cotter, M. Sud, and S. Subramanian. 2011. Lipid classification, structures and tools. *Biochimica et Biophysica Acta – Molecular and Cell Biology of Lipids* 1811 (11):637–47. doi:10.1016/j.bbalip.2011.06.009.
- Farinotti, M., L. Vacchi, S. Simi, C. D. Pietrantonj, L. Brait, and G. Filippini. 2012. "Dietary Interventions for Multiple Sclerosis." In *Cochrane Database of Systematic Reviews*, edited by Mariangela Farinotti, 12:CD004192. Chichester, UK: John Wiley & Sons, Ltd. doi:10.1002/14651858.CD004192.pub3.
- Farmer, K., C. A. Smith, S. Hayley, and J. Smith. 2015. Major alterations of phosphatidylcholine and lysophosphatidylcholine lipids in the *Substantia nigra* using an early stage model of Parkinson's disease. *International Journal of Molecular Sciences* 16 (8):18865–77. doi:10.3390/ijms160818865.
- Farooqui, A. A. 2009. Lipid mediators in the neural cell nucleus: Their metabolism, signaling, and association with neurological disorders. *Neuroscientist* 15 (4):392–407. doi:10.1177/10738540937035.
- Farooqui, A. A., L. A. Horrocks, and T. Farooqui. 2000. Glycerophospholipids in brain: Their metabolism, incorporation into membranes, functions, and involvement in neurological disorders. *Chemistry and Physics of Lipids* 106 (1):1–29. doi:10.1016/S0009-3084(00)00128-6.
- Fernandes, M. F., D. M. Mutch, and F. Leri. 2017. The relationship between fatty acids and different depression-related brain regions, and their potential role as biomarkers of response to antidepressants. *Nutrients* 9 (3):298. doi:10.3390/nu9030298.
- Fitzgerald, K. C., É. J. O'Reilly, G. J. Falcone, M. L. McCullough, Y. Park, L. N. Kolonel, and A. Ascherio. 2014. Dietary ω -3 polyunsaturated fatty acid intake and risk for amyotrophic lateral sclerosis. *JAMA Neurology* 71 (9):1102. doi:10.1001/jamaneurol.2014.1214.
- Fraser, T., H. Tayler, and S. Love. 2010. Fatty acid composition of frontal, temporal and parietal neocortex in the normal human brain and in Alzheimer's disease. *Neurochemical Research* 35 (3):503–13. doi:10.1007/s11064-009-0087-5.
- Frisardi, V., F. Panza, D. Seripa, T. Farooqui, and A. F. Akhlaq. 2011. Glycerophospholipids and Glycerophospholipid-Derived lipid mediators: A complex meshwork in Alzheimer's disease pathology. *Progress in Lipid Research* 50 (4):313–30. doi:10.1016/j.plipres.2011.06.001.
- Futerman, A. H. 2016. Sphingolipids. *Biochemistry of Lipids, Lipoproteins and Membranes*, 5th edition, 297–326. doi:10.1016/B978-0-444-63438-2.00010-9.
- Galvagnion, C., \ddagger Line, A. K. Buell, G. Meisl, T. C. T. Michaels, M. Vendruscolo, T. P. J. Knowles, and C. M. Dobson. 2015. Lipid vesicles trigger α -synuclein aggregation by stimulating primary nucleation. *Nature Chemical Biology* 11 (3):229–34. doi:10.1038/nchembio.1750.
- Gamba, P., G. Testa, B. Sottero, S. Gargiulo, G. Poli, and G. Leonarduzzi. 2012. The link between altered cholesterol metabolism and Alzheimer's disease. *Annals of the New York Academy of Sciences* 1259 (1):54–64. doi:10.1111/j.1749-6632.2012.06513.x.
- Ghosh, S., J. C. Strum, and R. M. Bell. 1997. Lipid biochemistry: Functions of glycerolipids and sphingolipids in cellular signaling. *FASEB Journal : Official Publication of the Federation of American Societies for Experimental Biology* 11 (1):45–50. United States:
- Gil-Mohapel, J., P. Brocardo, and B. Christie. 2014. The role of oxidative stress in Huntington's disease: Are antioxidants good therapeutic candidates? *Current Drug Targets* 15 (4):454–68. doi:10.2174/138945011566140115113734.
- Goldenberg, M. M. 2012. Multiple sclerosis review. *P & T: A Peer-Reviewed Journal for Formulary Management* 37 (3):175–84. <http://www.ncbi.nlm.nih.gov/article/abstract.fcgi?artid=3351877&tool=pmcentrez&rendertype=abstract>.
- González-Domínguez, R., T. García-Barrera, and J. L. Gómez-Ariza. 2014. Combination of metabolomic and phospholipid-profiling approaches for the study of Alzheimer's disease. *Journal of Proteomics* 104:37–47. doi:10.1016/j.jprot.2014.01.014.
- Gracia-Garcia, P., V. Rao, N. J. Haughey, V. V. Ratnam Banduru, G. Smith, P. B. Rosenberg, A. Lobo, C. G. Lyketsos, and M. M. Mielke. 2011. Elevated plasma ceramides in depression. *The Journal of Neuropsychiatry and Clinical Neurosciences* 23 (2):215–18. doi:10.1176/appi.neuropsych.23.2.215.
- Gray, E., J. R. Larkin, T. D. W. Claridge, K. Talbot, N. R. Sibson, and M. R. Turner. 2015. The longitudinal cerebrospinal fluid metabolic profile of amyotrophic lateral sclerosis. *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration* 16 (7–8):456–63. doi:10.3109/21678421.2015.1053490.
- Grosso, G., F. Galvano, S. Marventano, M. Malaguarnera, C. Bucolo, F. Drago, and F. Caraci. 2014. Omega-3 fatty acids and depression: Scientific evidence and biological mechanisms. *Oxidative Medicine and Cellular Longevity*. Hindawi Publishing Corporation 2014:1. doi:10.1155/2014/313570.
- Guardia-Laguarta, C., E. Area-Gomez, E. A. Schon, and S. Przedborski. 2015. A new role for α -synuclein in Parkinson's disease: Alteration of ER-mitochondrial communication. *Movement Disorders* 30 (8): 1026–33. doi:10.1002/mds.26239.
