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Review

Targeting Lipid Metabolism in Alzheimer's Disease: Emerging Insights and Future Directions

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Abstract

Alzheimer's disease (AD) is a multifactorial neurodegenerative disease that is conventionally characterized by amyloid-β and tau pathology. There is growing evidence, however, that lipid metabolic disturbances are part of the biology of the disease, and not a secondary phenomenon. Lipid signaling controls membrane organization, amyloid precursor protein, tau phosphorylation, mitochondrial energetics, neuroinflammatory signaling, and synaptic stability. The accumulating genetic evidence, including risk variants in the *APOE* (apolipoprotein E), *ABCA1* (ATP-binding cassette subfamily A member 1), *ABCA7* (ATP-binding cassette subfamily A member 7), and *TREM2* (Triggering receptor expressed on myeloid cells 2) genes, further makes lipid transport and lipid-sensing pathways central to late-onset AD vulnerability. Recent developments in lipidomics based on mass spectrometry have revealed concerted changes in phospholipids, sphingolipids, sterols, and oxidized lipid derivatives in brain tissue and peripheral biofluids. Instead of single abnormalities, directional metabolic imbalance is indicated by pathway changes, including decreased sphingomyelin-to-ceramide ratios and decreased polyunsaturated phospholipids. Co-analysis of lipidomic, genomic, and proteomic data has shown the existence of metabolically different subgroups, which aids genotype stratified risk evaluation and the lipid responder phenotype concept. Protein-centered therapies are complemented by therapeutic strategies that focus on lipid homeostasis, such as the regulation of cholesterol efflux, sphingolipid metabolism, pro-resolving lipid mediators, and metabolic reprogramming. There is also emerging evidence that implicates peroxisomal dysfunction and compromised glymphatic clearance in interfering with lipid balance. Although this field of research has come a long way, the issues of proving causality, standardizing lipidomic techniques, and converting pathway signatures into clinically useful resources persist. Restructuring AD as a lipid network instability disorder offers a systems level model of earlier diagnosis and targeted treatment.

Keywords: Alzheimer's disease; lipid metabolism; lipidomics; apolipoprotein E; neuroinflammation; mitochondria; precision medicine

1. Introduction

Alzheimer's disease (AD) is the most prevalent neurodegenerative condition (the major cause of dementia) in the world, with an estimated 60–80% of all cases of dementia [1]. The World Health Organization (2023) notes that there are over 55 million people living with dementia in the world today, and this figure is expected to rise to over 150 million by 2050 because of the aging population and extended lifespan. AD has a high socioeconomic impact, and the cost incurred by the world is much higher at USD 1.3 trillion annually, and there is a dire necessity for effective disease-modifying therapeutic measures.

AD has a neuropathological basis of extracellular amyloid-β (Aβ) plaques, intracellular neurofibrillary tangles made of hyperphosphorylated tau protein, progressive synaptic loss, neuroinflammation, and oxidative stress [2,3]. The AD pathogenesis has been suggested to be explained by multiple hypotheses: the amyloid cascade hypothesis, tau-mediated neurodegeneration, neuroinflammatory, vascular hypothesis, metabolic hypothesis, and the infectious hypothesis, as it is multifactorial and heterogeneous [4]. Notably, clinicopathological discordance as demonstrated by widespread amyloid deposition in cognitively normal humans and low correlations between amyloid load and cognitive loss has questioned the adequacy of protein-based models per se.

Although decades of interdisciplinary research have produced limited and inconsistent clinical benefits, therapeutic interventions directly affecting Aβ or tau have not had a beneficial effect on the disease [5–7]. These shortcomings have led to a paradigm shift in efforts to determine the upstream biological fields that predispose the aging brain to neurodegeneration. There is growing evidence that metabolic dysfunction, especially dysregulated lipid metabolism, is a primary and initial causal factor of AD pathophysiology instead of a secondary effect of protein aggregation [8–10].

The human brain is highly lipid, and lipids constitute about 50–60% of the dry weight [11]. In addition to structural functions of lipids in cellular membranes, lipids control synaptic transmission, receptor trafficking, membrane fluidity, mitochondrial bioenergetics, myelination, and neuroimmune homeostasis [12]. Strict control of cholesterol, phospholipids, sphingolipids and polyunsaturated fatty acids, thus, plays a key role in ensuring neuronal integrity. The modification of these pathways is directly related to the amyloid precursor protein processing, tau phosphorylation, oxidative stress reactions, and inflammatory signaling [8,9,13]. Interestingly, lipidomic analyses reveal that changes in ceramides, sphingomyelins, plasmalogens, and oxidized phospholipids at the early stages of the AD progression, in many cases, take place before neurons start to be lost and cognitive impairments are evident.

Genetic evidence also highlights the pre-eminence of lipid biology in AD. The most powerful genetic risk factor of late-onset AD is the apolipoprotein E (*APOE*) ε4 allele, which increases the risk and an earlier onset of the disease than the e3 alleles of *APOE* do [14,15]. APOE is a lipid transportation protein, and the *APOE* $\varepsilon 4$ isoform demonstrates ineffective lipid transportation, synaptic susceptibility, and inadequate Aβ clearance due to the poor lipid-binding ability, low structural stability, and high susceptibility to proteolytic cleavage [16–18]. Moreover, there are growing indications that amyloid accumulation can be instigated or aggravated by upstream insults, including infection or metabolic stress, which again places lipid dysregulation in the role of an integrative node between environmental, genetic, and inflammatory factors in AD pathogenesis [19]. This conceptual change has been enhanced by the development of lipidomics, which allows the resolution of lipid species in brain tissue, cerebrospinal fluid, and plasma. It is demonstrated consistently in these studies that disease and genotype-specific changes in the ceramides, sphingomyelins, plasmalogens, phospholipids, and sterols are correlated with the synaptic dysfunction, mitochondrial impairment, neuroinflammation, and cognitive decline [20–22]. These observations suggest the usefulness of lipid signatures as early biomarkers and mechanistic disease progression biomarkers.

This review is a synthesis of existing evidence that lipid metabolism is an upstream and integrative cause of Alzheimer's. We explore the basic guidelines of brain lipid biology, cell-type-specific lipid metabolic programs and mechanistic connections between lipid dysregulation and essential AD pathologies. Genetic modulators of lipid homeostasis, especially *APOE* and associated pathways, are addressed and lipidomics and biomarker discovery results are involved in the discussion. Lastly, we consider the new therapeutic approaches to lipid pathways and summarize the problems and future perspectives of precision lipid-based therapy in Alzheimer's disease.

The Emerging Role of Lipid Metabolism Beyond the Amyloid–Tau Paradigm

The classical amyloid cascade hypothesis has played a leading role in AD research but has not been able to account for the heterogeneity of AD in sporadic and late-onset cases or the discordance between amyloid load and cognitive impairment in a minority of individuals [7,23]. It is emerging that the metabolic and lipid abnormalities play an upstream role in Aβ and tau pathology and contribute to the genetic, inflammatory, and energetic failures to a singular disease model [10,15,24].

The metabolism of lipids intersects with the AD biology on several levels. The localization and activity of β and γ-secretases are regulated in membrane microdomains (lipid rafts), which are cholesterol and sphingolipid rich membrane microdomains and enhanced amyloidogenic processing of amyloid precursor protein (APP) occurs when cholesterol levels are elevated [25–27]. In the meantime, oxidative stress and apoptotic signals are enhanced by ceramides and oxidized phospholipids and oxidative damages membrane integrity and antioxidant protection by disrupting plasmalogen depletion [22,28,29].

Lipid biology is associated with disease susceptibility, which is connected to genetic factors, especially the *APOE* $\varepsilon 4$ allele, that modulate lipid transport, Aβ clearance, and neuroinflammatory tone [14,15,18]. Moreover, the multi-omics analysis unveils the *APOE* $\varepsilon 4$-mediated lipidomic signatures to be associated with the impaired mitochondrial dysfunction, deteriorated lipid droplet turnover, and energy deficiency in neurons [10,30]. Taken together, these data put lipid metabolism in the realm of an integrative upstream mechanism that affects various dimensions of AD pathology, fatigued in amyloid and tau aggregation as well as glial activation and oxidative damage. In the therapeutic approach, lipid pathway targeting has already been showing promising initial outcomes. Lipid homeostasis and Aβ clearance are restored with the help of *APOE* lipidation enhancers, liver X receptor (LXR)/retinoid X receptor (RXR) agonists, and ACAT (Acyl-CoA: cholesterol acyltransferase) inhibitors in the preclinical models [31–33]. Equally, omega-3 supplemented diets and ketogenic diets improve the composition of the membrane and energy metabolism and slow the cognitive impairment in mild cognitive impairment (MCI) and in the early AD [33–35]. Collectively, these developments underscore lipid metabolism as a promising avenue of therapeutics that serves as an interface between the molecular pathways and clinical therapy.

