

REVIEW ARTICLE

# Nutritional metabolism and cerebral bioenergetics in Alzheimer's disease and related dementias

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**Funding information**

National Institute on Aging, Grant/Award  
Numbers: R13AG069386, R21AG056518,  
R01AG055770, R01AG054434,  
R01AG067063, RF1AG076124,  
RF1AG078362, 2P01AG014930-15A1,  
R01AG043679; L.K. Whittier Foundation;  
W.M. Keck Foundation, Grant/Award  
Numbers: R01NS072497, P30072973; ERC  
Starting, Grant/Award Numbers: StG 678832,  
R01AG062550, R01AG060056,  
R01AG043398; NIH/NCCIH, Grant/Award  
Number: NCCIH90AT008924

**Abstract**

Disturbances in the brain's capacity to meet its energy demand increase the risk of synaptic loss, neurodegeneration, and cognitive decline. Nutritional and metabolic interventions that target metabolic pathways combined with diagnostics to identify deficits in cerebral bioenergetics may therefore offer novel therapeutic potential for Alzheimer's disease (AD) prevention and management. Many diet-derived natural bioactive components can govern cellular energy metabolism but their effects on brain aging are not clear. This review examines how nutritional metabolism can regulate brain bioenergetics and mitigate AD risk. We focus on leading mechanisms of cerebral bioenergetic breakdown in the aging brain at the cellular level, as well as the putative causes and consequences of disturbed bioenergetics, particularly at the blood-brain barrier with implications for nutrient brain delivery and nutritional interventions. Novel therapeutic nutrition approaches including diet patterns are provided, integrating studies of the gut microbiome, neuroimaging, and other biomarkers to guide future personalized nutritional interventions.

**1 | INTRODUCTION**

The human adult brain utilizes ~20% of the whole body's energy resources, yet it only represents ~2% of the body mass. This underscores an enormous metabolic workload, which is mainly fueled by glucose and several nutrients derived from the circulation.<sup>1</sup> Interplay between disrupted intracellular bioenergetic pathways is likely to be relevant to degenerative brain diseases. It is already suspected that relationships between changing efficiency of glycolysis, the pentose phosphate shunt, the Krebs cycle, and oxidative phosphorylation fluxes affect signaling and transcription changes observed in age-related neurodegenerative diseases. These metabolic relationships are currently being addressed on a mechanistic level, but extending such investigations to clinical interventions in diseases like Alzheimer's disease (AD) could provide valuable insights for prevention and therapeutics.<sup>2</sup> Specifically, these investigations should aim to substantiate the role of cerebral bioenergetics as a causal factor for the onset of AD rather than a consequence of brain cell degeneration. This may include demonstrations that AD genetic risk loci impact bioenergetics, bioenergetic deficits precede and contribute to the classical hallmarks of AD pathology (i.e., plaque and tangles), and, ultimately, restoration of cerebral bioenergetic disturbances to promote cognitive health and/or prevention of neurodegeneration in formal randomized-controlled interventions.

This review focuses on key mechanisms involved in cerebral bioenergetics, and how deficits in these pathways may contribute to cognitive decline in AD. Cell, animal, and clinical studies are presented that enhance our understanding of how genetic, environmental risk factors and emerging factors such as the gut microbiome affect brain uptake and utilization of nutrients. We then discuss current mechanistic understandings of mitochondrial energetic changes in aging and AD, which suggest that insufficient nutritional support of cerebral

bioenergetics may occur as early as mid-life prior to significant neuropathology and compounds with disturbed nutrient delivery to the brain. Finally, we present examples of promising single nutrients or combinations paired together with diet patterns and identify new areas of basic research, blood, and imaging biomarkers to guide future clinical interventions.

**2 | NUTRITIONAL REGULATION OF BRAIN ENERGY METABOLISM IN AD PATHOGENESIS**

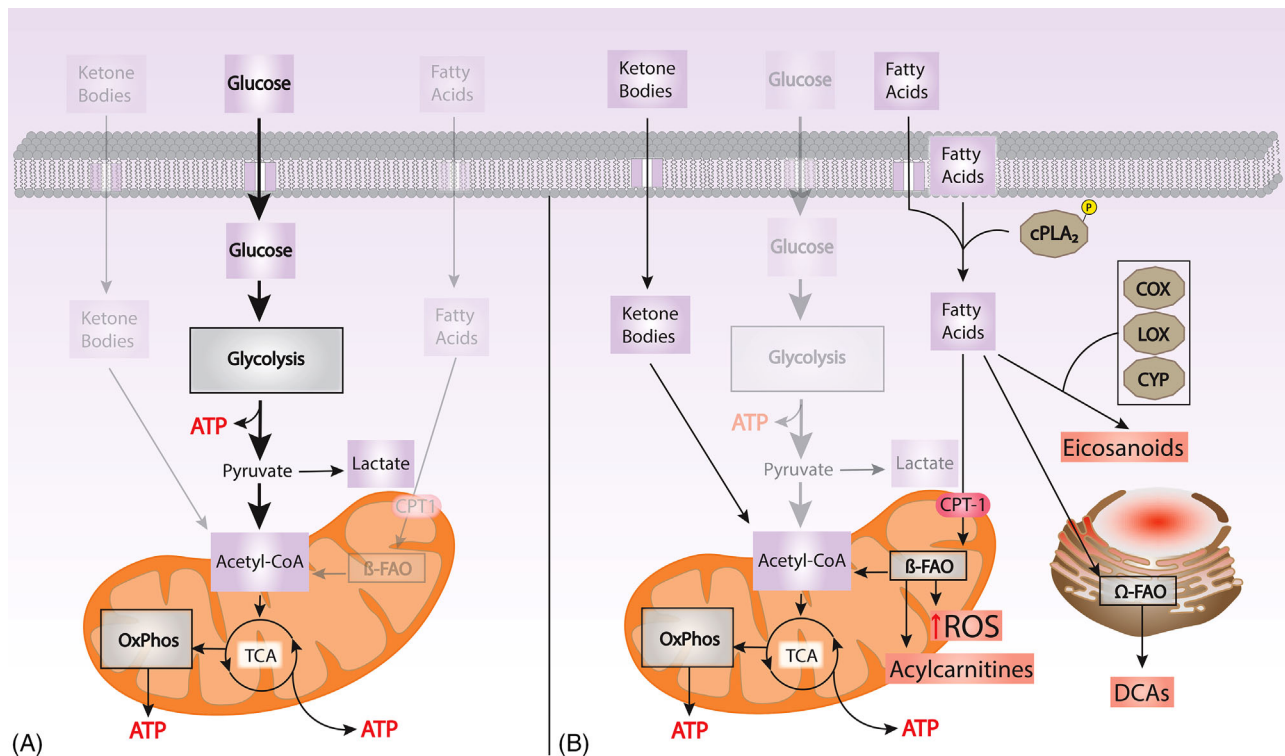
It is estimated that the brain consumes 120 g of glucose per day or about 20% of the body's glucose utilization during a resting state. Glucose undergoes glycolysis to pyruvate, which is metabolized to acetyl CoA as the key carbon source for respiration or oxidative phosphorylation to generate adenosine triphosphate (ATP) in mitochondria (Figure 1A). In resting conditions, the favored metabolic route is mitochondrial oxidative phosphorylation, while highly demanding activity states such as synaptic plasticity, learning, and memory require the additional contribution from glycolysis or lactate metabolism.<sup>3-5</sup> When the brain is starved for glucose during hypoglycemia or as a result of defective glucose transporters (GLUT) function,<sup>6</sup> cells utilize liver-derived ketone bodies such as acetoacetate and 3-hydroxybutyrate to form acetyl CoA. These ketone bodies temporarily replace glucose as the energy source in the brain, but the ketogenic brain must revert to a precise regulation of glucose oxidation to maintain prolonged CNS function.<sup>7</sup>

Several nutrients, including vitamins, amino acids, trace elements (e.g., iron and magnesium) and fatty acids derived from dietary intake of carbohydrates, fats, and proteins are concentrated in the brain and may have a role in meeting brain energy demand and their

brain delivery is affected by AD (Table 1). Several nutrients serve as cellular bioenergetic catalysts to produce key energetic substrates for sustained neuronal function (i.e., ATP). Some micronutrients serve as coenzymes and cofactors for enzymatic reactions while others play a structural role within the enzyme and the mitochondrial cytochromes. Others serve as electron and proton carriers in the ATP-generating respiratory chain, including B vitamins and ascorbic acid.<sup>8,9</sup> For example, thiamin pyrophosphate (TPP; vitamin B1), pantothenic acid (vitamin B5; precursor for co-enzyme A synthesis), flavin mononucleotide (FMN; derived from vitamin B2), flavin adenine dinucleotide (FAD; derived from vitamin B2) and nicotinamide adenine dinucleotide (NAD; derived from nicotinamide) are involved in the Krebs cycle and I and II complexes of the respiratory chain. Biotin, CoA, and FAD are involved in heme biosynthesis, which is an essential part of the cytochromes and important for mitochondrial respiratory chain reactions. Succinyl-CoA can nourish the respiratory chain or the Krebs cycle depending upon specific cellular needs.<sup>10,11</sup> Iron has important roles in maintaining the high metabolic and energetic requirements of neuronal tissues and is also involved in myelin synthesis, neurotransmitter synthesis, and metabolism.<sup>12</sup>

### RESEARCH IN CONTEXT

- 1. Systematic review:** Does providing adequate energy to the dementia-at-risk brain limit the progression to neurodegenerative diseases such as AD? Systematic reviews of randomized trials of dietary and nutritional supplements have reported largely null effects on cognitive outcomes.
- 2. Interpretation:** Because the aging brain and AD risk factors affect the delivery of nutrients to the brain before the onset of dementia, preventive nutritional interventions during mid-life may prove more effective when started early, while other nutritional interventions (such as the ketogenic diet) may work later in the disease process.
- 3. Future directions:** A better understanding of brain energy utilization pathways throughout the lifespan and in both healthy aging and disease states guided by nutrition-brain-specific biomarkers can inform personalized nutrition clinical trials.