- Guo, X., W. Song, K. Chen, X. P. Chen, Z. Zheng, B. Cao, R. Huang, B. Zhao, Y. Wu, and H.-F. Shang. 2015. The serum lipid profile of Parkinson's disease patients: A study from China. *International Journal of Neuroscience* 125 (11):838–44. doi:10.3109/00207454.2014.979288.
- Haag, M. 2003. Essential fatty acids and the brain. *The Canadian Journal of Psychiatry* 48 (3):195–203. doi:10.1177/070674370304800308.
- Halmer, R., S. Walter, and K. Faßbender. 2014. Sphingolipids: Important players in multiple sclerosis. *Cellular Physiology and Biochemistry* 34 (1):111–8. doi:10.1159/000362988.
- Hamazaki, K., K. H. Choi, and H. Y. Kim. 2010. Phospholipid profile in the postmortem hippocampus of patients with schizophrenia and bipolar disorder: No changes in docosahexaenoic acid species. *Journal of Psychiatric Research* 44 (11):688–93. doi:10.1016/j.jpsychires.2009.11.017.
- Hamazaki, K., T. Hamazaki, and H. Inadera. 2012. Fatty acid composition in the postmortem amygdala of patients with schizophrenia, bipolar disorder, and major depressive disorder. *Journal of Psychiatric Research* 46 (8):1024–28. doi:10.1016/j.jpsychires.2012.04.012.

- He, X., Y. Huang, B. Li, C.-X. Gong, and E. H. Schuchman. 2010. Deregulation of sphingolipid metabolism in Alzheimer's disease. *Neurobiology of Aging* 31 (3):398–408. doi:[10.1016/j.neurobiolaging.2008.05.010](https://doi.org/10.1016/j.neurobiolaging.2008.05.010).
- Henriques, A., H. Blasco, M.-C. Fleury, P. Corcia, A. Echaniz-Laguna, L. Robelin, G. Rudolf, T. Lequeu, M. Bergaentzle, C. Gachet, et al. 2015. Blood cell Palmitoleate-Palmitate ratio is an independent prognostic factor for amyotrophic lateral sclerosis. *Plos One* 10 (7):e0131512. doi:[10.1371/journal.pone.0131512](https://doi.org/10.1371/journal.pone.0131512).
- Henriques, A., V. Croixmarie, D. A. Priestman, A. Rosenbohm, S. Dirrig-Grosch, E. D'Ambra, M. Huebecker, G. Hussain, C. Boursier-Neyret, A. Echaniz-Laguna, et al. 2015. Amyotrophic lateral sclerosis and denervation alter sphingolipids and up-regulate glucosylceramide synthase. *Human Molecular Genetics* 24 (25):7390–7405. doi:[10.1093/hmg/ddv439](https://doi.org/10.1093/hmg/ddv439).
- Hong, C., and P. Tontonoz. 2014. Liver X receptors in lipid metabolism: opportunities for drug discovery. *Nature reviews drug discovery*. 13 (6):433–44. doi:[10.1038/nrd4280](https://doi.org/10.1038/nrd4280).
- Horres, C. R., and Y. A. Hannun. 2012. The roles of neutral sphingomyelinases in neurological pathologies. *Neurochemical Research* 37 (6):1137–49. doi:[10.1007/s11064-011-0692-y](https://doi.org/10.1007/s11064-011-0692-y).
- Hottman, D. A., D. Chernick, S. Cheng, Z. Wang, and L. Li. 2014. HDL and cognition in neurodegenerative disorders. *Neurobiology of Disease* 72 Pt A:22–36. doi:[10.1016/j.nbd.2014.07.015](https://doi.org/10.1016/j.nbd.2014.07.015).
- Huang, C., and C. Freter. 2015. Lipid metabolism, apoptosis and cancer therapy. *International Journal of Molecular Sciences* 16 (1):924–49. doi:[10.3390/ijms16010924](https://doi.org/10.3390/ijms16010924).
- Huang, X., R. D. Abbott, H. Petrovitch, R. B. Mailman, and G. W. Ross. 2008. Low LDL cholesterol and increased risk of Parkinson's disease: Prospective results from Honolulu-Asia aging study. *Movement Disorders* 23 (7):1013–18. doi:[10.1002/mds.22013](https://doi.org/10.1002/mds.22013).
- Huang, Y., and R. W. Mahley. 2014. Apolipoprotein E: Structure and function in lipid metabolism, neurobiology, and Alzheimer's diseases. *Neurobiology of Disease* 72 Pt A:3–12. doi:[10.1016/j.nbd.2014.08.025](https://doi.org/10.1016/j.nbd.2014.08.025).
- Hussain, G., A. Rasul, H. Anwar, N. Aziz, A. Razzaq, W. Wei, M. Ali, J. Li, and X. Li. 2018. Role of plant derived alkaloids and their mechanism in neurodegenerative disorders. *International Journal of Biological Sciences* 14 (3):341–57. doi:[10.7150/ijbs.23247](https://doi.org/10.7150/ijbs.23247).
- Hussain, G., A. Rasul, H. Anwar, M. U. Sohail, S. Kashif, S. Kamran, S. M. Baig, and A. Shabbir. 2017. Epidemiological data of neurological disorders in Pakistan and neighboring countries: A review epidemiological data of neurological disorders in Pakistan and neighboring countries: A review. *Pakistan Journal of Neurological Sciences* 8 (6):12.
- Hussain, G., F. Schmitt, A. Henriques, T. Lequeu, F. Rene, F. Bindler, and S. Dirrig-Grosch. 2013.. Systemic down-regulation of delta-9 desaturase promotes muscle oxidative metabolism and accelerates muscle function recovery following nerve injury. *PLoS ONE* 8 (6):e64525. doi:[10.1371/journal.pone.0064525](https://doi.org/10.1371/journal.pone.0064525).
- Hussain, G., F. Schmitt, J.-P. Loeffler, and J.-L. G. D Aguilar. 2013. Fattening the brain: a brief of recent research. *Frontiers in Cellular Neuroscience* 7:1–14. doi:[10.3389/fncel.2013.00144](https://doi.org/10.3389/fncel.2013.00144).