2. Basics of Lipid Metabolism in the Brain

2.1 Major Lipid Classes and Functions in the Central Nervous System (CNS)

Lipid metabolism has a fundamental effect on the metabolic formation, maturation and maintenance of the CNS. In addition to playing structural roles in cellular membranes, lipids control the membrane fluidity, vesicles in the synaptic cleft, intracellular movement, and intracellular signal transmission. The second-richest organ of the body in terms of lipid content is the brain, in which lipids constitute about 50–60% of the dry mass [8,11,12]. Phospholipids, sphingolipids, cholesterol and fatty acids are major lipid classes in the CNS, and each have their specific physiological roles to play. The structural framework of neuronal and glial membranes is made up of phospholipids, including phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol that also act as the precursors of intracellular signaling molecules [36]. The specific subclass of phospholipids, plasmalogens, is an enriched form of phospholipids, which is found in large amounts in neural tissue and plays a role in membrane stability, vesicular fusion, and antioxidant defense [37]. Sphingolipids such as sphingomyelin and gangliosides are inbuilt parts of membrane microdomains, which structure receptor localization and signal transmission [38]. Cholesterol synthesized *de novo* in the CNS plays a role in membrane organization, myelination and functioning of neurotransmitter receptors [39], and polyunsaturated fatty acids, including docosahexaenoic acid (DHA) in the maintenance of the structure of synaptic membranes and membrane-associated processes [40]. Table 1 (Ref. [8,10,13,15,18,22,28,32–34,38,41–52]) summarizes the major lipid classes, their mechanistic roles, and key study outcomes in Alzheimer's disease pathophysiology.

2.2 Lipid Transport and Storage in the Brain

Since most circulating lipids do not enter the CNS due to the blood-brain barrier, autonomous lipid production, transport, and recycling processes assist the CNS to stay at homeostasis [39]. The production of cholesterol and phospholipids and their transport into neurons occurs through lipoprotein particle-containing apolipoproteins produced by astrocytes and transported to the neurons by receptor-mediated endocytosis [53]. ATP (adenosine triphosphate) binding cassette transporters such as ABCA1 (ATP-binding cassette subfamily A member 1) and ABCG1 (ATP-binding cassette subfamily G member 1) mediate cholesterol efflux and loading lipids onto apolipoproteins and have central roles in the maintenance of lipid balance across neural cell types [54]. Other than the transport of lipids, lipid storage is also another facet of CNS lipid homeostasis. Lipid droplets are cytoplasmic organelles that store neutral lipids and serve as dynamic stores that compensate for changes in lipid supply and safeguard cells against lipotoxic stress [55].

2.3 Lipid Metabolic Pathways and Homeostatic Regulation

The lipid brain metabolism involves the well-coordinated mechanisms of synthesis, turnover, and consumption. The cholesterol biosynthesis is regulated by rate limiting enzymes and transcriptional regulators that are responsive to cellular lipid requirements through the mevalonate pathway [56,57]. Cholesterol 24-hydroxylase (CYP46A1) converts excess cholesterol to 24S-hydroxycholesterol, and this allows the body to regulate the amount of cholesterol across the blood-brain barrier [56]. Fatty acid synthesis is done by fatty acid synthase and elongation-desaturation systems, and the breakdown of fatty acids is done by β-oxidation in the mitochondria and peroxisomes [58]. A complex of transcriptional regulators directs lipid homeostasis in the CNS, regulating lipid synthesis, oxidation and efflux. SREBPs (sterol regulatory element-binding proteins) and the LXRs and RXRs mediate cholesterol biosynthesis, apolipoprotein lipidation and cholesterol efflux, and the PPARs (peroxisome proliferator-activated receptors) mediate fatty acid oxidation and lipid-responsive gene expression [41]. These regulatory systems combine to ensure cellular lipid balance in physiological conditions.

2.4 Cell-Type–Specific Lipid Metabolism in the CNS

There are several different types of neural cells with lipid metabolic programmes that are dependent on the CNS functions. Astrocytes are the main place of cholesterol production and lipid transport that provides neurons with the necessary lipids to turnover and maintain their membrane and synapses [59]. The neurons are extremely dependent on lipids delivered to support the rapid membrane restructuring and synaptic vesicle cycle [60]. It is observed that microglia change the dynamic organization of lipid metabolism depending on the environmental cues, which are indicators of the change in the cellular energetic and functional state [61]. As oligodendrocytes, which are highly cholesterol and sphingolipid-enriched, rely on a strong lipid biosynthesis to sustain and/or form myelin, their presence in the brain influences myelin regeneration [62]. Interconnectedness of these cell-type-specific lipid metabolic pathways is the basis of CNS structural integrity and functional resilience. Fig. 1 summarizes the lipid metabolic programs of neurons, astrocytes, microglia, and oligodendrocytes, and their roles in maintenance of synapses, neuroinflammation, and maintenance of myelin.

3. Alzheimer's Disease: Pathological Hallmarks

AD is a progressive neurodegenerative disease that is linked to the deposition of Aβ plaques, an increase in tau hyperphosphorylation and neurofibrillary tangles (NFT), impaired synapses, oxidative stress, neuroinflammation, and impaired mitochondria. Even though the historical traits of this conceptualization have been that the main origin of the disorder is an accumulation of proteins, the growing body of evidence suggests that lipid homeostasis is disrupted, and each of these pathological areas is crossed with and regulated by the other. The brain is very rich in cholesterol, sphingolipids, phospholipids and polyunsaturated fatty acids, whose actions are to control membrane

Table 1. Summary of major lipid classes, mechanistic roles, and key study outcomes in Alzheimer's disease.

Lipid class/Molecule	Mechanistic role in AD pathophysiology	Experimental/Clinical evidence	Key outcomes	References
Cholesterol and oxysterols	Regulate APP processing in lipid rafts; altered cholesterol efflux promotes amyloidogenic cleavage.	Brain and CSF studies show decreased 24S-hydroxycholesterol, disrupted CYP46A1 activity, and reduced cholesterol turnover.	LXR/RXR agonists enhance cholesterol efflux and reduce amyloid burden.	[8,10,32]
Ceramides and sphingolipids	Promote apoptosis, oxidative stress, and BACE1 stabilization; impair mitochondrial function.	Elevated plasma ceramides correlate with cognitive decline; early accumulation in hippocampus and cortex.	Ceramide synthesis inhibitors reverse neurodegeneration in models.	[13,22,38,51]
Plasmalogens	Antioxidant phospholipids critical for membrane stability and synaptic signaling.	Depletion observed in AD plasma and brain; correlated with oxidative stress markers.	Plasmalogen replacement restores antioxidant defenses and improves cognition in mice.	[28,46,50]
Phosphatidylcholine (PC) and Phosphatidylethanolamine (PE)	Maintain membrane curvature, vesicle fusion, and neurotransmission.	Loss of DHA-containing PC/PE species detected in postmortem AD cortex and plasma.	PUFA supplementation improves membrane dynamics and cognition in early AD.	[10,34]
Apolipoprotein E (*APOE*) and lipid transport proteins	Mediate cholesterol/phospholipid transport and amyloid clearance.	*APOE* $\varepsilon 4$ carriers show impaired lipidation, lipid droplet accumulation, and mitochondrial dysfunction.	APOE-targeted therapies enhance lipid homeostasis and reduce Aβ pathology.	[15,18,45]
Sphingosine-1-phosphate (S1P)	Regulates neurogenesis, synaptic plasticity, and inflammation.	Reduced S1P levels in AD brain and CSF; linked to microglial dysfunction.	S1P receptor modulators improve cognition and reduce neuroinflammation.	[42,43]
Fatty acids (DHA, EPA, ARA)	Structural components of neuronal membranes; precursors of pro- and anti-inflammatory mediators.	Reduced brain DHA in AD; supplementation improves synaptic function and reduces tau phosphorylation.	Omega-3 and ketogenic therapies improve energy metabolism and cognition.	[33,49,52]
Lipid droplets	Reflect glial metabolic stress; regulate lipid storage and immune responses.	LD-accumulating microglia exhibit impaired phagocytosis and chronic inflammation.	Restoring lipid droplet turnover improves glial function.	[10,41,44]
Gut microbiota-derived lipids	Influence bile acid metabolism, systemic inflammation, and brain lipid signaling.	AD-associated dysbiosis alters circulating bile acids and short-chain fatty acids.	Modulation via probiotics or diet improves cognition.	[47,48]

AD, Alzheimer's disease; APP, amyloid precursor protein; CSF, cerebrospinal fluid; CYP46A1, cholesterol 24-hydroxylase; LXR, liver X receptor; RXR, retinoid X receptor; BACE1, β-site amyloid precursor protein-cleaving enzyme 1; DHA, docosahexaenoic acid; PUFA, polyunsaturated fatty acids; Aβ, amyloid-β; EPA, eicosapentaenoic acid; ARA, arachidonic acid; LD, lipid droplet.