**FIGURE 1** (A) Glucose is the main energy substrate in the brain. Glucose undergoes glycolysis to pyruvate, which is metabolized to acetyl CoA, as the key source of carbon for oxidative phosphorylation (Oxphos) to generate adenosine triphosphate (ATP). In resting conditions, the favored metabolic route is Oxphos, while highly demanding activity require contributions from glycolysis or lactate metabolism. When the brain is starved for glucose, ketone bodies are metabolized to form acetyl CoA. (B) Failure to utilize glucose and energetic stress shifts metabolism into oxidation of fatty acids, which leads to ROS production. The activation of cPLA2 promotes the formation of inflammatory lipid mediators (eicosanoids). Incomplete fatty acid oxidation (FAO) in the mitochondria is reflected by levels of acylcarnitines in the blood and the brain. The oxidation of n-3 fatty acids in the ER results in DCA accumulation, a urinary biomarker of bioenergetic stress. COX, cyclooxygenase; cPLA2, calcium dependent phospholipase A2; OxPhos, oxidative phosphorylation; CPT-1, carnitine palmitoyltransferase 1; CYP, cytochrome P450; DCA, dicarboxylic acids; ER, endoplasmic reticulum; FAO, fatty acid oxidation; LOX, lipoxygenase; ROS, reactive oxygen species; TCA, tricarboxylic acid

**TABLE 1** Nutrients with a putative role in cerebral bioenergetics: function, concentration gradient, and transport mechanisms

Nutrient and reference	Function, concentration gradient	Transporters and location
B1 thiamine <sup>238,239</sup>	CSF/serum ratio 2.1:1 for thiamine, 8.3:1 for thiamin monophosphate	SLC25A19 mitochondria SLC19A3 brain unknown SLC19A2 ubiquitous
B6 pyridoxine, pyridoxal, PLP <sup>46</sup>	CSF/plasma ratio 1.3:1 PL = pyridoxal is most abundant in CSF; requires phosphorylation of PL to PLP centrally;	BBB Unknown bidirectional transport; facilitated diffusion BCSFB
B7 biotin <sup>240</sup>	CSF/serum ratio 1:3.2 CSF/serum ratio lower in AD	SMVT BCSFB
B9 folate <sup>241,242</sup>	CSF-blood ratio is 4:1 CSF folate levels are lower in AD Folate in enriched in mitochondrial fractions	FOLR1 BCSFB BBB folate receptor at the BCSFB; FR alpha blood to CSF; receptor mediated endocytosis
B12 cobalamin <sup>243-245</sup>	CSF/serum ratio 1:20 CSF/serum ratio is lower in AD Required for the oxidation of odd-chain fatty acids and catabolism of ketogenic amino acids Homocysteine metabolism	Cubam receptors at the BCSFB
Vitamin C, ascorbic acid <sup>246,247</sup>	CSF/Serum ratio 3:1 Essential for carnitine synthesis, involved in transport of long chain fatty acids into the mitochondria and fatty acid oxidation. Facilitates transport and uptake of non-heme iron at the mucosa, and reduction of folic acid intermediates.	SVCT-2 basolateral BCSFB GLUT1 (SLC2A1) as dehydroascorbic acid at BBB GLUT4 as dehydroascorbic acid within Astrocytes
DHA, docosahexaenoic acid <sup>108,248</sup>	CSF to plasma ratio 1:75 Component of structural phospholipids in the CNS CSF to plasma ratio lower in AD	MFS2A <sup>109</sup> Fatty acid binding proteins <sup>249</sup>
Vitamin D, cholecalciferol, 25 hydroxyvitamin D <sup>250-252</sup>	CSF to serum ratio 1.4: 1 Lower CSF/serum ratio in AD 1alpha-hydroxylase the enzyme responsible for the formation of the active form in the human brain	VDR VDBP

Abbreviations: PLP, Pyridoxal 5'-phosphate; PL, pyridoxal; SMVT, sodium dependent multivitamin transporter; BCSFB, blood cerebrospinal fluid barrier; SVCT, sodium dependent vitamin C transporter; BBB, blood brain barrier; CSF, cerebrospinal fluid; FOLR1, Folate receptor 1; FR alpha, folate receptor alpha; GLUT, glucose transporter; VDR, Vitamin D Receptor; VDBP, Vitamin D Binding Protein, MFS2A, major facilitator superfamily domain-containing protein 2a

Fatty acids are a minor source to fuel ATP production in the brain.<sup>13</sup> First, the high oxygen consumption associated with fatty acid  $\beta$ -oxidation (FAO) increases the risk of neurons becoming hypoxic because oxygen pressure is nonuniform and low.<sup>14</sup> Second, the utilization of fatty acids as fuel increases susceptibility to oxidative damage. The mitochondria are a major source of reactive oxygen species (ROS) generation.<sup>15</sup> Superoxide is formed by a one-electron transfer from certain sites within the mitochondrial electron transfer chain (ETC) to molecular oxygen.<sup>15</sup> FAO in both the mitochondria and peroxisomes is a source of superoxide production. Neuronal membranes are rich in polyunsaturated fatty acids (PUFAs), namely the n-6 arachidonic acid (AA) and n-3 docosahexaenoic acid (DHA), which constitutes a significant proportion of gray matter fatty acids.<sup>16,17</sup> The double bonds in PUFAs are particularly vulnerable to oxidative stress, so neurons are susceptible to oxidative damage and require constant antioxidant protection. In activated brain areas, the local increase in oxygen consumption is lower than that of the glucose consumption,<sup>18</sup> supporting the need to uncouple glucose use from oxygen consumption for ATP production. Indeed, elevated lactate observed during high neuronal activity supports this uncoupling of glucose use from oxygen consumption and indicates that selective activation of glycolysis is a major driver

of brain ATP production,<sup>19</sup> when oxidative ATP supply is at maximal capacity. In a resting, awake brain, most of the glucose is completely oxidized to CO<sub>2</sub> and water.

## 2.1 | Cell-specific bioenergetics

Brain cell types approach their energy needs and bioenergetic fluxes differently, and these routes align specific parts of the brain with cell-specific functions to determine nutrient needs. This impact is seen at the molecular level and involves glycolysis, the Krebs cycle, mitochondrial function, and overall strategies for making ATP. These signaling-related energy demands also involve metabolic plasticity, which is achieved by epigenetic and transcriptional activities.

### 2.1.1 | Neuron-astrocyte energy shuttles

Astrocytes are the most numerous glial cells and have a major role in supporting neuronal energy demands. Interestingly, despite their need to respire, neuronal mitochondria are not structured to

perform FAO, which could reflect the need of neurons to maintain an extensive membrane surface area. Conversely, respiration appears less critical for obtaining the overall bioenergetic needs of astrocytes. Astrocytes appear to maintain high rates of glycolysis, and to some extent manage the gateway through which glucose enters the brain parenchyma. Unlike neuronal mitochondria, astrocytic mitochondria can perform FAO, but this function is limited by low rates of long-chain fatty acid transport.<sup>20</sup> At face value, this might seem to contradict the astrocyte's reduced dependence on respiration for generating ATP. The logical explanation for this relates to the fact that astrocytes can provide carbon intermediates that fuel neuronal mitochondrial respiration.<sup>21</sup> In the brain, lactate produced via glycolysis or stored glycogen (glycogenolysis) is released from astrocytes via the monocarboxylate transporter 4 (MCT4). It is then taken up by monocarboxylate transporter 2 (MCT2) present on neuronal membranes.<sup>22</sup> This lactate, upon conversion to pyruvate, undergoes oxidation by neuronal mitochondria. The described "astrocyte-neuron lactate shuttle hypothesis" is thus activated under aerobic conditions in which activity at neuronal glutamatergic synapses promotes the production of lactate by astrocytes that supplements the basal production of neuronal ATP normally coming from the oxidation of glucose carbon derived directly from neuronal glycolysis.<sup>23</sup> In low glucose conditions, lactate glycogenolysis in astrocytes may be upregulated to fulfill demand by neurons. Lactate shuttling and the supply of carbon to neurons can be disrupted by various processes, including: a generalized decrease in glucose uptake via down-regulation of glucose transporter at the BBB, reduced expression of hexokinase, and alterations in the expression of astrocytic MCT4 and neuronal MCT2 during aging.<sup>24,25</sup> A similar "ketone body shuttle" is also postulated where beta-hydroxybutyrate and acetoacetate are generated from FAO in astrocytes that additionally support neuronal mitochondrial respiration.<sup>26</sup> This reduced reliance on respiration further enables astrocytic mitochondria to recover carbon for macromolecule synthesis.

### 2.1.2 | Oligodendrocytes

Oligodendrocytes are the glial cells that produce myelin. Recently findings have increased appreciation for the roles of myelin in the optimal functioning of the nervous system besides axonal integrity. Myelin provides trophic and metabolic support to axons by secretion of growth factors and by transfer of energy metabolites.<sup>27,28</sup> Oligodendrocytes also provide direct metabolic support to neurons as a source of lactate to the axon.<sup>29,30</sup> In the CNS, monocarboxylate transporter 1 (MCT1) is mainly expressed by oligodendrocytes.<sup>31</sup> Lactate is released to the periaxonal space, the space between the axonal membrane and the myelin sheath, through the MCT1 and is transported into the axonal cytoplasm via MCT2.<sup>29,30</sup> Oligodendrocytes can also supply glucose to the axons, as seen in the corpus callosum<sup>32</sup> and thalamus.<sup>32</sup> Oligodendrocytes also deliver glucose and lactate to the axons together with astrocytes.<sup>33</sup> Moreover, oligodendrocytes can directly modulate axonal energy metabolism by transferring sirtuin 2 (SIRT2) in exosomes, which in turn promote axonal

mitochondrial ATP production by deacetylation of mitochondrial proteins.<sup>34</sup>