- Hussain, G., A. Shahzad, H. Anwar, M. U. Sohail, S. M. Baig, A. Shabbir, J.-L. G. O. N. Z. A. L. E. Z. D. E. Aguilar, and J. Iqbal. 2017. Neurological disorder burden in Faisalabad, Punjab-Pakistan: Data from the major tertiary care centers of the city. *Pakistan Journal of Neurological Sciences* 12 (3):814.
- Hussain, G., L. Zhang, A. Rasul, H. Anwar, M. Sohail, A. Razzaq, N. Aziz, A. Shabbir, M. Ali, and T. Sun. 2018. Role of Plant-Derived flavonoids and their mechanism in attenuation of Alzheimer's and Parkinson's diseases: An update of recent data. *Molecules* 23 (4):814. doi:[10.3390/molecules23040814](https://doi.org/10.3390/molecules23040814).
- Huwiler, A., B. Johansen, A. Skarstad, and J. Pfeilschifter. 2001. Ceramide binds to the CaLB domain of cytosolic phospholipase A2 and facilitates its membrane docking and arachidonic acid release. *FASEB Journal: Official Publication of the Federation of American Societies for Experimental Biology* 15 (1):7–9. doi:[10.1096/fj.00-0370fje](https://doi.org/10.1096/fj.00-0370fje).
- Igarashi, M., R. A Santos, and S. Cohen-Cory. 2015. Impact of maternal N-3 polyunsaturated fatty acid deficiency on dendritic arbor morphology and connectivity of developing *Xenopus Laevis* Central neurons in vivo. *The Journal of Neuroscience* 35 (15):6079–92. doi:[10.1523/JNEUROSCI.4102-14.2015](https://doi.org/10.1523/JNEUROSCI.4102-14.2015).
- Iso, H., S. Sato, U. Umemura, M. Kudo, K. Koike, A. Kitamura, H. Imano, T. Okamura, Y. Naito, and T. Shimamoto. 2002. Linoleic acid, other fatty acids, and the risk of stroke. *Stroke* 33 (8):2086–93. doi:[10.1161/01.STR.0000023890.25066.50](https://doi.org/10.1161/01.STR.0000023890.25066.50).
- Jana, A., E. L. Hogan, and K. Pahan. 2009. Ceramide and neurodegeneration: Susceptibility of neurons and oligodendrocytes to cell damage and death. *Journal of the Neurological Sciences* 278 (1-2):5–15. doi:[10.1016/j.jns.2008.12.010](https://doi.org/10.1016/j.jns.2008.12.010).
- Janoska, M., K. Chorążka, and I. Domitrz. 2015. Migraine frequency and its association with dyslipidemia in women. *Neurologia i Neurochirurgia Polska* 49 (2):95–98. doi:[10.1016/j.pjnns.2015.02.001](https://doi.org/10.1016/j.pjnns.2015.02.001).
- Kahn, R. S., I. E. Sommer, M. M. Robin, A. Meyer-Lindenberg, R. W. Daniel, D. C. Tyrone, and M. O'Donovan. 2015. Schizophrenia. *Nature Reviews Disease Primers* 1:15067. doi:[10.1038/nrdp.2015.67](https://doi.org/10.1038/nrdp.2015.67).
- Karasinska, J. M., and M. R. Hayden. 2011. Cholesterol metabolism in Huntington disease. *Nature Reviews Neurology*. 7 (10):561–72. doi:[10.1038/nrneurol.2011.132](https://doi.org/10.1038/nrneurol.2011.132).
- Kim, S., A. J. Steelman, Y. Zhang, H. C. Kinney, and J. Li. 2012. Aberrant upregulation of astroglial ceramide potentiates oligodendrocyte injury. *Brain Pathology* 22 (1):41–57. doi:[10.1111/j.1750-3639.2011.00501.x](https://doi.org/10.1111/j.1750-3639.2011.00501.x).
- Kim, Y.-J., R. Nakatomi, T. Akagi, T. Hashikawa, and R. Takahashi. 2005. Unsaturated fatty acids induce cytotoxic aggregate formation of amyotrophic lateral Sclerosis-Linked superoxide dismutase 1 mutants. *Journal of Biological Chemistry* 280(22):21515–21. doi:[10.1074/jbc.M502230200](https://doi.org/10.1074/jbc.M502230200).
- Koch, M., G. S. M. Ramsaransing, M. R. Fokkema, D. J. Heersema, and J. De Keyser. 2006. Erythrocyte membrane fatty acids in benign and progressive forms of multiple sclerosis. *Journal of the Neurological Sciences* 244 (1-2):123–26. doi:[10.1016/j.jns.2006.01.010](https://doi.org/10.1016/j.jns.2006.01.010).
- Kong-González, M., J. G. Pérez-Cortéz, C. Hernández-Girón, N. Macías-Morales, and M. Flores-Aldana. 2015. [Polyunsaturated fatty acids for multiple sclerosis treatment: Scientific evidence]. *Medwave* 15 (1):e6062.
- Kori, M., B. Aydin, S. Unal, K. Y. Arga, and D. Kazan. 2016. Metabolic biomarkers and neurodegeneration: A pathway enrichment analysis of Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis. *OMICS: A Journal of Integrative Biology* 20 (11):645–61. doi:[10.1089/omi.2016.0106](https://doi.org/10.1089/omi.2016.0106).
- Kornhuber, J., M. Reichel, P. Tripal, W. G. Teja, W. H. Andreas, C. Mühlé, and E. Gulbins. The role of ceramide in major depressive disorder. *European Archives of Psychiatry and Clinical Neuroscience* 209, 259(Suppl. 2) :S199–S204. doi:[10.1007/s00406-009-0061-x](https://doi.org/10.1007/s00406-009-0061-x).
- Kosicek, M., and S. Hecimovic. 2013. Phospholipids and Alzheimer's disease: Alterations, mechanisms and potential biomarkers. *International Journal of Molecular Sciences* 14 (1): 1310–22. doi:[10.3390/ijms14011310](https://doi.org/10.3390/ijms14011310).