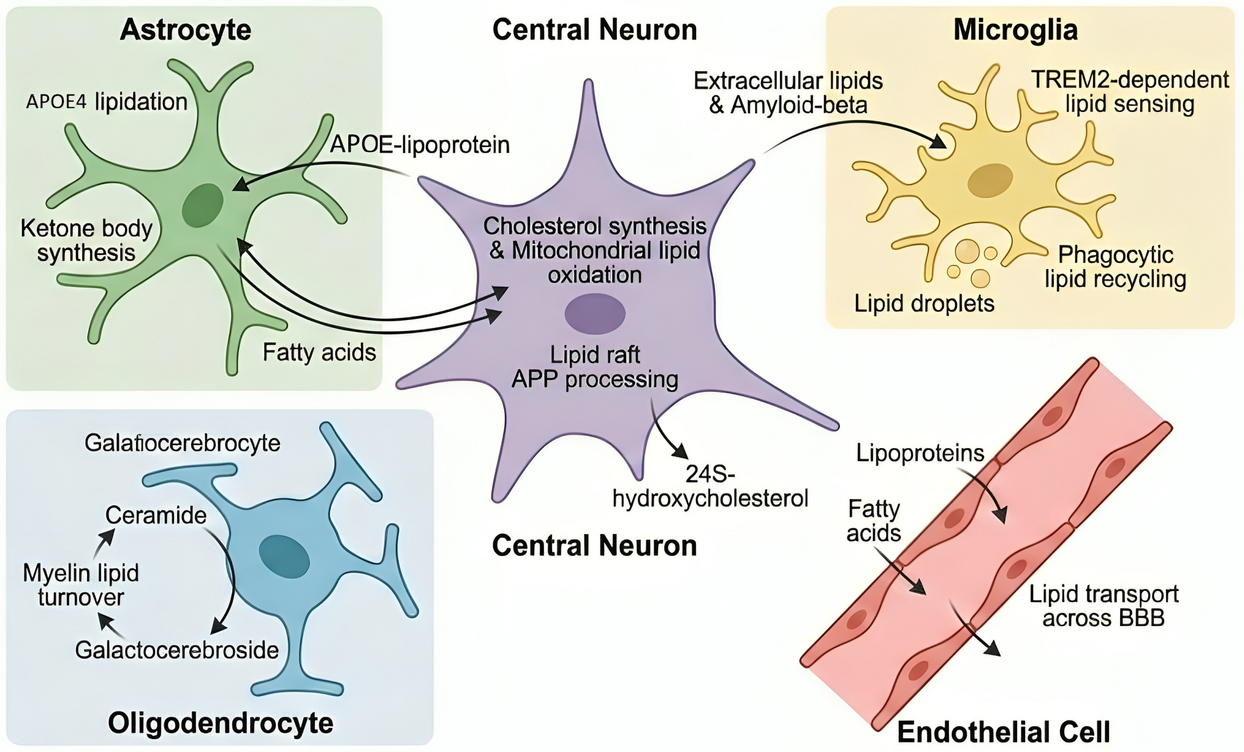

Fig. 1. Cellular crosstalk of lipid metabolism in the Alzheimer's brain. Astrocytes, neurons, microglia, oligodendrocytes, and endothelial cells coordinate lipid trafficking essential for brain homeostasis. Astrocytes supply cholesterol and fatty acids via APOE lipoproteins, while neurons regulate lipid oxidation and APP processing. Microglia sense extracellular lipids and amyloid through TREM2, forming lipid droplets during activation. Oligodendrocytes maintain myelin lipid turnover, and endothelial cells mediate lipid transport across the blood–brain barrier. Disruption of this lipid network contributes to neurodegeneration and inflammation in Alzheimer's disease. TREM2, Triggering receptor expressed on myeloid cells 2; BBB, blood–brain barrier.

structure, receptor organization, vesicle dynamics and bioenergetic activity. Changes in lipid composition affect protein processing, kinase activation, inflammatory signaling and organelle stability. Lipid perturbations can instead focus on a downstream effect of amyloid or tau accumulation, which can influence the cellular environment underlying the susceptibility to such pathologies. Therefore, it is possible to consider AD as a proteinopathy, as well as a membrane and metabolic instability disorder.

3.1 Amyloid-β Pathology

The amyloid cascade hypothesis postulates that aberrant cleavage of APP by β-secretase and γ-secretase leads to the formation of Aβ peptides, which subsequently aggregate into soluble oligomers and insoluble amyloid plaques [2]. Nevertheless, in some rare cases of AD, upstream metabolic and inflammatory conditions play a critical role in Aβ production and clearance. The primary determinant of APP processing is membrane lipid composition. Lipid rafts containing cholesterol concentrate β-site amyloid precursor protein-cleaving enzyme 1 (BACE1) and γ-secretase complexes, which prefer amyloidogenic cleavage. High cholesterol in the membrane stabilizes such microdomains and increases Aβ production, and redistribution of cholesterol to non-raft areas, transcription of APP processing to the α-secretase [8,26]. In this way, cholesterol homeostasis has a direct impact on the ratio between neurotoxic and non-amyloidogenic processing. Gangliosides, notably GM1 (Monosialotetrahexosylganglioside), mediate the early conformational changes of Aβ by GM1-Aβ complex formation that promotes oligomer formation [27]. These connections are made at the surface of the membrane, which emphasizes the importance of lipid microdomains at the beginning of plaque.

Sphingolipid imbalance also regulates amyloidogenic mechanisms. Ceramide stabilization makes BACE1 steady and increases its enzymatic performance. High levels of ceramide species are observed in the preclinical AD and associated with amyloid load and cognitive impairment [42,43]. Ceramides, mechanistically, make membranes stiffer and change endosomal trafficking, which promotes amyloidogenic APP pathways. Notably, lipid changes can lead to dysfunction of Aβ clearance. Maladaptive lipidation of APOE, especially in *APOE ε4* carriers, inhibits receptor-mediated Aβ uptake and extracellular Aβ elimination. Consequently, lipid dysregulation plays a role in enhancing both the production and deposition of Aβ.

3.2 Tau Pathology

Tau is a microtubule related protein that stabilizes the architecture of the axonal cytoskeleton. During AD, tau hyperphosphorylates, dissociates off microtubules and forms NFT [63]. Tau pathology can be modified by lipid perturbations via kinase activation, oxidative stress, and membrane signaling changes. The activation of the stress-responsive kinases such as glycogen synthase kinase 3 beta (GSK3β) and cyclin-dependent kinase 5 (CDK5) by ceramides and oxidized lipids leads to tau phosphorylation of pathological epitopes [42]. High ceramide concentrations can thus be linked to membrane stress with cytoskeletal destabilization. Oxysterols 24S-hydroxycholesterol and 27-hydroxycholesterol are accumulated in the parts of the AD brain and enhance the activation of kinases through oxidative stress [32]. The lipid peroxidation products, such as 4-hydroxynonenal (4-HNE), may covalently alter tau and increase aggregation potential and worsen microtubule binding. On the other hand, the lipid derivative of DHA like neuroprotectin D1 inhibits the activation of GSK3β and decreases tau phosphorylation [64]. These results indicate that the membrane lipid composition influences tau stability based on both degenerative and protective signaling pathways. In this way, lipid imbalance can determine tau pathology by altering the kinase signaling, oxidative modification, and membrane-cytoskeleton interactions.

3.3 Neuroinflammation

AD is characterized by chronic neuroinflammation, which is mainly caused by the activation of the microglial and astrocytic functions [65]. Metabolism of lipids is critical in the establishment of the tone of inflammatory processes. Nuclear factor kappa B (NF-κB) and cytokine releases are mediated by arachidonic acid-derived eicosanoids, which are inflammatory cascades, including prostaglandins and leukotrienes. Enhanced phospholipase A2 in AD releases arachidonic acid of membrane phospholipids, maintaining pro-inflammatory signaling. Conversely, the specific pro-resolving mediators (SPMs) derived out of DHA and eicosapentaenoic acid (EPA), such as resolvins and protectins, stimulate the resolution of inflammation by inhibiting the activation of inflammasomes and stimulating the repair of tissues [66]. The ratio of omega-6-produced pro-inflammatory lipids and omega-3 produced pro-resolving mediators determines microglial phenotype and persistence of inflammation. Lipid droplet-accumulating microglia (LDAM) is a pathologic form that is marked by the inability to phagocytose, a large number of ceramide and cholesterol deposition and elevated production of cytokines [44]. This lipid overload condition decreases the ability to clear the Aβ efficiently and facilitates complement-mediated synaptic pruning. In such a way, lipid composition defines the microglia taking on protective versus destructive identities, making lipid metabolism a determinant of neuroimmune homeostasis.

3.4 Oxidative Stress and Mitochondrial Dysfunction

Excessive production of reactive oxygen species (ROS) and dysfunctional antioxidant defenses are the causes of oxidative stress. The polyunsaturated fatty acids in the neuronal membranes are also highly susceptible to peroxidation, which produces the reactive aldehydes like 4-HNE and malondialdehyde [67]. These products of lipid peroxidation alter the proteins of synaptic transmission and mitochondrial respiration. The lipid composition of the mitochondria plays a vital role in the bioenergetic stability. Anchor Electron transport chain complexes are anchored by cardiolipin, a mitochondria-specific phospholipid. The oxidative damage of cardiolipin interferes with the respiratory chain assembly, decreases the production of ATP and facilitates the release of cytochrome c [68]. Synaptic terminal energy breakdown is a precursor to neuronal loss and leads to cognitive impairment. The further effect of the ceramide accumulation is the impairment of the mitochondrial membrane integrity and the amplification of the apoptotic signaling pathways. A change in the sterol structure affects the fluidity of the mitochondrial membrane and respiratory efficiency, too [10]. Accordingly, lipid dysregulation is a feed-forward mechanism: oxidative damage to lipids causes lipid damage, lipid damage causes mitochondrial impairment, and mitochondrial impairment produces further ROS.