### 2.1.3 | Microglia

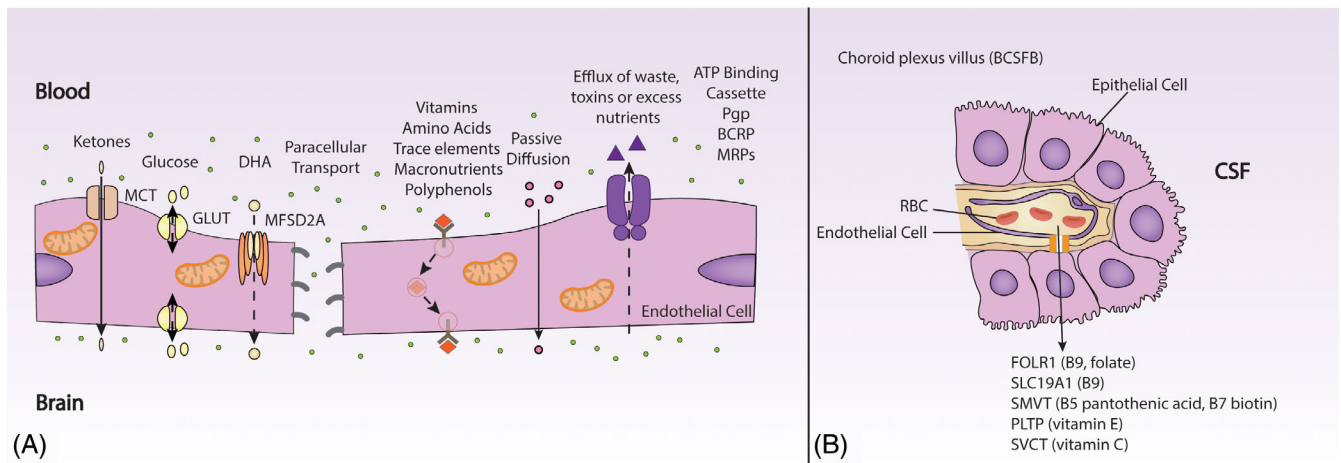
Microglia are mononuclear phagocytes in the CNS that are derived from myeloid progenitors outside of the brain during embryonic development.<sup>35</sup> Microglia predominantly rely on ATP as an energy substrate via glucose metabolism through glycolysis, the TCA cycle, and oxidative phosphorylation to remove apoptotic neurons,<sup>36</sup> prune non-functional synapses,<sup>37</sup> and produce trophic factors that increase neuronal survival<sup>38</sup> under homeostatic conditions. Lactate may also be an energy substrate for microglial metabolism, as recent reports demonstrated that microglia express MCTs and lactate dehydrogenase B which is responsible for catabolizing lactate into pyruvate.<sup>39</sup> Microglia show remarkable metabolic flexibility depending on the environmental conditions of the brain parenchyma *in vivo*, as recent studies using time-lapse two-photon imaging of the mouse brain demonstrate that microglia can adapt to use glutamine as a metabolic fuel in the absence of glucose.<sup>40</sup> This flexibility suggests that the microglia phenotypes and functions to maintain homeostasis in the central nervous system are directly tied to energy metabolism.

### 2.1.4 | Endothelial cells

Endothelial cells (EC) are key components of the blood-brain barrier (BBB). The layer of ECs represents a tightly sealed cell that results in high trans-endothelial electrical resistance and low paracellular and transcellular permeability,<sup>41</sup> separating the brain from the bloodstream. The endothelium of the BBB has multiple specific proteins acting as transporters and receptors (Figure 2A), which are responsible for the passage of metabolites, nutrients, and junction proteins. Glucose transport is regulated by GLUTs, and solute carrier family proteins (SLCs). Among them, the most highly expressed transporter is GLUT1.<sup>42</sup> SLCs, SLC carriers, organic cation transporters (OCTs), and facilitated diffusion carriers are additional transporters to facilitate the uptake of creatine,<sup>43</sup> choline,<sup>44</sup> amino acids (glutamate, aspartate, GABA, and glycine),<sup>45</sup> nucleosides, nucleoside triphosphate, nucleobases,<sup>42</sup> water-soluble vitamins, that is, thiamine, biotin, folate, and ascorbic acid<sup>46</sup> as well as essential metals acting as enzyme cofactors.<sup>47</sup> Interestingly, the number of mitochondria in ECs is five or six times greater than other tissues of the human body,<sup>48</sup> reflecting the high energy needs of ECs to maintain brain homeostasis. The major micronutrients with a putative role in cerebral bioenergetics, their function, concentration gradient, and transport mechanisms through ECs are summarized in Table 1.

### 2.1.5 | Epithelial cells

The blood CSF barrier (BCSFB) found at the lateral, third and fourth ventricle of the brain is composed of CSF facing cuboidal epithelial



**FIGURE 2** (A) Key transport proteins at the BBB include MCT for ketones, GLUTs for glucose, MFSD2A for DHA. Efflux of waste, drugs or excess nutrients is mediated by the Pgp, ATP binding cassette, BCRP and MRPs. Vitamin and nutrients are taken up via solute carriers and receptor mediated endocytosis pathways. An energy dependent mechanism regulates nutrient brain uptake transport. Endothelial cells of the BBB have a high density of mitochondria. Loss of BBB function affects gapping of tight junctions, cell surface transporters all of which are linked to mitochondrial dysfunction. (B) Key nutrient transporters at the choroid villus. ATP binding cassette, adenosine triphosphate binding cassette; BBB, blood-brain barrier; BCRP, breast cancer resistance protein; BCSFB, blood cerebrospinal fluid barrier; CSF, cerebrospinal fluid; FOLR1, Folate receptor 1; GLUTs, glucose transporters; MCT, monocarboxylate transporters; MFSD2A, major facilitator superfamily domain-containing protein 2a; MRPs, multidrug resistance proteins; Pgp, P-glycoprotein; PLTP, phospholipid transfer protein; RBC, Red blood cell; SLC19A1: Solute Carrier Family 19 Member 1; SMVT, sodium dependent multivitamin transporter; SVCT, sodium dependent vitamin C transporter

cells of the choroid plexus. These mitochondria-abundant epithelia have a Golgi apparatus, smooth endoplasmic reticulum, and lysosome-like vesicles to synthesize and aid in sustaining CSF and also facilitate CNS nutrition, including known transporters for vitamin C, B vitamins (folate, pantothenic acid, biotin) and vitamin E (PLTP)<sup>49</sup> (Figure 2B).

### 2.1.6 | Pericytes

Pericytes play an important role in the development of cerebral microcirculation and maintaining BBB integrity. Within the brain, pericytes actively relax or contract to change cerebral blood flow in response to localized changes in neuronal activity.<sup>50</sup>

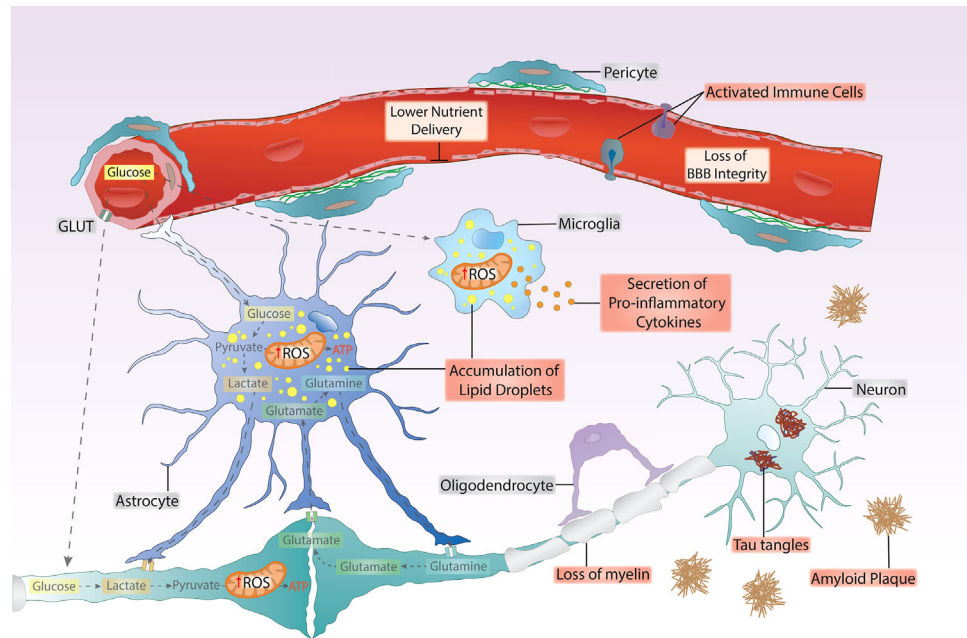
## 2.2 | Cerebral bioenergetics supply and dysfunction in AD

A myriad of cerebral bioenergetics failures in AD have been described that occur with changes in the immune system, protein and lipid homeostatic systems and intersect with brain nutrient delivery (Figures 1B and 3). These observations have led to the generation of hypotheses that impairment in the supply and utilization of energy sources to the brain can be a cause of synaptic dysfunction, neurodegeneration, and cognitive decline in AD, rather than just being a consequence of AD neuropathology and cell death characterized by the formation of extracellular amyloid-beta plaques and intracellular, insoluble tau tangles. In support of this rationale, amyloid plaques first appear in brain regions that feature high levels of aerobic glycolysis in patients with AD,<sup>51</sup> which suggests that brain regions that are most dependent on astro-

cyte assistance for meeting their bioenergetic needs are those that are most likely to acquire plaques. Moreover, mitochondrial bioenergetic stress associates with measures of chronic inflammation and oxidative stress.<sup>52</sup>

### 2.2.1 | Dysregulated glucose metabolism

Imaging biomarkers of brain glucose uptake, oxygen utilization, and blood flow in cognitively normal adults from 20 to 82 years revealed that aging associates with lower brain glucose uptake that exceeds the decrease in oxygen use, resulting in declining brain glycolysis.<sup>53</sup> In patients with mild cognitive impairment, lower brain glucose uptake using <sup>18</sup>F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) scans predicts progression to AD dementia<sup>54</sup>. Consistent with lower brain glucose uptake and neurovascular coupling, microvascular glucose transporters GLUT1 were shown to be decreased by nearly 50% in the cerebral endothelium of patients with AD dementia.<sup>55</sup> GLUT3 concentrations are also decreased in AD compared with age-matched controls.<sup>56,57</sup> Preclinical evidence suggests that changes in brain glycolysis is associated with defects in mitochondrial oxidative phosphorylation, reflecting an energy crisis.<sup>58</sup> The need for more energy substrates drives greater mobilization of fatty acids from neuronal membranes, increasing susceptibility to oxidative damage. For example, the metabolism of arachidonic acid (AA) leads to an increase in neuroinflammatory responses from astrocytes and microglia and oxidative stress byproducts.<sup>59,60</sup> Prostaglandins, leukotrienes, and pro-resolvins derived from liberated PUFAs appear to promote a state of unresolved chronic inflammation in AD that can ultimately lead to neuronal loss.<sup>61,62</sup>



**FIGURE 3** Cell-specific brain changes in Alzheimer's disease, showing interactions of brain nutrient uptake and utilization with blood-brain barrier (BBB) function. Bioenergetic failure and loss of BBB function is associated with chronic inflammation and oxidative stress (ROS) in several brain cell types, associating with an increase in lipid droplets in glial cells, loss of myelin, and the appearance of classic AD pathology markers of amyloid plaques and neurofibrillary tangles. Bioenergetic stress is reflected initially by an increase in glycolytic flux and dysfunctional mitochondrial oxidative phosphorylation.