- Kreilaus, F., A. S. Spiro, C. A. McLean, B. Garner, and A. M. Jenner. 2016. Evidence for altered cholesterol metabolism in Huntington's disease post mortem brain tissue. *Neuropathology and Applied Neurobiology* 42 (6):535–46. doi:[10.1111/nan.12286](https://doi.org/10.1111/nan.12286).
- Krycer, J. R., L. J. Sharpe, W. Luu, and J. B. Andrew. 2010. The Akt-SREBP nexus: Cell signaling meets lipid metabolism. *Trends in Endocrinology and Metabolism* 21 (5):268–76. doi:[10.1016/j.tem.2010.01.001](https://doi.org/10.1016/j.tem.2010.01.001).
- Lammert, E., and M. Zeeb. 2016. Metabolism of human diseases: Organ physiology and pathophysiology edited by Eckhard Lammert and Martin Zeeb. *The Quarterly Review of Biology* 91 (2):236. doi:[10.1086/686874](https://doi.org/10.1086/686874).
- Lehto, S. M., L. Niskanen, T. Tolmunen, J. Hintikka, H. Viinamaki, T. Heiskanen, K. Honkalampi, M. Kokkonen, and H. Koivumaa-Honkanen. 2010. Low serum HDL-Cholesterol levels are associated with long symptom duration in patients with major depressive disorder. *Psychiatry and Clinical Neurosciences* 64 (3):279–83. doi:[10.1111/j.1440-1819.2010.02079.x](https://doi.org/10.1111/j.1440-1819.2010.02079.x).
- Leoni, V., and C. Caccia. 2015. The impairment of cholesterol metabolism in Huntington disease. *Biochimica et Biophysica Acta* –

- Molecular and Cell Biology of Lipids* 1851 (8):1095–1105. doi: 10.1016/j.bbaplip.2014.12.018.
- Leoni, V., J. D. Long, J. A. Mills, S. Di Donato, and J. S. Paulsen. 2013. Plasma 24S-Hydroxycholesterol correlation with markers of Huntington disease progression. *Neurobiology of Disease* 55:37–43. doi:10.1016/j.nbd.2013.03.013.
- Lin, P.-Y., S.-Y. Huang, and K.-P. Su. 2010. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biological Psychiatry* 68 (2):140–47. doi:10.1016/j.biopsych.2010.03.018.
- Liu, C. C., T. Kanekiyo, H. Xu, and G. Bu. 2013. Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. *Nature Reviews Neurology* 9 (2):106–18. doi:10.1038/nrneurol.2012.263.
- Liu, J., and F. Wang. 2017. Role of neuroinflammation in amyotrophic lateral sclerosis: Cellular mechanisms and therapeutic implications. *Frontiers in Immunology* 8:1005. doi:10.3389/fimmu.2017.01005.
- Liu, Q., and J. Zhang. 2014. Lipid metabolism in Alzheimer's disease. *Neuroscience Bulletin* 30 (2):331–45. doi:10.1007/s12264-013-1410-3.
- Liu, X., J. Li, P. Zheng, X. Zhao, C. Zhou, C. Hu, X. Hou, H. Wang, P. Xie, and G. Xu. 2016. Plasma lipidomics reveals potential lipid markers of major depressive disorder. *Analytical and Bioanalytical Chemistry* 408 (23):6497–6507. doi:10.1007/s00216-016-9768-5.
- Luchtman, D. W., and C. Song. 2013. Cognitive enhancement by omega-3 fatty acids from Child-Hood to old age: Findings from animal and clinical studies. *Neuropharmacology* 64:550–65. doi:10.1016/j.neuropharm.2012.07.019.
- Maekawa, M., A. Watanabe, Y. Iwayama, T. Kimura, K. Hamazaki, S. Balan, H. Ohba, Y. Hisano, Y. Nozaki, T. Ohnishi, et al. 2017. Polyunsaturated fatty acid deficiency during neurodevelopment in mice models the prodromal state of schizophrenia through epigenetic changes in nuclear receptor genes. *Translational Psychiatry* 7(9):e1229–11. doi:10.1038/tp.2017.182.
- Mahad, D. H., B. D. Trapp, and H. Lassmann. 2015. Pathological mechanisms in progressive multiple sclerosis. *The Lancet Neurology* 14 (2):183–93. doi:10.1016/S1474-4422(14)70256-X.
- Martín, V., N. Fabelo, G. Santpere, B. Puig, R. Marín, I. Ferrer, and M. Díaz. 2010. Lipid alterations in lipid rafts from Alzheimer's disease human brain cortex. *Journal of Alzheimer's Disease* 19 (2):489–502. Netherlands: doi:10.3233/JAD-2010-1242.
- Martins, J. G., H. Bentsen, and B. K. Puri. 2012. Eicosapentaenoic acid appears to be the key omega-3 fatty acid component associated with efficacy in major depressive disorder: A critique of Bloch and Hannestad and updated meta-analysis. *Molecular Psychiatry* 17 (12):1144–9. doi:10.1038/mp.2012.25.
- Mastrokolas, A., R. Pool, E. Mina, M. H. Kristina, E. V Duijn, C. V D M. Roos, and G. J. V Ommen. 2016. Integration of targeted metabolomics and transcriptomics identifies deregulation of phosphatidylcholine metabolism in Huntington's disease peripheral blood samples. *Metabolomics* 12 (8)Springer US:1–15. doi:10.1007/s11306-016-1084-8.
- Mathews, C. K., and K. E. van Holde. 1991. Biochemistry. *Journal of Chemical Education* 68 (1):A21. doi:10.1021/ed068pA21.1.
- Matsumoto, J., H. Nakanishi, Y. Kunii, Y. Sugiura, D. Yuki, A. Wada, and M. Hino. 2017. Decreased 16:0/20:4-phosphatidylinositol level in the post-mortem prefrontal cortex of elderly patients with schizophrenia. *Scientific Reports* 7 (February):6–7. doi:10.1038/srep45050.
- Mattes, R. D. 2005. Fat taste and lipid metabolism in humans. *Physiology and Behavior* 86 (5):691–97. doi:10.1016/j.physbeh.2005.08.058.