3.5 Lipid-Driven Synaptic Dysfunction and Neurodegeneration

Loss of synapses is more strongly related to cognitive impairment than plaque or tangle load [69]. The phospholipids and cholesterol in synaptic membranes are very abundant in DHA, which control vesicle fusion, receptor movement and dendritic spine structural formation [12,40]. Membrane fluidity is reduced by lowering DHA and plasmalogen loss, which inhibits the assembly of the soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex, which inhibits neurotransmitter release, and reduces the plasticity of the synapse. The N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors are clustered by the cholesterol imbalance and disrupt the glutamatergic signaling [70]. Isoform dependent lipid transport also varies, aiding in regulating synaptic resilience by way of APOE. *APOE* $\varepsilon 4$ has less lipidation efficiency, which affects the redistribution of cholesterol to neurons and the process of synaptic repair [15]. Also, ceramide build-up enhances rigidity in the membrane and disturbs the provision of ATP in the mitochondrion in the presynaptic terminals, worsening synaptic failure. The GM1-enriched synaptic membranes are preferentially bound by Aβ oligomers, enhancing local toxicity. At the same time, complement-mediated synaptic pruning is increased by lipid-mediated microglial dysfunction. Thus, the function of the synaptic point is a meeting point of lipid imbalance with amyloid

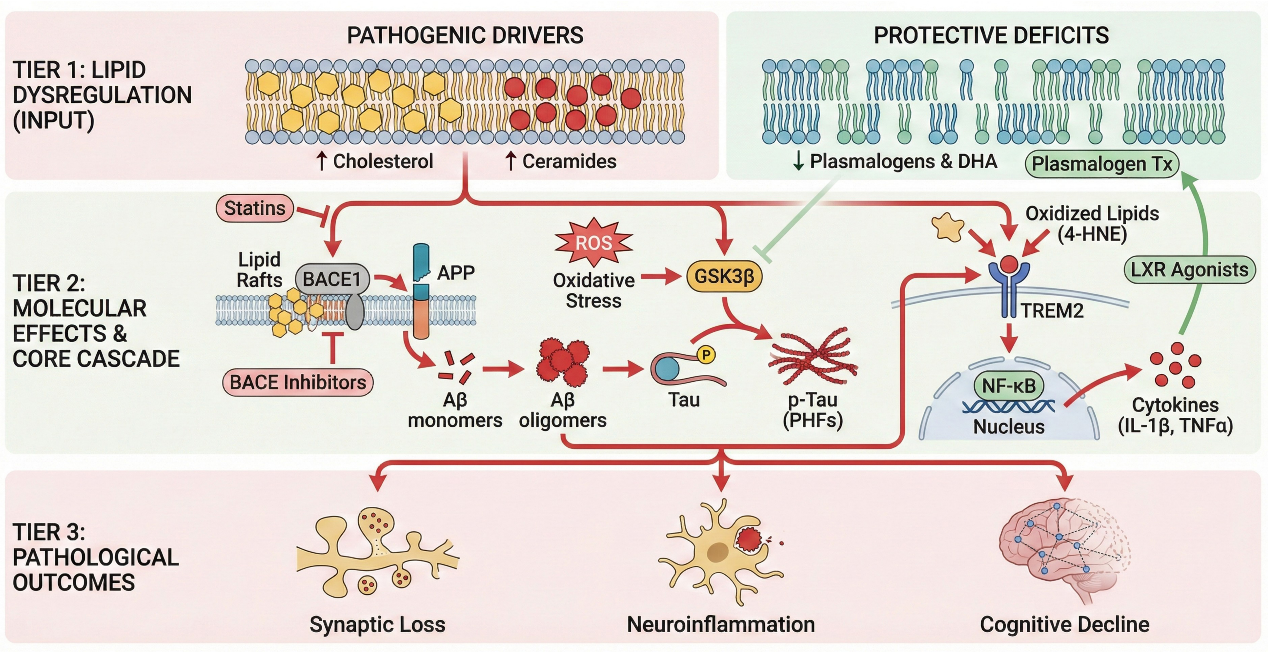

Fig. 2. Mechanistic pathways linking lipid dysregulation to Alzheimer's pathology. Lipid imbalances such as increased cholesterol and ceramides or reduced plasmalogens and DHA initiate amyloidogenic APP processing, tau phosphorylation, and inflammation. Ceramides stabilize BACE1 and enhance oxidative stress, while oxidized lipids activate microglial NF-κB signaling. These cascades lead to synaptic loss, neuroinflammation, and cognitive decline. Restoration of lipid homeostasis via statins, LXR agonists, or plasmalogen therapy may counteract these pathogenic processes. Solid red arrows represent pathogenic or activating processes, whereas green arrows denote protective or therapeutic effects. Blunt-ended lines indicate inhibition. Upward (↑) and downward (↓) arrows indicate increases or decreases in levels, respectively. Green T-shaped symbols indicate inhibitory effects. DHA, docosahexaenoic acid; ROS, reactive oxygen species; GSK3β, glycogen synthase kinase 3 beta; PHFs, paired helical filaments; 4-HNE, 4-hydroxynonenal; NF-κB, nuclear factor kappa B; IL-1β, interleukin-1 beta; TNFα, tumor necrosis factor alpha.

toxicity, tau pathology, inflammatory signalling, and mitochondrial failure. Membrane destabilization earlier in life can dictate the pathway between triggers of functional impairment and neurodegeneration that cannot be reversed.

4. Mechanistic Links Between Lipid Metabolism and Alzheimer's Disease

These giant pathological characteristics of Alzheimer's disease are described in section 3. In this paper, we consider the mechanisms by which disruptions in cholesterol transport, sphingolipid remodeling, phospholipid composition, and lipid mediated signalling have a direct effect on amyloid processing, tau phosphorylation, mitochondrial fitness, neuroinflammation, and synaptic resilience. These lipid-directed processes do not work in isolation, but they constitute feedback loops, which increase neurodegeneration. Fig. 2 shows the integrated molecular pathways connecting lipid dysregulation and amyloid processing, tau phosphorylation, mitochondrial dysfunction, oxidative stress, and neuroinflammation.

4.1 Cholesterol Metabolism and Amyloid Processing

The distribution of cholesterol in the membranes of neurons is a vital regulator of APP processing. More cholesterol in the membrane prefers β and γ-secretases localization to cholesterol-rich microdomains, which also increases amyloidogenic cleavage. On the other hand, a-secretase-mediated non-amyloidogenic processing is favored by increased cholesterol efflux or redistribution, decreasing the production of Aβ [10,13,32]. The brain has a large amount of cholesterol turnover that is regulated primarily by CYP46A1, which is the only way to convert cholesterol to 24S-hydroxycholesterol and then allow the substance to be taken across the blood-brain barrier. Lower cholesterol turnover enhances membrane rigidity and secretase clustering, and CYP46A1 activation enhances synaptic plasticity and decreases the amyloid burden in models. Likewise, defects in cholesterol efflux transporter including ABCA1 and ABCG1, reduce the effectiveness of APOE lipidation, which disrupts extracellular lipid transport and encourages the aggregation of Aβ [15,71]. Therefore, an unregulated cholesterol secretion and not the total levels of cholesterol, is what determines the balance between protective and pathogenic APP processing.

4.2 Sphingolipids, Ceramides, and Bioactive Lipid Signaling

The metabolism of sphingolipids has a strong impact on the survival of neurons and inflammatory signaling. The sphingomyelin hydrolysis or *de novo* synthesis produces ceramides that aid amyloidogenic processing and at the same time stimulate the mitochondrial permeability, oxidative stress, and apoptotic signalling [42,43]. Early lipidomic profiles in preclinical AD show that the species of ceramides such as C16:0 and C18:0 accumulate early [22]. These species disrupt membranes of mitochondria, elevate the production of reactive oxygen species and enhance inflammatory cascades. Conversely, the pro-survival sphingolipid metabolite, sphingosine-1-phosphate (S1P), is lower in AD, the loss of which hinders neurogenesis and synaptic plasticity [72]. Sphingomyelin to bioactive ceramide species transition is thus a directional metabolic imbalance, which strengthens amyloid toxicity and inflammatory susceptibility.

4.3 Phospholipid Dysregulation and Membrane Instability

Membrane curvature, vesicle fusion, and receptor trafficking is supported by phospholipids which are phosphatidylcholine (PC), phosphatidylethanolamine (PE), and plasmalogens. Polyunsaturated PC and PE species depletion impairs the fluidity of the membrane and decreases the formation of synaptic vesicles in AD [22]. Reactive aldehydes produced through oxidative modification of phospholipids (4-hydroxynonenal) covalently modify APP and tau and promote aggregation propensity [10,73]. The depletion of plasmalogens also impairs antioxidant buffering capacity, making one more vulnerable to lipid peroxidation. These structural changes of phospholipids destabilize synaptic membranes and provide a biochemical environment that promotes protein misfolding and neuronal stress.

4.4 Lipid Raft Remodeling and Signal Transduction

Lipid rafts are used in receptor clustering and intracellular signaling. Cholesterol and sphingolipid changes in composition impair raft integrity, which influences the localization of NMDA receptors, Tropomyosin receptor kinase B (Trkβ), insulin receptors, and other signaling proteins [74,75]. Different isoforms of APOE have varying effects on raft organization, with *APOE ε4* disrupting membrane microdomains and disrupting receptor clustering, rendering cells excitotoxically vulnerable [76]. The oxidation of sterols accumulating in rafts, including 7-ketocholesterol, also worsens receptor signaling and neuronal stress [32]. Raft remodeling is thus the connection between membrane lipid composition and defective synaptic signaling and metabolic dysfunction.

4.5 The Lipid–Neuroinflammation Interface

Neuroinflammation and lipid metabolism are closely coupled with lipid-sensing receptors and bioactive lipid mediators. Toll-like receptor 2 (TLR2), TLR4, and the lipid-sensing receptor Triggering receptor expressed on myeloid cells 2 (TREM2) are activated by oxidized phospholipids and ceramides to induce the activation of microglia and the assembly of inflammasomes [65,77]. TREM2 mutations affect lipid uptake and phagocytic capacity and cause the build-up of extracellular debris and increased inflammatory signaling. At the same time, the elimination of specialized pro-resolving lipid mediators based on omega-3 fatty acids impairs the resolution stage of inflammation, which prolongs chronic microglial activation [78]. Therefore, lipid imbalance not only initiates inflammatory activation but also inhibits its measurement, establishing a self-sustaining neuroimmune response cycle.