### 2.2.2 | Impaired mitochondrial FAO

There is good evidence of impaired FAO in AD. Disturbance in respiration-associated components are observed in AD. These include: pyruvate dehydrogenase complex, which catalyzes the entry of carbons derived from glucose into the citrate cycle; the  $\alpha$ -ketoglutarate dehydrogenase complex comprises a key catalytic step in the citrate cycle and is an enzyme of glutamate metabolism; and cytochrome oxidase or complex IV, the component of the electron transport chain which uses molecular oxygen as one of its substrates.<sup>63,64</sup> When glucose supply is reduced to the brain during metabolic challenges, FAO in mitochondria provides ketone bodies that can be a supplemental energy source for brain bioenergetics.<sup>65</sup> Compared to neurons and microglia, astrocytes preferentially express carnitine palmitoyltransferase-1 (CPT-1), which combines L-carnitine with long chain fatty acid (LCFA) to generate acylcarnitines that then enter mitochondria for FAO.<sup>20</sup> As such, carnitine/acylcarnitines metabolism may play an important role in brain bioenergetic failure states where FAO is detrimental for normal neuronal function. Medium chain acylcarnitines (MCA) are key substrates for FAO.<sup>66</sup> MCA can be converted to ketone bodies in the periphery and transported to the brain to support bioenergetics.<sup>67</sup> The contributions of MCA and LCA to FAO in AD warrant further investigation, as reports have shown that MCA levels are decreased<sup>68-70</sup> or elevated<sup>71,72</sup> in plasma and cerebrospinal fluid (CSF) of AD patients. Given that LCFA is enriched in polyunsaturated fatty acids that have numerous double bonds, they are susceptible to lipid peroxidation, thereby contributing to ROS genera-

tion. On the other hand, medium chain fatty acids (MCFA) likely contain fewer double-bonds, and this may contribute to lower levels of ROS generation.

### 2.2.3 | Oxidative damage

There is evidence of oxidative damage to proteins and lipids in AD,<sup>71</sup> and we anticipate effects from  $\omega$ -oxidation will be manifest in AD.  $\Omega$ -oxidation of lipids resulting in short- and medium-chain dicarboxylic acid (DCA) production is normally a minor pathway for normal fatty acid metabolism<sup>72</sup>; it is considered a rescue pathway that compensates for defects in FAO, and urinary excretion of DCAs increase in persons who have defects in fatty acid metabolism.<sup>73</sup> In addition, increased  $\omega$ -oxidation may provide succinyl-CoA for the Krebs cycle and gluconeogenesis.<sup>73,74</sup>  $\Omega$ -oxidation is also upregulated with increased cytochrome P450 enzyme activity.<sup>75</sup> C4-DCA modifies (succinylates) several mitochondrial proteins,<sup>76</sup> while other DCAs such as azelaic acid (C9-DCA) may have anti-inflammatory, antioxidative, and bactericidal activity.<sup>77</sup> Thus, changes in DCA levels can directly dysregulate energy pathways and influence AD-related mechanisms.

### 2.2.4 | Cell-specific bioenergetic failure in AD

All brain cell types all show evidence of inflammation, oxidative and bioenergetic stress contributing to neuronal energy failure (Figure 3).

Oligodendrocyte dysfunction and white matter loss are often among the earliest brain changes in AD,<sup>78–82</sup> suggesting that the supply of energy substrates from oligodendrocytes to the axons such as lactate will be diminished, resulting in aggravation of the neuronal dysfunction. A $\beta$  accumulation and tau hyperphosphorylation may lead to further disruption of myelin integrity and oligodendrocyte maturation and metabolism through oxidative stress, neuroinflammation, and/or excitotoxicity.<sup>80,83–87</sup> Like oligodendrocytes, astrocytic morphology and functions are abnormal in AD, resulting in deleterious effects that include reduced carbon delivery to neurons for oxidative phosphorylation, and dysregulated linkages between neuronal energy demand and regional blood supply.<sup>88</sup> Similarly, microglial metabolism shifts from oxidative phosphorylation to aerobic glycolysis as observed upon acute exposure to stressors such as fatty acids or A $\beta$ .<sup>89,90</sup> This metabolic shift to aerobic glycolysis in microglia can be a driver of AD pathology, as the increased production of lactate in microglia results in epigenetic modifications that activate glycolytic genes in a positive impact loop in the 5XFAD mouse model.<sup>91</sup> Endothelial cells and pericytes regulate the energy sensing pathways in response to changes in nutrient availability, allowing them to move between quiescent and proliferative states.<sup>92,93</sup> Dysfunctional FAO in pericytes can cause them to undergo apoptosis and detach from the endothelial cell, contributing to capillary pruning.<sup>93</sup> Pericyte loss plays an important role in neurovascular dysfunction. It leads to brain vascular damage by a reduction in brain microcirculation causing diminished brain capillary perfusion, cerebral blood flow, and cerebral blood flow responses to brain activation, which ultimately mediates chronic perfusion stress and hypoxia.<sup>94</sup> Taken together, these data suggest that changes to cellular bioenergetics are key factors that influence the onset AD pathophysiology. However, many questions remain about the causal role of individual cell type bioenergetics and AD, and future studies should aim to define these metabolic changes more clearly over the entire AD time course.

### 2.2.5 | Blood-brain barrier dysfunction, nutrient transport, and maintenance in the CNS

BBB breakdown as assessed with dynamic contrast enhanced MRI or through lumbar puncture derived CSF albumin index is associated with aging,<sup>95,96</sup> neuroinflammation,<sup>97</sup> AD,<sup>98</sup> and accelerated cognitive decline.<sup>97,98</sup> Compromise of BBB integrity is associated with brain accumulation of toxic molecules involved in neuronal degenerative changes.<sup>99</sup> Several types of neurotoxic blood-derived molecules that can enter brain after BBB breakdown leading to synaptic and neuronal dysfunction.<sup>100</sup> These include iron species derived from hemoglobin; fibrinogen that activates microglia promoting neuroinflammatory response, and also causing retraction of neurites and white matter injury to oligodendrocytes and pericytes; thrombin that is directly neurotoxic and reviewed in more detail by Sweeney et al.<sup>100</sup> A pro-inflammatory response may also cause BBB disruption via upregulating various factors, and this can cause leukocytes to enter perivascular spaces and may further cause an inflammatory cascade.

Dysregulation in BBB function occurs with known risk factors for AD such as aging,<sup>95</sup> APOE genotype,<sup>101</sup> and conditions such as metabolic syndrome.<sup>102</sup>

The functional changes at the BBB and BCSFB can alter brain perfusion and delivery of glucose, oxygen, and other nutrients to the brain from the blood, which may have implications for nutritional interventions across disease stages and age strata, even in the absence of whole-body tissue deficiencies. This may occur through elevated rates of catabolism due to accumulating neurovascular pathology (i.e., cerebral amyloid angiopathy and arteriosclerosis) or inflammation or a combination of both. Aging and conditions leading to BBB breakdown may disturb the brain's capacity to meet its nutritional requirements through several mechanisms, including gapping of tight junctions of BBB (endothelia) or BCSFB (cuboidal epithelia), cell surface transporter dysfunction (i.e., solute carriers and receptor mediated transcytosis damage), and mitochondrial dysfunction leading to loss of energy potentials.<sup>103</sup> BBB breakdown may cripple the brain's capacity to maintain nutrient concentrations to battle reactive oxygen species (i.e., leaking of vitamin C from the CNS into periphery or damage to SVCT at the choroid plexus)<sup>104</sup> and support DNA methylation reactions (one carbon metabolism).<sup>105,106</sup> Defects in BBB function affect not only brain glucose metabolism<sup>107</sup> and some micronutrients but also important fatty acids such as the transport of DHA to the brain<sup>108</sup> via MFSD2A.<sup>109</sup>

### 2.3 | APOE4 and cerebral bioenergetics

Apolipoprotein E  $\epsilon$ 4 polymorphism (APOE4) is by far the strongest genetic risk factor for late-onset AD.<sup>110</sup> As its name suggests, apolipoprotein E (ApoE) is a surface protein component of lipoprotein particles, and thus it is perhaps unsurprising that it affects several metabolic functions. This encompasses ApoE isoform-specific alterations ranging from cholesterol trafficking and efflux, intracellular lipid storage, glucose uptake and utilization patterns, brain insulin signaling, and mitochondrial function.<sup>110</sup> These various APOE-associated changes in cerebral (and peripheral) metabolism have been extensively reviewed.<sup>111–115</sup> APOE4 may affect BBB integrity before the onset of cognitive decline through chronic unresolved inflammation,<sup>101</sup> is associated with presymptomatic brain glucose hypometabolism,<sup>116</sup> and may lower delivery of n-3 PUFAs to the brain prior to the onset of dementia.<sup>108</sup> Whether APOE4 affects the transport of ketones into the brain is still not clear.

More recent studies have highlighted emerging areas of interest regarding the effects of APOE4 on cerebral metabolism, particularly in glial cells. Glial carbohydrate metabolism was shown to be a primary pathway associated with cognitive impairment and AD pathology by a comprehensive proteomics analysis.<sup>117</sup> Although the effect of APOE was muted in the study, several other publications highlight important roles for APOE in modulating glucose metabolism. For example, APOE4-expressing astrocytes increase glycolytic flux relative to APOE3 and APOE2 astrocytes.<sup>118</sup> A follow-up translational study suggests that this APOE4-associated increase in glycolysis in astrocytes



appears to be mirrored in whole-body metabolic measures of *APOE4* mice as well as in the plasma metabolome and breath-based calorimetry of young women carrying *APOE4*.<sup>119</sup> Effects of *APOE* isoforms on glial metabolism appear to also include microglia, as a recent study showed that *APOE4*-expressing human iPSC-derived microglia have lower rates of both oxygen consumption and glycolysis.<sup>120</sup> Younger *APOE4* carriers have higher brain uptake of DHA,<sup>121</sup> suggesting preference for PUFAs, possibly due to increased DHA consumption.