- Maulik, M., D. Westaway, J. H. Jhamandas, and S. Kar. 2013. Role of cholesterol in APP metabolism and its significance in Alzheimer's disease pathogenesis. *Molecular Neurobiology* 47 (1):37–63. doi:10.1007/s12035-012-8337-y.
- Mielke, M. M., N. J. Haughey, V. V. R. Bandaru, D. D. Weinberg, E. Darby, N. Zaidi, V. Pavlik, R. S. Doody, and C. G. Lyketsos. 2011. Plasma sphingomyelins are associated with cognitive progression in Alzheimer's disease. *Journal of Alzheimer's Disease* 27 (2):259–69. doi:10.3233/JAD-2011-110405.
- Misiak, B., B. Stańczykiewicz, Ł. Łaczmański, and D. Frydecka. 2017. Lipid profile disturbances in antipsychotic-naïve patients with first-episode non-affective psychosis: A systematic review and meta-analysis. *Schizophrenia Research* 190: 18–27. doi:10.1016/j.schres.2017.03.031.
- Mocking, R. J. T., I. Harmsen, J. Assies, M. W. J. Koeter, H. G. Ruhé, and A. H. Schene. 2016. Meta-analysis and meta-regression of omega-3 polyunsaturated fatty acid supplementation for major depressive disorder. *Translational Psychiatry* 6 (3):e756. doi:10.1038/tp.2016.29.
- Mocking, R. J. T., H. F. Verburg, A. M. Westerink, J. Assies, F. M. Vaz, M. W. J. Koeter, H. G. Ruhé, and A. H. Schene. 2015. Fatty acid metabolism and its longitudinal relationship with the Hypothalamic-Pituitary-Adrenal Axis in major depression: Associations with prospective antidepressant response. *Psychoneuroendocrinology* 59:1–13. (September). Elsevier: doi:10.1016/j.psyneuen.2015.04.027.
- Mubarak, M., A. Shaija, and T. V. Suchithra. 2015. A review on the extraction of lipid from microalgae for biodiesel production. *Algal Research* 7:117–123. doi:10.1016/j.algal.2014.10.008.
- Mühle, C., M. Reichel, E. Gulbins, and J. Kornhuber. 2013. Sphingolipids in psychiatric disorders and pain syndromes. *Handbook of Experimental Pharmacology* 216:431–56. doi:10.1007/978-3-7091-1511-4-22.
- Mullen, T. 2012. Ceramide and apoptosis: Exploring the enigmatic connections between sphingolipid metabolism and programmed cell death. *Anti-Cancer Agents in Medicinal Chemistry* 12 (4):224–25. doi:10.2174/187152012800228661.
- Müller, C. P., M. Reichel, C. Mühle, C. Rhein, E. Gulbins, and J. Kornhuber. 2015. Brain membrane lipids in major depression and anxiety disorders. *Biochimica et Biophysica Acta - Molecular and Cell Biology of Lipids* 1851 (8):1052–65. Elsevier B.V. doi:10.1016/j.bbaplip.2014.12.014.
- Neu, I. S., G. Metzger, J. Zschocke, R. Zelezny, and E. Mayatepek. 2002. Leukotrienes in patients with clinically active multiple sclerosis. *Acta Neurologica Scandinavica* 105 (1):63–66. doi:10.1034/j.1600-0404.2002.00070.x.
- Nhan, H. S., K. Chiang, and E. H. Koo. 2015. The multifaceted nature of amyloid precursor protein and its proteolytic fragments: Friends and foes. *Acta Neuropathologica* 129(1):1. doi:10.1007/014-1347-2.
- Ntambi, J. M., M. Miyazaki, J. P. Stoehr, H. Lan, C. M. Kendziora, B. S. Yandell, Y. Song, P. Cohen, J. M. Friedman, and A. D. Attie. 2002. Loss of stearoyl-CoA desaturase-1 function protects mice against adiposity. *Proceedings of the National Academy of Sciences* 99 (17):11482–86. doi:10.1073/pnas.132384699.
- Olsen, A. S. B., and N. J. Faergeman. 2017. Sphingolipids: Membrane microdomains in brain development, function and neurological diseases. *Open Biology* 7 (5):170069. doi:10.1098/rsob.170069.
- Orrenius, S., V. Gogvadze, and B. Zhivotovsky. 2015. Calcium and mitochondria in the regulation of cell death. *Biochemical and Biophysical Research Communications* 460 (1):72–81. doi:https://doi.org/10.1016/j.bbrc.2015.01.137.
- Orth, M., and S. Bellosta. 2012. Cholesterol: Its regulation and role in Central nervous system disorders. *Cholesterol* 2012:1–19. doi:10.1155/2012/292598.
- Os, J. V., and S. Kapur. 2009. Schizophrenia. *The Lancet* 374:635. doi:10.1016/S0140-6736(09)60995-8.
- Pardo, A. D., E. Amico, A. Basit, A. Armiratti, P. Joshi, M. N. Diana, and R. Vuono. 2017. Defective sphingosine-1-phosphate metabolism is a druggable target in Huntington's disease. *Scientific Reports* 7 (1):1–14. doi:10.1038/s41598-017-05709-y.
- Pardo, A. D., A. Basit, A. Armiratti, E. Amico, S. Castaldo, G. Pepe, F. Marraccino, F. Buttari, F. D. Anna, and V. Maglione. 2017. De novo synthesis of sphingolipids is defective in experimental models of Huntington's disease. *Frontiers in Neuroscience* 11:1–10. doi:10.3389/fnins.2017.00698.
- Park, Y., S. Nam, H.-J. Yi, H.-J. Hong, and M. Lee. 2009. Dietary N-3 polyunsaturated fatty acids increase oxidative stress in rats with intracerebral hemorrhagic stroke. *Nutrition Research (New York, N.Y.)* 29 (11):812–18. Elsevier Inc.: doi:10.1016/j.nutres.2009.10.019.
- Patel, D., and S. N. Witt. 2017. Ethanolamine and phosphatidylethanolamine: Partners in health and disease. *Oxidative Medicine and Cellular Longevity*. Hindawi 2017:1–18. doi:10.1155/2017/48290.