4.6 Mitochondrial–Lipid Crosstalk and Energetic Failure

Lipid composition is very sensitive in mitochondria. Mitochondria-specific phospholipid (cardiolipin) stabilizes respiratory chain complexes. Its oxidation interferes with the efficiency of electron transport and favors the release of cytochrome c [68]. An increase in the levels of ceramides in the mitochondrial membranes increases permeability transition and apoptotic signaling, whereas a breakdown in β-oxidation contributes to the accumulated toxic lipid intermediates [10]. Additional changes in lipid trafficking that occur in association with *APOE ε4* worsen the effects of fragmentation and bioenergetic decline in mitochondria [45]. This reciprocal interaction in which lipid imbalance leads to decreased mitochondrial function, and mitochondrial dysfunction increases lipid peroxidation, leads to a vicious circle where energetic failure progressively increases synaptic degeneration.

4.7 Lipid-Mediated Coupling of Amyloid and Tau Pathways

The lipid dysregulation offers a mechanistic intermediation of the amyloid and tau pathology. Ceramides and oxidized lipids stimulate oxidation-stimulated lipids GSK3β and CDK5, facilitating tau phosphorylation and increasing amyloidogenic processing at the same time [10]. Lipid aldehydes reacting with APP and tau induce aggregation propensity and seeding potential [46]. The clustering of membrane microdomains also promotes pathological interactions of Aβ oligomers and tau species. Early metabolic imbalance is converted to convergent proteinopathy by common lipid-sensitive signaling pathways.

4.8 Gut–Brain–Lipid Axis

The peripheral lipid metabolism and gut-derived metabolites have an impact on central lipid homeostasis. Gut microbiota control the bile acid composition and production of short-chain fatty acids that adjust the lipid metabolism in the system and neuroinflammatory tone [47]. Bile acids and trimethylamine-N-oxide (TMAO) cross the blood-brain barrier and encourage oxidative stress and microglial activation [48]. Lipid changes related to dysbiosis thus play roles in systemic-central metabolic interrelation with dietary habits and peripheral lipid dysbalance, being related to neurodegenerative susceptibility.

4.9 Pathway-Level Lipidomic Networks

In addition to the individual lipid species, coordinated changes in the lipid pathways give information on the AD progression. Directional metabolic flux ratios, e.g., sphingomyelin-to-ceramide, are associated with cognitive deterioration [79]. Lipidomic analyses combined with other techniques have shown that cholesterol turnover, sphingolipid remodeling, and phospholipid oxidation are not cascades but networks of interrelated processes [10]. These perturbations at the pathway level affect the amyloid processing, phosphorylation of tau, and activation of inflammation. The mechanistic basis of metabolic intervention, along with stratification of precision, of lipid metabolism can be achieved by seeing lipid metabolism as a dynamic systems network, as opposed to a set of discrete abnormalities.

5. Genetic and Molecular Insights

Genetic studies firmly position lipid metabolism at the core of late-onset Alzheimer's disease. While mutations in APP, PSEN1 (Presenilin 1), and PSEN2 (Presenilin 2) underlie early-onset familial forms, most sporadic AD cases arise from polygenic risk networks that converge on cholesterol transport, membrane remodeling, endosomal trafficking, and microglial lipid sensing [8,9,15]. Rather than acting independently, these loci define interconnected lipid–immune–metabolic circuits that influence amyloid processing, tau vulnerability, and neuronal resilience. Genome-wide association studies consistently implicate *APOE*, *ABCA1*, *ABCA7*, *TREM2*, *CLU* (Clusterin), and *SORL1* (Sortilin-related receptor 1) genes central to lipid transport or membrane dynamics. The convergence of risk alleles on lipid regulatory pathways supports the conceptualization of AD as a disorder of impaired lipid homeostasis embedded within inflammatory and mitochondrial stress networks.

5.1 APOE: Central Modulator of Lipid Homeostasis and AD Risk

APOE $\varepsilon 4$ allele is the most potent genetic risk factor of sporadic AD that presents dose-related contributions to the risk and earlier onset [14,15,80]. Contrary to the mutations that directly augment the production of Aβ, the APOE affects the disease by the dysfunction of lipid transport. The lipid carrier in the brain is APOE, which facilitates the redistribution of cholesterol and phospholipids between astrocytes and neurons by a process of lipidation via ABCA1. *APOE* $\varepsilon 4$ isoform has weakened lipid-binding capacity, a change in structural stability, and proteolytic vulnerability [16,18]. Unstable lipoprotein particles are the result of poor lipidation, and they disrupt the maintenance of the membrane and the synaptic integrity. In *APOE* $\varepsilon 4$ carriers, the defective lipid conveyance impacts the receptor-mediated Aβ clearance and the organization of membrane microdomains, indirectly preferentially supporting amyloidogenic processing. Markedly, this is a sign of defective lipid-dependent trafficking but not mere overproduction of Aβ. In addition to the neuronal action, APOE interferes with the lipid metabolism of glial populations. Disturbed cholesterol movement in oligodendrocytes disrupts lipid synthesis of the myelin [81]. *APOE* $\varepsilon 4$ enhances the lipid droplet accumulation, decrease β-oxidation, and increases inflammatory activation in microglia [44,82,83]. These cell-type selective effects define *APOE* $\varepsilon 4$ as a cause of extensive metabolic susceptibility and not a specific amyloid modulator.

5.2 Convergent Lipid Regulatory Networks Beyond APOE

Other susceptibility loci support the lipid regulation vicinity in AD. ABCA1 and ABCG1 regulate cholesterol and phospholipid efflux that is essential in the normal APOE lipidation. The decreased ABCA1 activity leads to the production of lipidated APOE particles of poor quality and to disruption of cholesterol distribution in the membrane [84,85]. ABCA7 combines lipid translocation and microglial phagocytosis; the loss-of-function variants disrupt the uptake of Aβ and modify the phospholipid composition [86]. CLU is a lipid chaperone that maintains extracellular lipid-protein complexes and complement activation, which connects lipid stress with amplification of inflammation [87]. SORL1 regulates the APP intracellular trafficking between the trans-Golgi and endosomes; impaired function increases the amyloidogenic sorting in the cholesterol-rich compartments [88]. *TREM2* plays a vital role in microglial lipid sensing as it binds phospholipids and *APOE*-containing particles. Lipid uptake and metabolic adaptation are impaired by risk variants, which decreases the phagocytic efficiency and increases the activation of inflammation [77]. *APOE-TREM2* functionality creates a lipid-sensing circuit that identifies microglial state changes with deposition of amyloid. Phospholipase C gamma 2 (PLCG2), bridging integrator 1 (BIN1), and phosphatidylinositol-binding clathrin assembly protein (PICALM) variations also modify phosphoinositide breakdown and clathrin-mediated endocytosis, which changes vesicular transport and receptor intake [89]. The combination of these loci creates a network of interconnected lipid trafficking and membrane remodeling that regulates neuronal and microglial activity in response to metabolic stress.

5.3 Gene–Environment and Metabolic Interactions

Metabolic conditions and exposure to the environment make significant adjustments to genetic susceptibility. Lipid metabolism is a primary nexus by which diet, insulin sensitivity, and endocrine contributions to the disease path are mediated and especially in *APOE* $\varepsilon 4$ carriers. *APOE* $\varepsilon 4$ carriers regulate systemic lipid processing and neuronal membrane lipid incorporation. *APOE ε4* carriers have less incorporation of the DHA into neuronal membranes when supplemented [34,49]. Since DHA promotes membrane fluidity and anti-inflammatory communication, reduced delivery could be a limiting factor to synaptic resilience and therapeutic responsiveness. This is increased by metabolic disorders. The resistance to insulin increases the synthesis of ceramide and interferes with Akt signaling, which favors the accumulation of mitochondrial stress [90]. Such metabolic stress increases the rate of lipid droplet formation in glial cells and maintains cellular inflammatory activity in genetically susceptible subjects. Gene expression is also controlled by lipid metabolites. The availability of acetyl-CoA regulates histone acetylation, which affects the transcription of lipid synthesis and mitochondrial functioning genes [76,91]. Ketone bodies that increase the resistance to the resistance pathways of oxidative stress are b-hydroxybutyrate as signaling metabolites [92]. Nuclear receptors such as PPARs and LXRs are activated using fatty acids and coordinate transcriptional programs that control lipid oxidation and immune tone. Therefore, the AD risk is a combination of variants inherited in lipid regulation and metabolism.

5.4 Integrative Lipid–Genetic and Epigenetic Networks

Multi-omics studies indicate that AD is caused by the concerted breakdown of lipid-immune-metabolic modules, but not individual gene mutations. The co-expression network of *APOE*, *ABCA1*, *SORL1*, and *CLU* is associated with inflammatory and mitochondrial genes in large data sets, such as Alzheimer's Disease Neuroimaging Initiative (ADNI) [10,22]. The modules linked to ceramide are also related to complement activation and synaptic vulnerability, whereas the decrease in phosphatidylcholine and plasmalogen species correlates with the inhibition of oxidative phosphorylation genes. These synchronized changes can be identified before more complex neurodegeneration, and this shows that lipid network destabilization is a systems-level process. Lipid metabolism is also further tied to the process of gene regulation by epigenetic means. The histone acetylation under the influence of acetyl-CoA affects the transcription of lipid and mitochondrial genes [93]. The products of lipid peroxidation can alter transcriptional regulators, which strengthens expression designations by oxidative stress [94]. Lipid-sensitive nuclear receptors are activated to remodel chromatin accessibility and orchestrate the cholesterol efflux and immune regulation. There is another modulatory layer of sex hormones. The estrogen controls the expression of *APOE* and *ABCA1* and modulates the activity of the mitochondrial function [95]. Reduced estrogen levels can thus increase lipid regulation in those genetically predisposed, which explains sex-specific differences in AD risk. Taken together, these results place AD as a disease of genetically regulated lipid network instability, which is influenced by metabolic and epigenetic contexts.