Multiple studies also highlight a role for *APOE* in modulating the accumulation and storage of intracellular lipids in astrocytes. For example, the expression of *APOE4* by astrocytes led to an increased accumulation of lipid droplets in multiple model systems.<sup>122–124</sup> Qi et al. recently expanded upon these findings by similarly showing that *APOE4* leads to lipid accumulation in astrocytes and further suggested that a decreased capacity of these astrocytes to buffer neuronal lipids and degrade fatty acids via oxidation or other mechanisms may compromise metabolic support to neurons.<sup>125</sup> Similarly, a recent study by Rawat et al. highlighted the susceptibility of apoE4 protein aggregates to decrease recycling and lipidating functions of ATP binding cassette A1 (ABCA1).<sup>126</sup> While there is strong evidence that FAO is impaired in AD, particularly among *APOE4* carriers, the mechanism by which *APOE* genotype contributes to bioenergetic deficits in AD remains to be fully investigated. Studies show that *APOE4* carriers affect the metabolism of PUFAs,<sup>121,127</sup> which could be due to their increased breakdown or reduced transport into the brain.<sup>128</sup> Deficits in maintaining adequate brain bioenergetics in *APOE4* carriers can also be attributed to FAO of intracellular lipid pools.<sup>122</sup> *APOE4* carriers with dementia are unable to adequately compensate energy generation through FAO.<sup>129</sup> Mouse models of human *APOE* show that acylcarnitine levels decline with age in *APOE4* mice, whereas *APOE3* mice maintain adequate supplies and *APOE2* mice have elevated acylcarnitine levels in blood with age.<sup>130</sup> In sum, these studies highlight *APOE4*-associated increases in intracellular lipid accumulation, decreased cholesterol efflux, and incomplete FAO, with some of these changes appearing early in life and impacting brain energy metabolism.

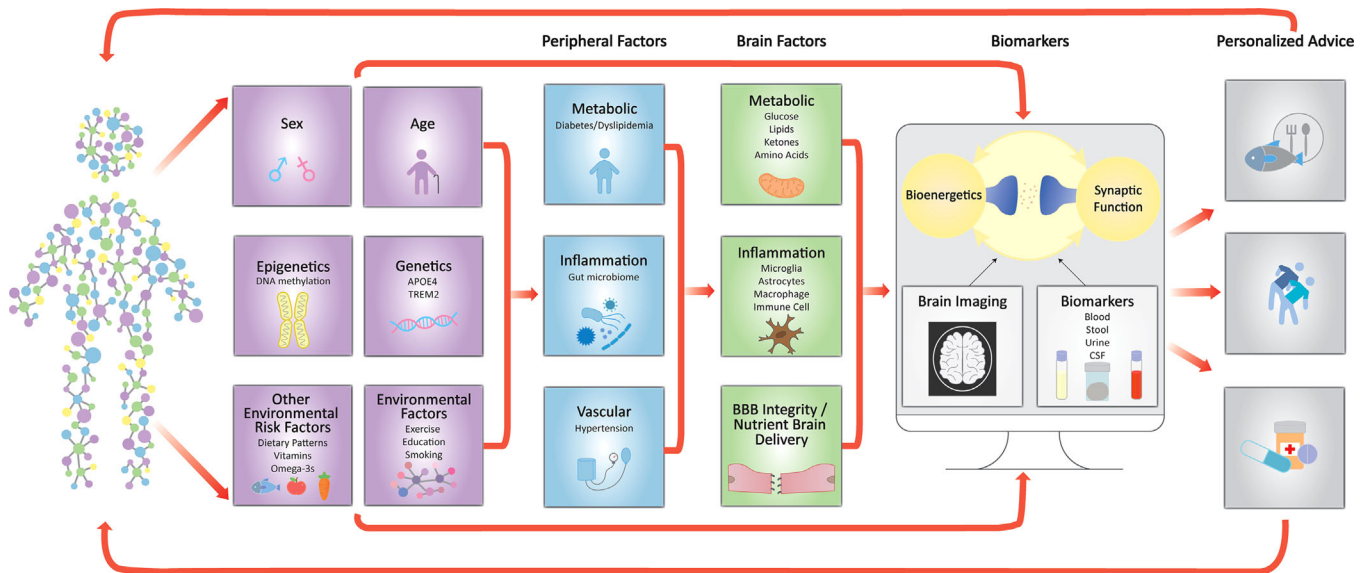
## 2.4 | Gut microbiome dysbiosis and cerebral bioenergetics

A key factor that determines nutrient absorption and metabolism from dietary components are the trillions of microorganisms that reside in the gut and the vast array of enzymes encoded in their metagenomes, colloquially known as the gut microbiome. Diet and nutritional status play a major role in the symbiotic relationship between the gut microbial diversity and host metabolism. Nutritional imbalance impacts both microbial communities in the gut and host physiological functions including brain homeostasis that is heavily dependent on gut-derived secondary metabolites, which include neurotransmitters.<sup>131</sup> The gut microbiota-derived secondary metabolites exert their effects either locally or via systemic circulation as stored energy reserves in external organs.<sup>132</sup> Gut-brain signaling has

been widely studied, and one of the areas of interest linking the digestive system with the brain is satiety and appetite regulation. However, in the last decade, the focus has dramatically shifted towards a better understanding of the microbiota-gut-brain relationship, which is frequently referred to as the MGB axis.<sup>133</sup> MGB represents a bidirectional communication pathway mediated by microbiota and their secondary derivatives. Gut microbes release a range of neuromodulatory metabolites, including  $\gamma$ -aminobutyric acid (GABA), dopamine, serotonin, acetylcholine, trimethylamine oxide (TMAO) and short chain fatty acids (SCFAs).<sup>134–136</sup> Bacteria-derived neuromodulators enter the brain either via afferent vagal nerve fibers that directly connect the enteric nervous system (ENS) and central nervous system (CNS) or cross the BBB from portal circulation.<sup>137,138</sup>

Age is a key factor that influences gut microbiome composition and function. While normal health in adulthood is characterized by a stable microbiome,<sup>139</sup> late life changes in gut microbiome composition shifts toward less stable states. A persistent imbalance of gut microbial communities, termed dysbiosis, has been reported in a variety of neuropsychiatric and neurodegenerative disorders, including AD, prompting the question of whether age-related microbiome changes combined with differential gut metabolites could contribute to mitochondrial dysfunction linked to neuropsychiatric disorders.<sup>140–146</sup> Mounting evidence also links an abnormal increase in specific enteric microbes to a range of chronic late life inflammatory diseases with primary pathologies outside the GI, including CNS disorders.<sup>132,137</sup> Many neurological disorders are shown to be associated with microbiota-associated GI symptoms and possibly stemming from altered gut microbial diversity.

Microbiome-derived secondary metabolites may contribute to brain bioenergetic dysfunction during aging. Microbiota-derived SCFAs including butyrate, acetate and propionate, are essential for normal brain health.<sup>147</sup> Several studies have highlighted the importance of SCFAs in understanding pathogenesis associated with multiple neurodegenerative disorders, including AD.<sup>142,143</sup> Although the precise mechanism of action of SCFAs on brain is still being explored, mounting data suggest SCFAs are essential factors for the effective functioning of mitochondria. SCFAs are associated with the mitochondrial function specifically with the ETC involved in ATP production, oxygen consumption and membrane potential in the brain. A recent study in germ-free mice demonstrated that gut microbiota and the acetate they produce are important contributors to brain mitochondrial bioenergetics, particularly microglia function via regulation of mitochondrial oxidative phosphorylation.<sup>148</sup> SCFA concentrations are lower in CSF of AD participants, providing further support that changes in microbiota metabolism may contribute to brain energetic failure in AD.<sup>149</sup> Conversely, TMAO, a gut metabolite derived from microbial metabolism of dietary carnitine and choline, has been shown to influence brain function. A combination of gut dysbiosis and increased levels of TMAO is observed in anxiety and cognitive deficits,<sup>150</sup> and TMAO is reported to be elevated in the CSF of dementia patients.<sup>151</sup> TMAO also promotes vascular aging as well as impairment of mitochondrial function and increased oxidative stress.<sup>150</sup> This evidence strongly suggests that gut microbiota and their



**FIGURE 4** An illustration of how capturing information on environmental, genetic, systemic and brain risk factors that affect neuronal survival and synaptic function can lead to personalized dietary and lifestyle recommendations. BBB, blood-brain barrier; CSF, cerebrospinal fluid

metabolites may play a role in aging and mitochondrial dysfunction observed in AD.

### 3 | EVIDENCE FOR TARGETING CEREBRAL BIOENERGETICS DEFICITS IN AD WITH NUTRITION

The effect of diet on the brain is complex, modulated by several factors that may affect the transport and metabolism of nutrients making them readily available to the brain. Novel modeling approaches such as network analysis is needed in a much more diverse sample.<sup>152</sup> This network may vary by region, social, and cultural practices and includes genetics (e.g., APOE4), vascular risk factors (hypertension, exposure to air pollution), nutritional intake, diet patterns, or other lifestyle factors such as social, cognitive, and physical activities. The complex interaction of these factors on brain energy homeostasis and neuronal survival has implications toward personalized recommendations, and is illustrated in Figure 4. Given this complexity, it is not surprising that most dietary supplement interventions using a single or a few nutrients in a single “average population” have been disappointing in their ability to slow cognitive decline or AD progression<sup>152</sup> compared to the effect of the major diet patterns on dementia risk seen in observational cohorts (Table 2). These issues notwithstanding, there remain open questions of whether certain targeted nutrient interventions can restore cerebral bioenergetics in populations selected with signs of disturbed nutritional and cerebral bioenergetic dysfunction when guided by selected biomarkers. Efforts to advance our understanding of the role of cerebral bioenergetics in AD etiology will need to account for the appearance and characteristic biology of its classic histopathology including beta amyloid or tau perturbations the field associates with AD.