- Paul, R., A. Choudhury, and A. Borah. 2015. Cholesterol – A putative endogenous contributor towards parkinson's disease. *Neurochemistry International* 90:125–33. Elsevier Ltd: doi:[10.1016/j.neuint.2015.07.025](https://doi.org/10.1016/j.neuint.2015.07.025).
- Peters, B. D., M. Duran, E. J. Vlieger, C. B. Majoe, G. J. den Heeten, D. H. Linszen, and L. de Haan. 2009. Polyunsaturated fatty acids and brain white matter anisotropy in recent-onset schizophrenia: A preliminary study. *Prostaglandins, Leukotrienes, and Essential Fatty Acids* 81 (1):61–63. Elsevier: doi:[10.1016/j.plefa.2009.04.007](https://doi.org/10.1016/j.plefa.2009.04.007).
- Posse de Chaves, E., and S. Sipione. 2010. Sphingolipids and gangliosides of the nervous system in membrane function and dysfunction. *FEBS Letters* 584 (9):1748–59. doi:[10.1016/j.febslet.2009.12.010](https://doi.org/10.1016/j.febslet.2009.12.010).
- Pyszko, J. A., and J. B. Strosznajder. 2014. The key role of sphingosine kinases in the molecular mechanism of neuronal cell survival and death in an experimental model of Parkinson's disease. *Folia Neuropathologica* 3(3):260–69. Poland: doi:[10.5114/fn.2014.45567](https://doi.org/10.5114/fn.2014.45567).
- Ransohoff, R. M., D. A. Hafler, and C. F. Lucchinetti. 2015. Multiple sclerosis—A quiet revolution. *Nature Reviews Neurology* 11 (3): 134–42. doi:[10.1038/nrneurol.2015.14](https://doi.org/10.1038/nrneurol.2015.14).
- Reda, Diala, M., Ali, NKamal Abd-El-Fatah, Tarek El, S. Ismail Omar, Olfat, and A. Hamid Darwish. 2015. Fish oil intake and seizure control in children with medically resistant epilepsy. *North American Journal of Medical Sciences* 7 (7):317. doi:[10.4103/1947-2714.161248](https://doi.org/10.4103/1947-2714.161248).
- Reddy, R. D., M. S. Keshavan, and J. K. Yao. 2004. Reduced red blood cell membrane essential polyunsaturated fatty acids in first episode schizophrenia at neuroleptic-naïve baseline. *Schizophrenia Bulletin* 30(4):901–11. Oxford University Press: doi:[10.1093/oxfordjournals.schbul.a007140](https://doi.org/10.1093/oxfordjournals.schbul.a007140).
- Reed, B., S. Villeneuve, W. Mack, C. DeCarli, H. C. Chui, and W. Jagust. 2014. Associations between serum cholesterol levels and cerebral amyloidosis. *JAMA Neurology* 71 (2):195–200. doi:[10.1001/jamaneurol.2013.5390](https://doi.org/10.1001/jamaneurol.2013.5390).
- Rist, P. M., C. Tzourio, and T. Kurth. 2011. Associations between lipid levels and migraine: Cross-sectional analysis in the epidemiology of vascular ageing study. *Cephalgia* 31 (14):1459–65. doi:[10.1177/0333102411421682](https://doi.org/10.1177/0333102411421682).
- Rombaldi Bernardi, J., R. D S. Escobar, C. F. Ferreira, and P. P. Silveira. 2012. Fetal and neonatal levels of omega-3: Effects on neurodevelopment, nutrition, and growth. *TheScientificWorldJournal* 2012:1. (January):doi:[10.1100/2012/202473](https://doi.org/10.1100/2012/202473).
- Saberi, A., H. R. Hatamian, E. Kazemnejad, and N. Ghorbannejad. 2011. Hyperlipidemia in migraine: Is it more frequent in migraineurs? *Iranian Journal of Neurology* 10 (3–4):46–50.
- Sadeghi, O., Z. Maghsoudi, F. Khorvash, R. Ghiasvand, and G. Askari. 2015. The relationship between different fatty acids intake and frequency of migraine attacks. *Iranian Journal of Nursing and Midwifery Research* 20 (3):334–9.
- Santos, C. R., and A. Schulze. 2012. Lipid metabolism in cancer. *FEBS Journal* 279 (15):2610–23. doi:[10.1111/j.1742-4658.2012.08644.x](https://doi.org/10.1111/j.1742-4658.2012.08644.x).
- Sarandol, A., E. Sarandol, S. S. Eker, E. U. Karaagac, B. Z. Hizli, M. Dirican, and S. Kirli. 2006. Oxidation of apolipoprotein B-containing lipoproteins and serum paraoxonase/arylesterase activities in major depressive disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 30 (6):1103–8. England: doi:[10.1016/j.pnpbp.2006.04.012](https://doi.org/10.1016/j.pnpbp.2006.04.012).
- Sato, N., and R. Morishita. 2015. The roles of lipid and glucose metabolism in modulation of β -amyloid, tau, and neurodegeneration in the pathogenesis of Alzheimer disease. *Frontiers in Aging Neuroscience* 7 (Oct):1–9. doi:[10.3389/fnagi.2015.00199](https://doi.org/10.3389/fnagi.2015.00199).
- Satogami, K., S. Takahashi, S. Yamada, S. Ukai, and K. Shinosaki. 2017. Omega-3 fatty acids related to cognitive impairment in patients with schizophrenia. *Schizophrenia Research: Cognition* 9:8–12. Elsevier: doi:[10.1016/j.scog.2017.05.001](https://doi.org/10.1016/j.scog.2017.05.001).
- Schaeffer, E. L., H. D. Skaf, B. D A. Novaes, E. R. da Silva, B. A. Martins, H. D. G. Joaquim, and W. F. Gattaz. 2011. Inhibition of phospholipase a 2 in rat brain modifies different membrane fluidity parameters in opposite ways. *Progress in Neuro-Psychopharmacology and Biological Psychiatry* 35 (7):1612–17. doi:[10.1016/j.pnpbp.2011.05.001](https://doi.org/10.1016/j.pnpbp.2011.05.001).