6. Lipidomics and Biomarker Discovery

Lipidomics using mass spectrometry can now be used to quantitatively profile hundreds of lipid species in brain tissue, cerebrospinal fluid (CSF) and plasma. Rather than being alone, lipid abnormalities are coordinated in the plasma of Alzheimer's disease to occur in conjunction with phospholipids, sphingolipids, sterols, and oxidized products. Notably, a lot of these changes occur on preclinical or prodromal stages, meaning that lipidomic disturbance is a manifestation of early metabolic disequilibrium but not end-stage neuronal death. Modern lipidomics, as opposed to simple measurements, focuses on the direction of pathways and network-level understanding. Combination with genetic and proteomic data is gradually pioneering lipid profiles as the mechanistic outputs of membrane remodeling, mitochondrial strain, inflammatory stimulation, and lipid transport proficiency.

6.1 Lipidomics in AD Brain Tissue

Consistent with a large-scale decrease in PC and PE species enriched with DHA, such as PC 38:6 and PE 40:6, postmortem lipidomic analyses of AD cortex and hippocampus show such decreases [20,28]. Plasmalogens, especially plasminyl-PE species, are significantly decreased, that weaken the stability of the membrane curvature and antioxidant buffering activity. Ceramide species, including Cer d18:1/16:0 and Cer d18:1/18:0, on the contrary, are increased [22,42,50], indicating increased sphingomyelin hydrolysis and transition to pro-apoptotic lipid signaling. The sphingomyelin-to-ceramide ratio is consequently shifted in favor of pathway activation that is congruent with inflammatory and mitochondrial stress. The total cholesterol can be quite stable, but the decreased level of 24S-hydroxycholesterol and the enhanced level of oxidized sterols such as 7-ketocholesterol show evidence of the disrupted cholesterol turnover and oxidative modification [96]. Spatial lipidomics proves the idea of enrichment of ganglioside GM1 in amyloid plaques and peri-plaque areas, accumulation of ceramide to show the anatomically localized lipid remodeling related to the pathological lesions [97]. Together, brain tissue lipidomics can show a predictable course of lipid degradation, plasmalogen disappearance, ceramide increase, and sterol oxidation that may be observed before severe neuronal damage.

6.2 Peripheral Lipid Biomarkers: Plasma and CSF

Peripheral lipid profiling detects consistent patterns that are related to cognitive decline and phenoconversion. Lipidomic profiles reported by Huynh K *et al.* [98] (2020), encompassing multiple lipid classes such as phospholipids and sphingolipids, are associated with both prevalent Alzheimer's disease and future disease risk. Ceramide species are one of the strongest predictors of the plasma. The high Cer d18:1/16:0 and Cer d18:1/18:0 levels are associated with hippocampal atrophy and progressive acceleration [99]. Notably, the pathway-level measures are better than those based on individual species. A decrease in the ratios of sphingomyelin-to-ceramide, especially SM d18:1/24:0, reflects a higher activity of the sphingomyelinase and metabolic directionality [51]. AD plasma raises the levels of oxidized phospholipids including POVPC (1-palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphocholine) and PGPC (1-palmitoyl-2-glutaroyl-sn-glycero-3-phosphocholine) [100], which is associated with systemic oxidative stress and the activation of inflammation. Reduced levels of 24S-hydroxycholesterol and disturbed levels of desmosterol in CSF indicate impaired neuronal cholesterol metabolism [101]. Even though the effect of peripheral lipids on predictive performance can be enhanced by systemic metabolism, their combination with genotype and longitudinal imaging data is more effective.

6.3 Lipid Biomarkers and APOE Genotype

The genotype of *APOE* plays a significant role in altering the systemic and central lipidomic architecture that can modify the baseline lipid transport efficiency and the susceptibility to metabolic stress. $\varepsilon4$ carriers have an increased level of circulating ceramide species, especially Cer d18:1/16:0 and Cer d18:1/18:0, and more oxidized phospholipids and lower levels of plasmalogen [10,45]. These changes are in line with the dysfunction of the *APOE* lipidation, the decreased cholesterol efflux via ABCA1, and the modified redistribution of cholesterol and phospholipids among astrocytes and neurons. Ineffective lipidation of *APOE* $\varepsilon4$-carrying lipoproteins results in reduced capacity of aiding membrane repair and synaptic remodeling with the lipid needed, making them more vulnerable to lipid peroxidation and to inflammatory signalling. Notably, genotype not only alters lipid abundance but also pathway directionality. $\varepsilon4$ carriers simply show reduced sphingomyelin-to-ceramide ratios, which indicates an increase in sphingolipid metabolism, sphingomyelinase activity and a shift to a more pro-apoptotic sphingolipid metabolism. Combining plasma ceramide levels with *APOE* genotype allows predicting atrophy of the hippocampal and cognitive decline better than either of these factors alone [102]. It is an interaction that implies that genotype sets a fundamental lipid transport structure, and that lipidomic profiling records dynamic metabolism perturbation imposed on that structure.

6.4 Multi-Omics Integration and Pathway Modules

Lipid species do not tend to work individually. Systems-level analyses of ADNI and associated multi-cohort data reveal that lipid changes come together in coordinated metabolic modules, which combine inflammatory, mitochondrial, and complement pathways [30,103]. Such modules are more biologically resolved than individual biomarkers and represent pathway-wide dysregulation. A reproducible module is based on ceramide enrichment and complement cascade proteins (C1q, C3), and inflammatory mediators. Higher levels of ceramide species are associated with higher complement activation levels and microglial inflammatory signals, which are predictors of faster cognitive impairment and increased cortical atrophy. Mechanically, the presence of ceramide facilitates rigidification of membranes, the activation of the inflammasome, and mitochondrial strain, which strengthens complement-mediated synaptic pruning. A second modular association is between loss of polyunsaturated phosphatidylcholine and plasmalogen species in connection with decreased oxidative phosphorylation proteins and abnormal acylcarnitine. This trend indicates that there is impaired membrane remodeling and reduced mitochondrial β-oxidation capacity. A decreased supply of phospholipids interferes with the process of synaptic vesicle dynamics, and the changes in acylcarnitines show that fatty acid oxidation is not fully performed, and the process is not efficient. Combined with genomic data, this again indicates that these lipid-protein modules agree with risk loci such as *APOE*, *ABCA1*, and *TREM2* that genetic vulnerability is manifested via a network of coordinated metabolism. Compared to single-analytes techniques, module-based modelling enhances the ability to measure prognostic and increases the ability to interpret biologically.

6.5 Standardization and Translational Challenges

Regardless of technological progress, the clinical application of lipidomics is limited by the lack of methodological consistency. The pre-analytical variables, such as diet, fasting condition, and sample manipulation, cause a lot of variability [104]. Differences between analytical procedures, ionization platforms, and internal standardization cause problems in cross-study comparability. Biological heterogeneity also makes interpretation difficult. Lipid baseline is dependent on age, sex, metabolic comorbidities, and *APOE* genotype. Clinical implementation is restrained by the lack of standardized reference ranges. Efforts are being undertaken to standardize nomenclature, reporting, and data processing systems like the Lipidomics Standards Initiative [104]. A reproducible panel of pathways at the panel level, and established cutoffs will be required to move lipidomics past exploratory profiling and establish lipidomics as the precision diagnostic and therapeutic monitoring instrument in AD.

7. Therapeutic Implications and Interventions

The identification of lipid dysregulation as a mechanistic cause of AD has broadened therapeutic conceptualization of amyloid and tau as sole targets to include therapies that alter cholesterol flux, membrane composition, inflammatory lipid mediators and cerebral energy metabolism. Some of these strategies are outlined below and include pharmacologic manipulation of lipid