#### 3.1 | Single or few nutrient trials

Some dietary supplements, B vitamins, n-3 PUFAs, and ketones have shown preliminary promising effects on brain bioenergetics in the aging brain. Closer examination of these nutrient trials identifies the need for more targeted or personalized approaches and to define neuroprotective ranges of nutrients to enroll individuals outside this beneficial range for intervention.<sup>153</sup> We discuss here some encouraging single or few nutrient interventions:

##### 3.1.1 | B1 vitamins

There is evidence linking abnormalities in thiamine (vitamin B1) availability and metabolism to the pathophysiology of AD through brain bioenergetics. Thiamine-deficient humans with Wernicke Korsakoff syndrome have significant neurofibrillary tangles.<sup>154,155</sup> In mice, thiamine deficiency increases the phosphorylation of tau,<sup>156</sup> and treatment with benfotiamine diminishes phosphorylation of tau in at least three different animal models of AD.<sup>157,158</sup> These results stimulated a single site blinded Phase 2a randomized placebo-controlled pilot trial of benfotiamine to provide preliminary evidence of feasibility, safety, and efficacy. The trial tested whether a 12-month treatment with benfotiamine would delay clinical decline in amyloid positive patients (ascertained with amyloid PET) with amnesic mild cognitive impairment (MCI) (MMSE  $\geq$  26) or mild AD (26 > MMSE > 21) compared to placebo.<sup>159</sup> The primary clinical outcome was AD Assessment Scale-Cognitive Subscale (ADAS-Cog), and secondary outcomes were the clinical dementia rating (CDR) score and brain glucose uptake measured by FDG-PET. The trial showed that benfotiamine at a dose of 600 mg per day is safe in patients with early AD. The treatment

**TABLE 2** Dietary and nutrient biomarker patterns associated with cognitive function and dementia risk

Diet or biomarker pattern	Micro/macronutrient emphasis	Dementia risk, cognitive outcomes and biomarkers
MIND diet <sup>173,253</sup>	Higher intake of vitamin E, folate, flavonoids, carotenoids, dietary fiber, monounsaturated fats, and lower intake of saturated and trans fatty acids	Lower incident AD and cognitive decline
DASH diet <sup>254</sup>	Higher intake in potassium, magnesium, fiber, calcium, monounsaturated fats, and protein; low in saturated fats, cholesterol, and sodium	Less cognitive decline and lower incident AD <sup>255</sup>
MeDi <sup>256</sup>	High intake of folate, vitamin E, carotenoids, flavonoids, and other antioxidants, dietary fiber, omega-3 fatty acids; lower intake of saturated fatty acids	Lower incident AD <sup>257</sup>
MMKD <sup>174</sup>	Low carbohydrate (5%–10%), high fat (60%–65%) and 30% protein. Like MeDi guidelines that emphasizes protein sources low in saturated fat (fish, lean meats), healthy fats, fruits and vegetables, whole grains, and 1 glass of wine per day	Lower indication of AD pathology (higher CSF abet42 and lower CSF tau); Increased cerebral perfusion and increased cerebral ketone body uptake ( <sup>11</sup> C-acetoacetate PET) following MMKD
Nutrient biomarker pattern Oregon Brain Aging Study <sup>258</sup>	Higher blood levels of B1, B2, B6, folate, B12, C, D, E, omega-3 fatty acids, carotenoids (lutein and zeaxanthin) and lower levels of trans fatty acids	Superior cognitive function, less white matter lesions and higher total brain volume
Nutrient biomarker pattern Three-City study <sup>259</sup>	Higher blood levels of vitamin D, carotenoids, and polyunsaturated fatty acids and lower levels of saturated fats associated with less risk of dementia	Lower incident dementia
Nutritional Risk Index Multi-domain Alzheimer prevention trial <sup>260</sup>	Higher blood levels of vitamin D and omega-3 fatty acids and lower levels of homocysteine	Participants with optimum nutritional status had superior cognitive performance

Abbreviations: DASH, dietary approaches to stop hypertension; MeDi, mediterranean style diet; MIND, mediterranean-DASH diet intervention for neurodegenerative delay; MMKD, modified mediterranean ketogenic diet.

delivery was efficacious as shown by a 161-fold mean increase in blood thiamine. The change in the primary outcome did not reach statistical significance, and there were signals that secondary outcomes were improving. These encouraging preliminary findings support validation in targeted/personalized interventions with responsive clinical outcomes.

### 3.1.2 | Vitamin B12, vitamin B6, and folate

A systematic review of 21 trials explored the preventive efficacy of vitamin B12, vitamin B6, or folic acid alone or in combination in any form on cognitive decline of patients with mild cognitive impairment or elderly adults without cognitive impairment.<sup>160</sup> This analysis demonstrated that vitamin B supplements significantly lowered the levels of serum homocysteine levels and prevented the decline of global cognitive function, but did not affect other cognitive domains. Nevertheless, the effect sizes for those treated with vitamin B supplements compared to placebo were modest. Like B1, targeted and well-designed randomized controlled trial (RCT) in participants with high baseline homocysteine levels and responsive cognitive outcomes can clarify whether they have preventive efficacy.

### 3.1.3 | PUFAs

Brain PUFAs have important roles in brain bioenergetics and synaptic functions, but PUFA supplementation clinical trials have not succeeded in showing benefit on cognition, despite several observational cohorts linking higher n-3 PUFA intake or blood levels with better cognition or lower AD incidence.<sup>153,161</sup> Brain autopsy studies in APOE4 carriers with dementia demonstrate the activation of pathways that increase the breakdown of brain PUFAs (e.g., via calcium-dependent phospholipase A2 [cPLA2] activation<sup>162</sup>) and PUFAs with numerous double-bonds are more susceptible to lipid peroxidation, thereby contributing to ROS generation. However, there might be a role for PUFA supplementation in AD prevention for vulnerable populations. Using 11-C DHA PET imaging, the APOE4 brain appears to extract more DHA from blood than the non-APOE4 brain several decades before any evidence of cognitive decline.<sup>121</sup> This greater dependence on systemic DHA as a brain substrate in APOE4 poses vulnerability to lower DHA intake, since blood DHA levels are largely determined by dietary consumption. As the APOE4 brain ages with a lower BBB function and the accompanied lower ability to extract DHA from the circulation,<sup>108</sup> the ability of dietary DHA intake to reverse AD pathology appears to wane. The field awaits more personalized interventions (e.g., younger APOE4

carriers without high n-3 PUFA intake and prior to the onset of clinical disease) with high dose and long term PUFA supplementation to address this question.<sup>163</sup>

### 3.1.4 | Ketones

Given the difficulty in restoring disrupted brain glucose metabolism, another therapeutic strategy involves improving brain energy metabolism with ketones in MCI or AD. This question was addressed with a ketogenic medium chain triglyceride (kMCT) supplement. The largest investigation to date included 152 older participants with mild to moderate AD, followed-up over 90 days with 20 g/day of kMCT (tricaprylin) supplementation. A significant improvement in the ADAS-Cog score was observed only in *APOE4* non-carriers.<sup>164</sup> A higher dose of kMCT (42 g/day of tricaprylin) improved cognitive stability in mild-moderate AD in 20 participants who underwent a 6-month double-blinded, randomized, placebo-controlled cross-over study with a 6-month open label phase.<sup>165</sup> In older adults with MCI, Fortier et al. showed that 30 g of kMCT supplementation per day over a 6-month period significantly improved cognitive function.<sup>166</sup> At baseline, the brain glucose deficit was about 10%, which was reduced to about 7% by ketones from the kMCT.<sup>166</sup> Post-intervention, scores for episodic memory, executive function, and language were all significantly improved in the kMCT group only.<sup>167</sup> These cognitive improvements were directly associated with increased brain ketone uptake and/or increased plasma ketones in the kMCT group. However, there were no changes in brain FDG uptake, cortical thickness, volume of brain regions, or brain blood flow. Analysis of diffusion and PET imaging before and at the end of the intervention period showed that ketones were actively utilized by multiple white matter tracts in the kMCT group and that the uptake of ketones in these tracts was directly related to improvement in processing speed<sup>168</sup> and attention.<sup>169</sup> A double-blind, randomized, placebo-controlled crossover study of kMCT was undertaken in 53 mild to moderate AD patients and showed cognitive improvements in the ADAS-Cog-C among *APOE4* non-carriers.<sup>170</sup> In a recent systematic review of RCTs with ketogenic therapy in AD, an *APOE4* genotype treatment effect was noted with *APOE4* negative participants having a better treatment response than those who were *APOE4* positive.<sup>171</sup> In addition to AD, impaired brain glucose metabolism is a feature of other neurodegenerative disorders including frontotemporal dementia.<sup>172</sup> Large randomized controlled trials with long-term follow-up and appropriate clinical and biological outcomes (including plasma, CSF, or brain metabolism biomarkers) are needed to validate the outcomes and long-term acceptability of ketone interventions in MCI or AD. The effect of *APOE4* on ketone brain uptake requires further studies.

## 3.2 | Diet patterns and whole diet interventions

While specific nutrients uniquely impact bioenergetics pathways potentially leading to AD, these nutrients are contained in foods and

consumed together within a diet. Moreover, they may have synergistic (or at least additive) effects on metabolic pathways, so that their co-consumption within a diet may potentiate benefits (or harms) in relation to brain health. Thus, dietary patterns are tremendously important to consider when studying nutrition and the brain. There is emerging evidence from human neuroimaging studies that diet patterns overall may influence cerebral bioenergetics, possibly as early as middle adulthood, prior to any effect on other AD biomarkers and brain structural changes.

The Mediterranean diet (MeDi), DASH (Dietary Approaches to Stop Hypertension), and the MIND (Mind-DASH Intervention for Neurodegenerative Delay) are each associated with less cognitive decline and dementia incidence (Table 2). These diets are characterized by high intake of vegetables, fruits, fish, legumes, and less processed foods, red meat, and confectionary foods. Although there are similarities among these dietary patterns (fish and vegetable intake), there are also differences such as berries and emphasis of dark leafy greens in the MIND and olive oil (monounsaturated fatty acids) as the main source of fat in both the MeDi and MIND.<sup>173</sup> A modified Mediterranean Ketogenic Diet that requires low carbohydrate and high mono and polyunsaturated fat intake and lower saturated fat intake has been associated with lower signs of AD pathology and increases in cerebral blood flow in early interventions.<sup>174</sup>

Other studies have identified dietary patterns or nutrient biomarker patterns associated with less brain atrophy and white matter lesions,<sup>175</sup> but the estimated effects on outcomes related to cerebral bioenergetics such as arterial spin labeling derived cerebral blood flow, FDG PET and BOLD imaging have been limited. Measuring brain glucose metabolism with FDG PET as a proxy of neuronal activity, a few longitudinal neuroimaging studies of cognitively intact adults (aged 30–60 years) with other risk factors for AD suggested that healthy diets, such as the Mediterranean diet, or healthy nutrient patterns, influence brain glucose metabolism in mid-to-late adulthood. For example, an analysis of 70 participants from the cohort found that lower adherence to a Mediterranean diet was associated with reduced FDG-PET and a faster rate of FDG decline over 3 years in AD-affected regions (3.3% per year decline in those with lower adherence to a Mediterranean diet [i.e., scored 0–4 over a total of 9 possible points], versus 0.3% per year in those with higher adherence [score 5–9]).<sup>176</sup> This reported decrease in glucose metabolism in persons with lower adherence to Mediterranean diet paralleled significant 11C-Pittsburgh compound B (PIB) increases, while volumetric MRI results were unaffected by treatment. In 52 participants from the same cohort study, a healthy nutrient pattern combining unsaturated fats; vitamins A, B12, C, D, and E; zinc; carotenoids; and fiber, was associated with increased FDG-PET glucose metabolism<sup>177</sup> providing some evidence of potential key nutrients influencing brain glucose metabolism. In fact, there are emerging studies of the impact of antioxidant-rich fruits and vegetables, n-3 PUFA and low-glycemic index carbohydrates,<sup>178</sup> zinc,<sup>179</sup> fish oil supplementation rich in n-3 PUFA,<sup>180</sup> vitamins B12, E, D, PUFA, antioxidants and fibers,<sup>177</sup> and multi-nutrient supplements<sup>181,182</sup> on FDG PET derived cerebral glucose metabolism. There are also diet patterns such as a Mediterranean-type diet that have been associated

with beneficial cerebral metabolism profiles in both cross-sectional<sup>183</sup> and longitudinal<sup>176</sup> studies.