- Schiess, N., and P. A. Calabresi. 2016. Multiple Sclerosis. *Seminars in Neurology* 36 (4):350–56. doi:[10.1016/j.brainresrev.2004.12.020](https://doi.org/10.1016/j.brainresrev.2004.12.020).
- Schmid, S. P., E. D. Schleicher, A. Cegan, C. Deusche, S. Baur, A.-K. Hauser, M. Synofzik, K. Srulijes, K. Brockmann, D. Berg, and W. Maetzler. 2012. Cerebrospinal fluid fatty acids in glucocerebrosidase-associated Parkinson's disease. *Movement Disorders* 27 (2):288–92. doi:[10.1002/mds.23984](https://doi.org/10.1002/mds.23984).
- Schmitt, F., G. Hussain, L. Dupuis, J.-P. Loeffler, and A. Henriques. 2014. A plural role for lipids in motor neuron diseases: energy, signaling and structure. *Frontiers in cellular neuroscience* 8 (February): 25. doi:[10.3389/fncel.2014.00025](https://doi.org/10.3389/fncel.2014.00025).
- Shevchenko, A., and K. Simons. 2010. Lipidomics: Coming to grips with lipid diversity. *Nature Reviews Molecular Cell Biology* 11 (8): 593–8. doi:[10.1038/nrm2934](https://doi.org/10.1038/nrm2934).
- Smitherman, T. A., R. Burch, H. Sheikh, and E. Loder. 2013. The prevalence, impact, and treatment of migraine and severe headaches in the United States: A review of statistics from national surveillance studies. *Headache* 53 (3):427–36. doi:[10.1111/head.12074](https://doi.org/10.1111/head.12074).
- Snowden, S. G., A. A. Ebshiana, A. Hye, Y. An, O. Pletnikova, R. O'Brien, J. Troncoso, C. Legido-Quigley, and M. Thambisetty. 2017. Association between fatty acid metabolism in the brain and Alzheimer disease neuropathology and cognitive performance: A nontargeted metabolomic study. edited by Carol Brayne. *PLoS Medicine* 14(3):e1002266. Public Library of Science: doi:[10.1371/journal.pmed.1002266](https://doi.org/10.1371/journal.pmed.1002266).
- Solberg, D. K., H. Bentsen, H. Refsum, and A. A. Ole. 2016. Lipid profiles in schizophrenia associated with clinical traits: a five year follow-up study. *BMC Psychiatry* 16 (1):1–9. doi:[10.1186/s12888-016-1006-3](https://doi.org/10.1186/s12888-016-1006-3).
- Staley, K. 2015. Molecular mechanisms of epilepsy. *Nature Neuroscience* 18 (3):367–72. doi:[10.1038/nn.3947](https://doi.org/10.1038/nn.3947).
- Sugiyama, A., S. Sawai, S. Ito, H. Mukai, M. Beppu, T. Yoshida, and S. Kuwabara. 2015. Incidental diagnosis of an asymptomatic adult-onset alexander disease by brain magnetic resonance imaging for preoperative evaluation. *Journal of the Neurological Sciences* 354 (1–2):131–32. Elsevier B.V.: doi:[10.1016/j.jns.2015.05.001](https://doi.org/10.1016/j.jns.2015.05.001).
- Sveinbjornsdottir, S. 2016. The clinical symptoms of Parkinson's disease. *Journal of Neurochemistry* 139 Suppl 1:318–24. doi:[10.1111/jnc.13691](https://doi.org/10.1111/jnc.13691).
- Thomas, J., C. J. Thomas, J. Radcliffe, and C. Itsopoulos. 2015. Omega-3 fatty acids in early prevention of inflammatory neurodegenerative disease: a focus on Alzheimer's disease. *BioMed Research International* 2015:1. doi:[10.1155/2015/172801](https://doi.org/10.1155/2015/172801).
- Thomas, M. H., P. Sandra, N. Vitale and O. Jean Luc. 2016. Arachidonic acid in Alzheimer's disease. *Journal of Neurology & Neuromedicine* 1:1–6.
- Tohidi, M., R. Mohebi, L. Cheraghi, F. Hajsheikhholeslami, S. Aref, S. Nouri, F. Azizi, and F. Hadaegh. 2013. Lipid profile components and incident cerebrovascular events versus coronary heart disease; the result of 9years follow-up in Tehran lipid and glucose study. *Clinical Biochemistry* 46 (9):716–21. doi:[10.1016/j.clinbiochem.2013.03.012](https://doi.org/10.1016/j.clinbiochem.2013.03.012).
- Uauy, R., and A. D. Dangour. 2006. Nutrition in brain development and aging : Role of essential fatty acids. *Nutrition Reviews* 64 (5 Pt 2):S24–S33. doi:[10.1301/nr.2006.may.S24](https://doi.org/10.1301/nr.2006.may.S24).
- Vejux, A., A. Namsi, T. Nury, T. Moreau, and G. Lizard. 2018. Biomarkers of amyotrophic lateral sclerosis: Current status and interest of oxysterols and phytosterols. *Frontiers in Molecular Neuroscience* 11 (January):1–13. doi:[10.3389/fnmol.2018.00012](https://doi.org/10.3389/fnmol.2018.00012).
- Ward, S., M. I. Page, P. McHugh, and N. T. Powles. 2017. Sphingosine and dihydrosphingosine as biomarkers for multiple sclerosis identified by metabolomic profiling using coupled UPLC-MS." analytical. *Methods* 9 (41):5929–34. Royal Society of Chemistry: doi:[10.1039/c7ay01922j](https://doi.org/10.1039/c7ay01922j).
- Weinstock-Guttman, B., R. Zivadinov, N. Mahfooz, E. Carl, A. Drake, J. Schneider, B. Teter, S. Hussein, B. Mehta, M. Weiskopf, et al. 2011. Serum lipid profiles are associated with disability and MRI outcomes in multiple sclerosis. *Journal of Neuroinflammation* 8 (1): 127. doi:[10.1186/1742-2094-8-127](https://doi.org/10.1186/1742-2094-8-127).