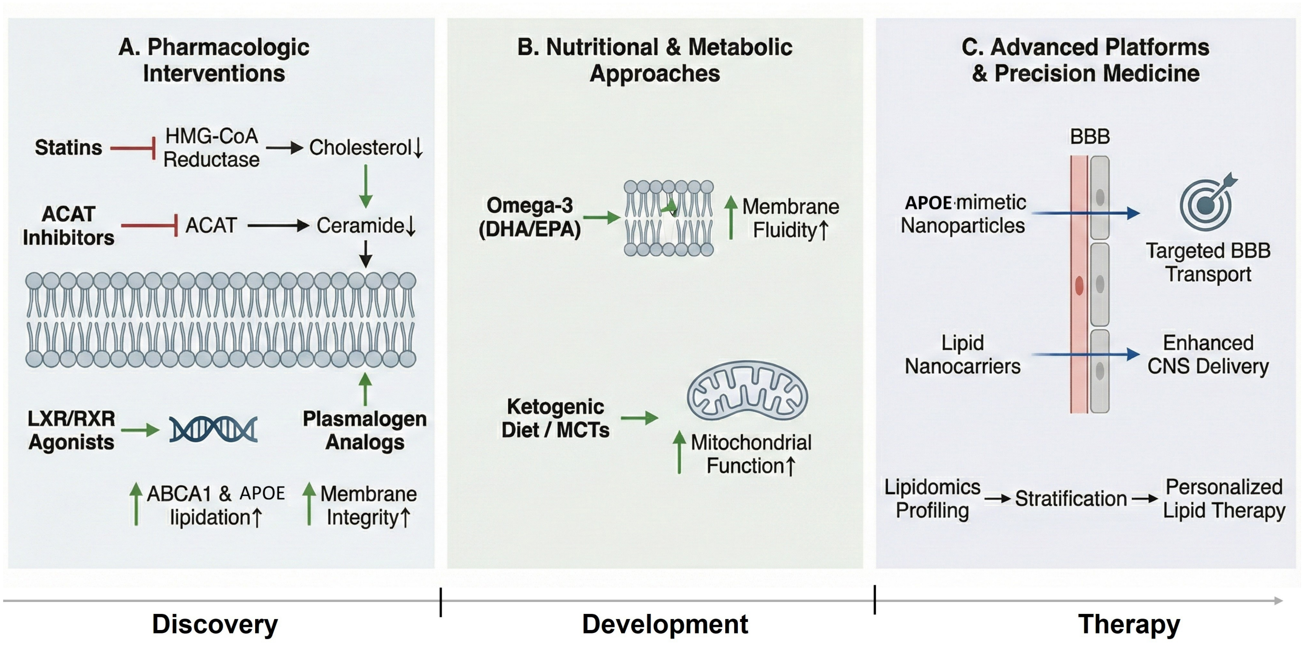

Fig. 3. Translational and therapeutic landscape of lipid-targeted interventions. Lipid-based therapeutic strategies span pharmacologic, nutritional, and nanotechnological approaches. Statins, ACAT inhibitors, and LXR/RXR agonists modulate cholesterol and ceramide metabolism. Nutritional interventions such as omega-3 supplementation and ketogenic diets improve membrane and mitochondrial function. Advanced lipid nanocarriers and APOE-mimetic nanoparticles enhance targeted brain delivery, while lipidomic profiling supports personalized treatment strategies in Alzheimer's disease. Black arrows represent biochemical or mechanistic pathways. Green arrows indicate beneficial or enhancing effects, whereas red blunt-ended lines denote inhibition. Upward (↑) and downward (↓) arrows indicate increases or decreases in levels or activity, respectively. HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; ACAT, acyl-CoA:cholesterol acyltransferase; ABCA1, ATP-binding cassette subfamily A member 1; MCTs, medium-chain triglycerides; CNS, central nervous system.

metabolism, metabolic reprogramming through dietary interventions and new forms of precision based on lipidomic and genetic stratification. The relationship between pharmacologic modulation, dietary methods, lipidomic stratification, and organelle-targeting at the precision framework is summarized in Fig. 3.

7.1 Statins and Cholesterol-Modulating Therapies

Statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have also been suggested as possible neuroprotective agents due to their effects on the lowering of peripheral cholesterol and their possible impact on cerebral cholesterol turnover. Epidemiological research indicates that statins can prevent the onset of dementia over the long term, and greater evidence indicates this effect is stronger in *APOE* $\varepsilon 4$ non-carriers [105,106]. Statins have also been reported to have a mechanistic effect in the modulation of secretase activity, preferential processing of non-amyloidogenic APP, and enhancement of endothelial functioning and cerebral perfusion [107]. Nevertheless, the results of randomized controlled trials have been inconclusive in terms of cognitive effects, probably because of a heterogeneity of blood-brain barrier permeability to statins, intervention timing, underlying vascular risk, and disease severity [108]. There are some results in emerging lipidomic and imaging, which suggest that lipophilic statins (e.g., simvastatin, atorvastatin) have the potential to normalize features of cholesterol turnover and decrease Aβ -related burden when they are administered at early or preclinical stages [10,32], but these claims cannot be conclusively proven by clinical methods. In general, the data available indicate stage and subgroup effect and not homogeneous benefit in established AD.

7.2 Liver X Receptor and Retinoid X Receptor Agonists

Cholesterol efflux, *APOE* lipidation and inflammatory tone are controlled by LXRs and RXRs. Expressions of ABCA1 and ABCG1 are augmented by pharmacologic activation, which boosts the export of cholesterol and possibly facilitates Aβ clearance. Proper agonist bexarotene also decreases the load of the plaque and enhances cognition in transgenic mouse brains [109], although further clinical trials in humans showed inconsistent results, which could be due to the pharmacokinetic properties and dose-related toxicity. Emerging data in preclinical research indicate that integrating the actions of LXR and Peroxisome Proliferator-Activated Receptors (PPARs) can have more extensive effects on lipid homeostasis, mitochondrial dysfunction and neuroinflammation [110,111]. Since hepatic steatosis can be caused by pan-LXR activation, novel LXRβ (Liver X receptor beta) modulators are underway to enhance safety in the long-term whilst retaining central lipid regulation functions.

7.3 Ketogenic Diets and Metabolic Reprogramming

The goal of ketogenic dietary interventions is to reverse the cerebral hypometabolism in AD by enhancing the levels of circulating β-hydroxybutyrate and acetoacetate, which are relatively accessible as substrates to brain oxidation in case glucose metabolism is compromised [33,52]. The ketone bodies join the tricarboxylic acid cycle as acetyl-CoA to aid with ATP-generation and β-hydroxybutyrate also acts as a signaling metabolite to inhibit class I histone deacetylases and activate transcriptional programs associated with antioxidant defense and mitochondrial biogenesis [112]. Preclinical trials indicate a reduction in amyloid load and inflammatory biomarkers, whereas small clinical trials in mild cognitive impairment indicate slight positive cognitive effects [33]. Disadvantages are the problem of compliance, fluctuating cardiovascular outcomes based on the fat composition, and a lack of long-term disease-modifying data. Its therapeutic utility is best likely to be used in the early or prodromal phase and preferably directed by biomarkers of hypometabolism and stratified by genotype and metabolic situations.

7.4 Mediterranean and Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) Diets

The Mediterranean and MIND diets, which are based on monounsaturated fats, omega-3 polyunsaturated fatty acids, antioxidants, and polyphenol-rich diets, are linked with decreased AD risk and slower cognitive deterioration [48]. Mechanistically, oleic acid of olive oil and omega-3 fatty acids are membrane-stabilising in nature and can reestablish lipid mediator balance towards anti-inflammatory eicosanoids. The components of Polyphenols and antioxidants minimize lipid peroxidation and oxidative alteration of membrane phospholipids. The MIND diet also focuses on factors that are associated with vascular and metabolic well-being (leafy greens, berries, whole grains) and minimizes the intake of saturated fats, which can indirectly lower the levels of insulin resistance and lipid-induced inflammatory priming. Nevertheless, causality is challenging to determine because of confounding lifestyle factors, whereas evidence in the form of randomized trials is still scarce. Individual effects of genotypes can be different; *APOE* ε*4* carriers tend to exhibit less incorporation of DHA into brain phospholipids, which can counteract the action of omega-3-dependent pathways [34]. Overall, these diets can be classified as the low-risk preventive or modulatory measures with the possibility of increased accuracy when used with lipidomic and genetic stratification.

7.5 Neuroprotectin D1 and Specialized Pro-Resolving Lipid Mediators

Neuroprotectin D1 (NPD1) is a DHA-derived specialized pro-resolving mediator that is produced through the action of 15-lipoxygenase and serves as a bioactive signal to counteract the action of Aβ -induced stress response. NPD1 enhances the anti-apoptotic response via boosting the Bcl-2 family level of protective proteins (Bcl-2, Bcl-xL) and inhibiting the pro-apoptotic mediators (Bax, Bad), which stabilize mitochondrial integrity and inhibit caspase-3 activation [113]. NF-κB activation is also reduced by NPD1, as well as the expression of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNFα) and interleukin-1 beta (IL-1β) [12,114]. Simultaneously, NPD1 is also reported to suppress BACE1 and facilitate non-amyloidogenic APP processing [115], which is a viable way of lowering amyloid synthesis and cellular susceptibility. It is interesting to note that the lowering of NPD1 in the AD hippocampus with the presence of DHA indicates that pro-resolving signaling changes are impaired by DHA [12]. Lipid mediator stability and delivery issues limit translational development and genotype-specific variations in DHA delivery (especially through *APOE* ε*4* carriers) can affect NPD1 bioavailability and response.

7.6 Arachidonic Acid Signaling and Amyloidogenic Amplification

Membrane phospholipid-released arachidonic acid (AA) is a key precursor of bioactive eicosanoids that regulate inflammatory and excitotoxic signalling. Higher activity of PLA2 (Phospholipase A2) and free AA was also reported in AD-affected areas [116]. AA oxidation through cyclooxygenase (COX) and lipoxygenase (LOX) produces prostaglandins and leukotrienes that encourage microglial action, cytokine production, and oxidative stress, which amplifies inflammatory responses that depend on NF-κB. The amyloidogenic processing is also affected by AA signaling, changing membrane properties and microdomain organization, and evidence indicates that AA metabolites can also elevate BACE1 expression and stabilize its localization to lipid rafts, promoting APP cleavage to produce Aβ [21]. Oxidative stress produced by AA can further enhance the formation of reactive aldehydes, supporting the oligomerization of Aβ and leukotriene signaling is elevation of calcium influx and excitotoxic susceptibility, which contributes to the downstream activation of tau kinases. Since AA and DHA are in competition on incorporation in the membrane, a high omega-6/omega-3 ratio encourages the production of pro-inflammatory mediators, and DHA enrichment encourages pro-resolving pathways. Selective COX inhibition has not been very effective in developed AD, as predicted by the timing of AA-mediated amplification of this inhibitor and the physiological functions of AA signaling in synaptic activity.