### 3.3 | Emerging targets for cerebral bioenergetic restoration

There are emerging bioenergetic targets that have yet to be fully explored in human trials, but preliminary evidence is promising. These mechanisms include targeting FAO, the gut microbiome, and epigenetic modifications to restore cerebral bioenergetics in AD.

#### 3.3.1 | Acetyl-L-carnitine

Acetyl-L-carnitine is a mitochondrial bioenergetic substrate that may improve brain functions through FAO, but clinical trial findings are inconsistent. A small-scale study placebo-controlled randomized trial (RCT) of acetyl-L-carnitine in 36 AD participants showed some trends in improvement in short-term memory.<sup>184</sup> Another RCT of acetyl-L-carnitine in 130 clinically diagnosed AD patients showed that participants treated with acetyl-L-carnitine had significantly better scores on tests that assessed verbal abilities and verbal memory as well as attention.<sup>185</sup> However, another RCT of acetyl-L-carnitine among early onset AD cases<sup>45–60,62–66</sup> did not achieve its primary outcome of cognitive decline.<sup>186</sup> Others have explored acetyl-L-carnitine as part of nutritional cocktail showing some efficacy on cognitive outcomes,<sup>187</sup> but these studies lack efficacy biomarkers other than supporting overall bioenergetic processes in the brain. Given the uncertainty with acetyl-L-carnitine doses, brain delivery and with the short duration of these preliminary trials, the potential therapeutic effects of targeting FAO via L-carnitine remain unknown. Whether acetyl-L-carnitine is serving as a direct supplement for FAO or is being converted into ketone bodies in the periphery and then supplied to the brain also remains unknown.

#### 3.3.2 | Nicotinamide adenine dinucleotide (NAD<sup>+</sup>) precursors

NAD is a coenzyme for multiple metabolic reactions, including glycolysis, the electron transport chain and sirtuin activity.<sup>188</sup> The ratio of reduced (NADH) to oxidized NAD (NAD<sup>+</sup>) increases with aging.<sup>188</sup> It has been postulated that NAD<sup>+</sup> boosters may improve mitochondrial metabolism during aging. Two major NAD<sup>+</sup> precursors are nicotinamide riboside (NR) and nicotinic mononucleotide (NMN) that within cells can be converted to NAD<sup>+</sup> and may raise NAD<sup>+</sup>. Some of the animal studies with NAD<sup>+</sup> supplements have shown promise with aging<sup>188</sup> and reducing microglial inflammation and cellular senescence,<sup>189</sup> although in the largest mouse span extension study, Intervention Testing Program (ITP), NAD<sup>+</sup> precursors did not extend lifespan.<sup>190</sup> The challenge with these supplements is the lack of efficacy biomarkers at the cellular level, their unclear brain delivery, and very

limited data for cognitive outcomes, although several smaller trials are in progress.<sup>191</sup>

#### 3.3.3 | Microbial metabolites and probiotics

Direct supplementation of secondary metabolites or stimulation of their production by providing either a specific medication, appropriate bacterial strains (i.e., probiotics), or microbiota-enhancing diet features (prebiotics), are an emerging opportunity for a wide range of disorders, including AD. Increases in SCFA production can be achieved by direct supplementation, or via high fiber supplementation.<sup>192</sup> In general, in vitro experiments have shown SCFAs inhibits AD-related A $\beta$  aggregation.<sup>143</sup> However, SCFA supplementation in preclinical animal models of neurodegenerative diseases has yielded conflicting results. Butyrate supplementation inhibits neuroinflammation and helps maintain BBB integrity in mice,<sup>193</sup> possibly through improvement of mitochondrial function by reducing oxidative stress and increasing oxidative phosphorylation.<sup>194</sup> However, in a pre-clinical model of Parkinson's disease, microbiomes from PD patients and propionate led to enhanced motor dysfunction.<sup>195</sup> Synbiotics, defined as combinations of probiotics and prebiotics mixed in appropriate proportions have been shown to ameliorate a host of CNS disorder pathologies. *Lactobacillus salivarius*, a probiotic when used in combination with prebiotics has engendered enhanced mitochondrial function in 6-hydroxydopamine (6-OHDA)-induced PD rats.<sup>196</sup> Similarly, *Lactobacillus paracasei*, another probiotic belonging to the same genus and a prebiotic XOS, when used as synbiotics, is shown to attenuate mitochondrial dysfunction and prevent hippocampal oxidative stress and apoptosis.<sup>197</sup> However, *Akkermansia muciniphila* as a standalone probiotic supplement has been shown to produce increased CSF nicotinamide levels in mouse model of amyotrophic lateral sclerosis.<sup>198</sup>

#### 3.3.4 | Mitochondrial complex IV

Complex IV is part of the electron transport chain and this complex becomes negatively affected in AD. Importantly, Complex IV is the site of molecular oxygen consumption. Interestingly, studies with dietary creatine,<sup>199</sup> and also other compounds,<sup>200</sup> have shown promise to reverse Complex IV deficits in transgenic mouse models. These findings become important for therapeutically targeting aging and age-related diseases, such as AD and obesity with potential nutritional interventions that may slow or reverse these processes. In fact, key roles have been found for Complex IV dysfunction during aging that have been linked to age-dependent obesity<sup>201</sup> and associated inflammatory processes. Surprisingly, there are currently no FDA-approved mitochondrial medicines and only one European Medicines Agency approved drug Idebenone (Raxone) is available for treating mitochondrial dysfunction in Leber's hereditary optic neuropathy (LHON). However, so-called *mito cocktails* containing vitamins and minerals, mitochondrial transfusions, and druggable mitochondrial targets are now being aggressively explored.

## 4 | FUTURE DIRECTIONS TO GUIDE NUTRITION INTERVENTIONS TARGETING CEREBRAL BIOENERGETICS

As the aging brain and AD risk factors such as *APOE4* adversely affect the delivery of nutrients to the brain even before the onset of dementia,<sup>108,121</sup> certain nutritional interventions during mid-life may prove more effective if started before the onset of clinical symptoms, while others may work later in the disease process. Ultimately, improved insulin sensitivity seems to have an important role in reducing the risk of AD. A better understanding of brain energy utilization pathways throughout the lifespan and in both healthy aging and disease states can inform personalized nutrition trials aimed at testing the hypothesis that providing adequate energy to the dementia-at-risk brain limits the progression to neurodegenerative diseases such as AD. Here, brain bioenergetics biomarkers can have key roles in guiding the efficiency of supplements and nutrients. We provide here examples of promising molecular pathways, modeling of dietary patterns, imaging and blood biomarkers, and target populations that can guide nutritional interventions. There are major research and funding gaps that exist and therefore the following recommendations are made.

### 4.1 | Preclinical studies of chronic inflammation and cerebral bioenergetics

Given the coupling of disrupted brain energy utilization with chronic inflammation, future studies targeting brain inflammation pathways promise to restore brain energy utilization and limit oxidative damage that leads to synaptic loss and neurodegeneration. For example, repairing the BBB can enhance brain glucose and nutrient uptake, but this remains to be determined. One such target involves cyclophilin A–matrix metalloproteinase 9 (CypA–MMP9) pathway that is activated in *APOE4* carriers and associated with BBB integrity loss and cognitive decline.<sup>101,99</sup> Another example involves the increase activation of cPLA2 that promotes greater breakdown of neuronal fatty acids, leading to neuroinflammation and oxidative stress. Inhibiting cPLA2 activity may limit the oxidation of brain PUFAs, and shift brain energy utilization toward alternative sources of energy production and repair the BBB.<sup>202</sup> Moreover, targeting systemic inflammation in the periphery may hold promise in restoring cerebral bioenergetics in the brain, as a recent study demonstrated that blockade of prostaglandin E2 signaling in peripheral myeloid cells was sufficient to restore cognition in aged mice.<sup>203</sup> Another aspect implicates targeting enzymes or other indirect processes involved in cerebral lipid storage, particularly in glia, to support neuronal energetics. For example, depletion of lipoprotein lipase in microglia increased the accumulation of lipid droplets, decreased cholesterol efflux, decreased PPAR signaling, and increased expression of inflammatory markers suggesting that microglial LPL deficiency could play a role in dysregulated lipid metabolism,<sup>204</sup> and conversely facilitating cholesterol and lipid efflux via ABCA1<sup>126</sup> or ABCA7<sup>222</sup> ameliorates AD pathology and inflammation. Several other pathways involving oxidative stress, inflammatory

signaling, insulin sensitivity, and lipid metabolism influence brain bioenergetics and still need to be explored. It will be crucial to elucidate how these pathways complement nutrition-based interventions in AD.