- Whiteford, H. A., L. Degenhardt, J. Rehm, A. J. Baxter, A. J. Ferrari, H. E. Erskine, F. J. Charlson, R. E. Norman, A. D. Flaxman, N. Johns., et al. 2013. Global burden of disease attributable to mental and substance use disorders: Findings from the global burden of disease study 2010. *The Lancet* 382 (9904):1575–86. doi:[10.1016/S0140-6736\(13\)61611-6](https://doi.org/10.1016/S0140-6736(13)61611-6).
- Wong, M. W., N. Braidy, A. Poljak, R. Pickford, M. Thambisetty, and S. S. Perminder. 2017. Dysregulation of lipids in Alzheimer's disease and their role as potential biomarkers. *Alzheimer's and Dementia* 13 (7):810–27. doi:[10.1016/j.jalz.2017.01.008](https://doi.org/10.1016/j.jalz.2017.01.008).
- Woods, A. G., I. Sokolowska, R. Taurines, M. Gerlach, E. Dudley, J. Thome, and C. C. Darie. 2012. Potential biomarkers in psychiatry: Focus on the cholesterol system methods for proteomic analysis. *Journal of Cellular and Molecular Medicine* 16 (6):1184–95. doi:[10.1111/j.1582-4934.2012.01543.x](https://doi.org/10.1111/j.1582-4934.2012.01543.x).
- Wysokiński, A., D. Strzelecki, and I. Kłoszewska. 2015. Levels of triglycerides, cholesterol, LDL, HDL and glucose in patients with schizophrenia, unipolar depression and bipolar disorder. *Diabetes and Metabolic Syndrome: Clinical Research and Reviews* 9 (3):168–76. doi:[10.1016/j.dsx.2015.04.004](https://doi.org/10.1016/j.dsx.2015.04.004).
- Yaemsiri, S., S. Sen, L. F. Tinker, W. R. Robinson, R. W. Evans, W. Rosamond, S. Wasserthiel, and K. He. 2013. Serum fatty acids and incidence of ischemic stroke among postmenopausal women. *Stroke* 44 (10):2710–17. doi:[10.1161/STROKEAHA.111.000834.Serum](https://doi.org/10.1161/STROKEAHA.111.000834.Serum).
- Yakunin, E., V. Loeb, H. Kisos, Y. Biala, S. Yehuda, Y. Yaari, D. J. Selkoe, and R. Sharon. 2012. α -Synuclein Neuropathology is controlled by nuclear hormone receptors and enhanced by docosahexaenoic acid in a mouse model for Parkinson's disease. *Brain Pathology* 22 (3):280–94. doi:[10.1111/j.1750-3639.2011.00530.x](https://doi.org/10.1111/j.1750-3639.2011.00530.x).
- Yanai, H. 2017. Effects of N-3 polyunsaturated fatty acids on dementia. *Journal of Clinical Medicine Research* 9 (1):1–9. doi:[10.14740/jocmr2815w](https://doi.org/10.14740/jocmr2815w).
- Yang, X., L. Sun, A. Zhao, X. Hu, Y. Qing, J. Jiang, C. Yang, T. Xu, P. Wang, J. Liu., et al. 2017. Serum fatty acid patterns in patients with schizophrenia: A targeted metabonomics study. *Translational Psychiatry* 7 (7):e1176. doi:[10.1038/tp.2017.152](https://doi.org/10.1038/tp.2017.152).
- Yip, P. K., C. Pizzasegola, S. Gladman, M. L. Biggio, M. Marino, M. Jayasinghe, F. Ullah, S. C. Dyall, A. Malaspina, C. Bendotti, et al. 2013. The omega-3 fatty acid eicosapentaenoic acid accelerates disease progression in a model of amyotrophic lateral sclerosis.” edited by Christoph Kleinschmitz. *PLoS ONE* 8 (4):e61626. doi:[10.1371/journal.pone.0061626](https://doi.org/10.1371/journal.pone.0061626).
- Yoshizawa, T., M. F. Karim, Y. Sato, T. Senokuchi, K. Miyata, T. Fukuda, C. Go, M. Tasaki, K. Uchimura, T. Kadomatsu, et al. 2014. SIRT7 controls hepatic lipid metabolism by regulating the Ubiquitin-Proteasome pathway. *Cell Metabolism* 19(4):712–21. doi:[10.1016/j.cmet.2014.03.006](https://doi.org/10.1016/j.cmet.2014.03.006).
- Yu, R. K., E. Bieberich, T. Xia, and G. Zeng. 2004. Regulation of ganglioside biosynthesis in the nervous system. *Journal of Lipid Research* 45 (5):783–93. doi:[10.1194/jlr.R300020-JLR200](https://doi.org/10.1194/jlr.R300020-JLR200).
- Zarrouk, A., M. Debbabi, M. Bezine, E. M. Karym, A. Badreddine, O. Rouaud, T. Moreau., et al. 2017. “Lipid Biomarkers in Alzheimer's Disease.” *Current Alzheimer Research* 14 (999): 1–1. doi:[10.2174/1567205014666170505101426](https://doi.org/10.2174/1567205014666170505101426).
- Zechner, R., R. Zimmermann, O. E. Thomas, D. K. Sepp, G. Haemmerle, A. Lass, and F. Madeo. 2012. FAT SIGNALS - Lipases and lipolysis in lipid metabolism and signaling. *Cell Metabolism* 15 (3):279–91. doi:[10.1016/j.cmet.2011.12.018](https://doi.org/10.1016/j.cmet.2011.12.018).
- Zhang, H., J.-R. Wang, L. F. Yau, H. M. Ho, C. L. Chan, P. Hu, L. Liu, and Z.-H. Jiang. 2012. A cellular lipidomic study on the A β -Induced Neurotoxicity and neuroprotective effects of EGCG by using UPLC/MS-based glycerolipids profiling and multivariate analysis. *Molecular BioSystems* 8 (12):3208. doi:[10.1039/c2mb25126](https://doi.org/10.1039/c2mb25126).
- Zhang, J., and Q. Liu. 2015. Cholesterol metabolism and homeostasis in the brain. *Protein & Cell* 6 (4):254–64. Springer: doi:[10.1007/s13238-014-0131-3](https://doi.org/10.1007/s13238-014-0131-3).