7.7 Lipid Responder Phenotypes and Precision Therapeutic Stratification

Lipid responder phenotypes, where the exceptional pathway-wide lipid dysfunction can be used to predict treatment responses, are supported by integrating the lipidomics of plasma with genetic stratification [10,22]. High levels of ceramides and low levels of sphingomyelin-ceramide ratios accompanied by complement activation and rapid progression are known to be associated with a ceramide-dominant inflammatory phenotype, often based on *APOE* $\varepsilon 4$ carriers. Due to the presence of the signs of disrupted oxidative phosphorylation, a phospholipid-deficient bioenergetic phenotype is characterized by depletion of plasmalogens and polyunsaturated phosphatidylcholine species [30]. Altered oxysterols and lower signs of efficiency of lipidation of APOE are seen in a cholesterol-carrying-deficient phenotype. These patterns do not exclude each other but are rather dominant network imbalances that may be determined using systems modeling. The machine learning methods that combine lipid species, genotype and proteomic markers enhance the prediction of the progression and it has the potential to decrease heterogeneity in intervention studies [117]. Potential validation and standardized phenotype definitions are important, followed by an ordinary clinical translation.

7.8 Peroxisomal–Lipid Crosstalk and Redox Dysregulation

Peroxisomes control very-long-chain fatty acid β-oxidation, plasmalogen biosynthesis, and ROS detoxification, which makes them significant factors in lipid homeostasis and redox regulation in AD. Damaged peroxisomal oxidation may cause the build-up of the very-long-chain fatty acids that destabilize the membrane properties and can indirectly influence the microdomain organization [118]. Peroxisomal dysfunction is also damaging to plasmalogen synthesis, in line with the plasmalogen depletion found in AD cortex, impairing antioxidant buffering, and making them susceptible to lipid peroxidation. The lowered detoxification rate accompanied by catalase-dependence can further allow the build-up of hydrogen peroxide, which escalates oxidative injuries. There is an essential crosstalk with mitochondria; the inability to perform peroxisomal oxidation may augment lipid load to mitochondria to strengthen oxidative stress [119]. Transcriptomic research findings of alteration of peroxisome biogenesis factors and ether lipid enzymes in AD brain tissue indicate peroxisome implication other than a secondary effect [120]. Plasmalogen supplementation and regulation of PPAR-controlled lipid oxidation signalling have been found to be therapeutically promising in preclinical trials, with larger clinical trials required.

7.9 Glymphatic System and Lipid Clearance

The glymphatic system helps in the exchange of CSF-interstitial fluid and the clearance of soluble metabolites. Although it is best examined in the context of Aβ and tau removal, dysfunctional glymphatic activity may also be a contributing factor to the build-up of oxidized lipids, inflammatory lipid mediators, and cholesterol metabolites [121]. Polarized expression of the aquaporin-4 (AQP4) on astrocytic end feet depends on glymphatic flow. The mislocalization of AQP4 and decreased effectiveness in clearance are linked to aging and AD and could contribute to the heightened extracellular retention of lipid peroxidation end products and lipid pro-inflammatory mediators [122]. Since the extracellular membrane lipid transport is partially achieved through APOE-carrying lipoproteins, defective APOE lipidation in *APOE* $\varepsilon 4$ carriers may augment defective clearance capability. Loss of sleep also impairs glymphatic functioning and could increase the rate of lipid-derived oxidative species, which connects sleep biology with lipid homeostasis [123]. Stiffness of the vasculature and decreased plasticity also impair the perivascular fluid dynamics, creating another point of convergence between vascular risk and metabolic condition and inefficient clearance. Even though human biomarkers of glymphatic functionality are still in development, a promising avenue of approach to indirectly change lipid clearance dynamics in AD is through targeting sleep and vascular health.

8. Gaps, Challenges, and Future Directions

Despite the fast development of lipidomics and neurobiology, some important gaps are still present in the definition of the role of lipid dysregulation in AD onset and progression. Recent evidence incriminates lipid pathways in amyloid processing, tau susceptibility, neuroinflammation, as well as organelle stress, yet a host of conceptual and methodological constraints still impede mechanistic inference and clinical translation. One major question that is yet to be answered is causality. Several lipidomic discoveries are based upon cross-sectional, case-control comparisons, and it is hard to determine whether lipid changes are initiating events, early parallel processes, or secondary effects of proteinopathy. Stage-resolved biospecimen collection combined with longitudinal cohorts is vital to establishing a temporal order. Recent methods, such as single-cell and spatial lipidomics, can be used to identify the localization of lipid remodeling to cell types and pathological niches at different stages of the disease [22]. Complementary stable isotope tracer experiments may help clarify the direction-dependent pathway flux and at which point the cholesterol turnover, sphingolipid remodeling and phospholipid depletion are directionally perturbed over the course of progression [10].

The second difficulty is biological heterogeneity. There are diverse lipid signatures among individuals depending on the genotype, metabolic status, diet, vascular risk, and endocrine factors. The modification influence of the *APOE* genotype is well-identified, whereas other loci (e.g., *ABCA7*, *TREM2*, *CLU*) probably determine lipid-mediated susceptibility due to variations in lipid transportation and immune-metabolic adjustment [124]. Sex-specific lipid regulation (estrogen-linked lipid transport and mitochondrial activity) can also be a source of different risk patterns and that ought to be included in stratified analyses [30,125]. Subgroup-specific lipid architectures are going to have to be solved with large, ethnically diverse cohorts with harmonized phenotyping in the future.

A major impediment to the validation of biomarkers is methodological standardization. Variations in sample treatment, extraction chemistry, setting of a platform, and reference standards reduce cross-study comparability and complicate cutoff definitions actionable in the clinic. Efforts like the Lipidomics Standards Initiative (LSI) and wider metabolomics quality-control work to coordinate nomenclature, reporting and analytical pipelines [104]. Advances in this field will be determining in bringing lipidomics to the discovery to clinical phases.

Multi-omics integration is becoming a requirement, particularly under systems biology. Lipid pathways are tightly interacting with proteomic, transcriptomic, mitochondrial and immune networks and single-modality biomarkers may not reflect this coupled biology. Integrative modelling systems that relate lipid patterns with genetic framework and inflammatory systems will probably offer more powerful and biologically comprehensible stratification [10]. Models generated by machine learning can help determine predictive signatures and dominant pathway phenotypes; however, must be validated in external cohorts and confounded by medications, diet, and metabolic disease [125].

Therapeutic translation is at an early phase. Several lipid-modulating approaches demonstrate preclinical efficacy, but human trials are typically constrained by safety, lack of interaction with brain targets, and intervention timing as well as disease heterogeneity [126]. A further step in this direction will probably be brain selective modulators, pathway-informed combination regimens and biomarker directed trial designs that will enrich against people with the desired lipid aberration. Lipidomics combined with genotype and metabolic profiling could be used to create precision strategies to enhance the detection of therapeutic signals and to help define responder subgroups [34,48,49]. Another boundary is that of peripheral-central coupling, especially the gut-brain axis. The effects of gut microbiota-derived metabolites on systemic lipid metabolism and neuroimmune tone are possible as well as central lipid remodeling [47,48]. Precision of metabolite-lipid pathway interactions can provide available biomarkers and intervention targets, which could supplement brain-directed therapies.

Lastly, sealing the clinical implementation gap will need synchronous work to create normative lipidomic reference ranges, validate pathway-level panels in diverse populations, and use lipidomic endpoints in longitudinal studies and clinical trials. When rigorously standardized, stage-resolved validated, and pathway-stratified studies of lipid metabolism, lipid metabolism can become more than an associative marker to provide a mechanistically based platform of early disease detection and target therapy in AD.

9. Conclusion

AD is showing growing acceptance as a pathology of lipid homeostasis disturbance that overlaps with amyloid pathogenesis, tau pathology, neuroinflammation and/or mitochondrial malfunction. The converged genetic risk factors that include *APOE*, *ABCA1*, *ABCA7* and *TREM2* are implicated in transporting lipids and remodeling of the membrane, which emphasizes the centrality of lipid regulation in disease susceptibility. Lipidomic analyses also indicate a perturbation of pathways such as ceramide enrichment, plasmalogen loss, and sterol peroxidation that predict overt neurodegeneration and are coordinated by metabolic changes. An intervention mechanism with mechanical foundations is provided by therapeutic interventions that regulate lipid metabolism in response to nuclear receptor modulation to ketogenic interventions and pro-resolving lipid mediators. A lipid framework at the systems level thus offers a harmonizing framework that bridges genetic vulnerability, metabolic strain and synaptic hardening, and is a promising future direction of diagnosis and disease-modulating treatments in AD.

Author Contributions

JB contributed to the conceptualization, methodology, investigation, data curation, visualization, and drafting of the original manuscript. SK—literature review, investigation, data curation, methodology, drafting of supporting sections, and critical review and editing of the manuscript. KS contributed to supervision, validation of scientific content, methodology, and critical revision and editing of the manuscript. DS—supervision, methodology, validation, and critical review and editing of the manuscript. All authors read and approved the final version of the manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work, the authors used Consensus AI tool to assist in the identification and summarization of relevant peer-reviewed literature. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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