### 4.2 | Epigenetic and translational network malfunctions

Network malfunctions during AD or cognitive aging such as the destabilization of firing rates, synaptic dysfunction, or learning and memory deficits<sup>205–207</sup> are accompanied by metabolic malfunctions such as decreased oxygen and glucose consumption, dysregulated histone acetylation, as well as altered gene expression profiles.<sup>208–212</sup> Conversely, interventions aimed at restoring glucose metabolism, like lifestyle paradigms to enhance exercise and mental stimulation, not only significantly improve cognitive dysfunctions,<sup>213</sup> but also reinstate chromatin and transcriptional plasticity.<sup>214,215</sup> What is more, several bioactive dietary components are known to influence cognitive performance through the regulation of cellular physiology and function, via the intermediate of different epigenetic states.<sup>216,217</sup> For instance, the reduction in vitamin A observed in AD patients has been linked to aberrant HAT-dependent histone acetylation patterns, subsequent learning and memory deficits, as well as accumulations of A $\beta$  aggregates.<sup>218,219</sup> In addition, many other nutrients such as folate, B, C, D, and E vitamins, methionine, turmeric, catechins, and betaine range among potent dietary epigenetic mediators affecting DNA methylation and histone acetylation.<sup>220,221</sup> Another example of how nutrients can affect brain energy utilization through epigenetic modifications is provided with the B1 vitamin thiamin. The complexity of how thiamine maintains brain function has been studied for decades, but new technologies suggest that the field exponentially underestimated its roles. Future research needs to address how thiamine dependent enzymes regulate cell function through hundreds of post-translational modifications under conditions that do not alter ATP. Experiments must address the role of thiamine dependent enzymes in the nucleus and their role in epigenetic modifications.

### 4.3 | Biomarkers

One of the major challenges in nutrition and cognition research is patient heterogeneity that associates with a large variability in the risk of cognitive decline and dementia incidence. Focusing on individuals with dementia risk factors<sup>223</sup> but before the onset of clinical symptoms is of great interest. Cost-effective biomarkers to easily identify dementia risk factors in diverse populations and enrich future studies with these participants are urgently needed. While amyloid and tau-based biomarkers have been useful in identifying evolving AD pathology with increases in amyloid deposition and tau hyperphosphorylation in the brain, to date, there are no validated biomarkers available that can provide information about cerebral bioenergetic changes that precede or follow amyloid and tau changes in the brain. As such, there is a

**TABLE 3** Promising bioenergetic and nutritional biomarkers and their implications for brain functions

Biomarker	Implications for nutritional and metabolic interventions
<b>Fluid biomarkers</b>	
Omega-3 index	Lower blood omega-3 index is associated with increased dementia risk. <sup>161,261,262</sup> Screen vulnerable populations (with low blood omega-3 index) for LC n-3 PUFA supplementation before the onset of AD dementia.
DHA/AA ratio	A lower plasma or CSF DHA/AA ratio in AD and APOE4 <sup>127,263</sup> may reflect activation of lipid catabolism pathways and serve as a biomarker for therapies (such as cPLA2 inhibitors). <sup>162</sup>
Homocysteine	An increase in plasma homocysteine is associated with increased risk of AD. <sup>264–266</sup> Reducing homocysteine using vitamin B complexes may be beneficial to reducing AD risk before the onset of clinical dementia.
25-OH vitamin D	Screen vulnerable populations (with 25-OH-D deficiency [ $<25$ nmol/L]) or insufficiency [25–50 nmol/L]) for vitamin D supplementation. <sup>267,268</sup>
Acylcarnitines	Lower levels ACC found in AD serum, <sup>269</sup> as a biomarker of dysfunctional FAO.
sPDGFR $\beta$	CSF sPDGFR $\beta$ levels is a marker of pericyte function, lower in APOE4 and those with lower cognitive function, independently of CSF amyloid beta 42. <sup>101</sup> Interventions that restore pericyte integrity may improve brain nutrient delivery.
SCFA	SCFA concentrations are lower in CSF of AD participants and are markers of brain energetic failure in AD. <sup>149</sup> SCFA levels can guide screening and validation of multitudes of pre- and probiotic co-culture combinations.
Urinary DCA	Biomarker of unsaturated fatty acids oxidative damage. <sup>270</sup> Urine DCAs can help select individuals with oxidative damage and guide antioxidant therapeutics.
<b>Imaging biomarkers</b>	
DHA PET scans	APOE4 carriers may have a greater vulnerability to omega-3 deficiency before onset of clinical disease. <sup>121</sup> DHA PET scan can help identify vulnerable groups and guide supplementation interventions and selection of cognitive outcomes.
Ketone PET scans	Ketone PET guides the uptake of ketones in brain regions directly related to improvements in cognitive outcomes <sup>166</sup> including processing speed <sup>168</sup> and attention. <sup>169</sup> Ketone PET scans can help identify individuals responsive to a ketogenic intervention and selection of cognitive outcomes.
FDG - H <sub>2</sub> <sup>15</sup> O PET scans	FDG-PET is a presymptomatic marker of brain hypometabolism and AD risk. Dietary behaviors may affect regional cerebral blood flow which may be used as an efficacy endpoint for appropriate initial trial fine tuning. <sup>271</sup>
Infra-red spectroscopy	The effects of different interventions (caffeine, wine and tea polyphenols such as resveratrol or epigallocatechin gallate, creatine, DHA-rich fish oil) in infra-red spectroscopy markers may provide surrogate end points in proof-of-concept nutritional trials. <sup>272–277</sup>
MR proton or phosphorus spectroscopy	The effect of potential interventions with precursors of brain neurotransmitters important for brain metabolism such as choline or citicholine that are derived from diet may be directly measured in the brain using MR spectroscopy approaches. <sup>278,279</sup>
MRI CBV	Cerebral blood volume has been enhanced in concert with improved cognitive performance in the hippocampal dentate gyrus after a flavanol intervention. CBV can be used as preliminary efficacy target. <sup>280</sup>
Structural connectivity MRI DTI	The effect of potential interventions with a variety of nutrients ( $\omega$ 3 and $\omega$ 6, $\omega$ 6, vitamin E, different lipids <sup>236,281</sup> ) and dietary patterns such as the MeDi <sup>282</sup> may be estimated with structural connectivity measures.
Functional connectivity fMRI	The effects of potential interventions <sup>236</sup> including ketones, <sup>169</sup> MUFA, SFA, n-3 and n-6 PUFAs, <sup>283</sup> B vitamins, vitamin E, carotenoid, carotene and lycopene, <sup>283</sup> resveratrol, <sup>284,285</sup> cholesterol related lipids, <sup>286</sup> beetroot juice <sup>287</sup> can be captured with functional connectivity neuroimaging techniques.
MRI DCE	DCE MRI can define BBB integrity and is lower with APOE4 and AD. <sup>95</sup> Interventions that restore BBB integrity may improve brain nutrient uptake and metabolism.

Abbreviations: AA, Arachidonic Acid, ACC, Acylcarnitines; DHA, Docosahexaenoic acid; CBV, cerebral blood volume; CSF, cerebrospinal fluid; cPLA2, Calcium-dependent phospholipase A2; DCA, Dicarboxylic Acid; DCE, Dynamic contrast enhancement; DTI, diffusor tensor imaging; FAO, fatty acid oxidations; FDG, Fluorodeoxyglucose; PDGFR $\beta$ , soluble platelet-derived growth factor receptor  $\beta$ ; SCFA, short chain fatty acids. BBB, blood-brain barrier; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; PUFAs, polyunsaturated fatty acids; MeDi, mediterranean style diet;

need for validated diagnostic and prognostic biomarkers of cerebral bioenergetics failure that predict future cognitive decline in AD and indicate cerebral bioenergetic changes that correspond with disease progression in AD. We summarize promising nutritional and metabolic biomarkers in Table 3. The pathogenesis in AD begins decades before the onset of clinical symptoms and, among  $\epsilon$ 4-carriers, bioenergetic changes can be detected prior to amyloid deposition in the brain. As such, biomarkers that can detect APOE genotype effects on brain

bioenergetics, particularly in conjunction to nutritional status will be extremely valuable.

#### 4.3.1 | Blood, urinary, and CSF based biomarkers

Lipidomics and metabolomics provide an unprecedented opportunity to map the multiple biological system failures occurring in

dementia/AD. However, these methods are limited by intrinsically large heterogeneity (i.e., varying over time, across sex, according to exposures and disease status), which hampers reliability and reproducibility of measurements and replicability of findings. Most studies have used targeted metabolomics leveraging a specific platform, and comparability with findings obtained with a different platform is limited. Moreover, gains in sensitivity and reproducibility through using targeted metabolomic approaches must ignore some parts of the metabolome and, therefore, do not capture the system globally.<sup>224</sup> Once validated, candidates resulting from lipidomic and metabolomic screens can help model brain mitochondrial functions in relation to cognitive decline and neurodegeneration. Careful longitudinal studies with cognitive and imaging outcomes will help validate the information from these biomarkers. They may also assist as surrogate biomarkers of dietary or other interventions aimed at targeting lipid metabolism and bioenergetics in aging and in AD. There are several biomarkers that can provide insight direct or indirect evidence of brain energy metabolism. For example, brain and blood acylcarnitines could help identify the role of FAO deficiencies in AD pathogenesis, particularly among  $\epsilon 4$  carriers before the onset of dementia. Lipidomics and metabolomics have further identified lower Krebs cycle components (succinate and glutamate) and higher levels of oxidized dicarboxylic acids as evidence of abnormal mitochondrial stress in early and established AD.<sup>225</sup> Isoprostanes formed by free-radical-mediated peroxidation of PUFAs in response to inflammation are AD biomarkers,<sup>226</sup> though studies associate them with other dementias.<sup>227</sup> Novel metabolomic studies can reveal several potential AD biomarkers in urine, including DCAs and lysophospholipids.<sup>228</sup> The extensive loss of brain tissue in AD may alter urinary lipid-derived metabolites, tested against cognitive performance, CSF, and imaging biomarkers.<sup>229</sup> Another promising biomarker includes the platelet-derived growth factor receptor- $\beta$  (PDGFR $\beta$ ), that is expressed in the brain by vascular mural cells-brain capillary pericytes and arterial vascular smooth muscle cells. BBB disruption and increased permeability positively correlate with elevated levels of soluble PDGFR $\beta$  in CSF of patients with mild dementia.<sup>230</sup>

### 4.3.2 | Neuroimaging biomarkers

The use of neuroimaging tools in nutritional research has increased substantially over the past 2 decades. However, this is the case mostly for structural imaging studies,<sup>175,231–234</sup> while investigations in nutrition research using functional imaging approaches such as the above that bring us closer to cerebral metabolism and bioenergetics has been relatively more limited. Additionally, not many functional imaging studies have been performed in elderly at risk for cognitive decline individuals. Furthermore, most such studies have been of relatively limited power and mainly cross-sectional while multiple other methodological limitations are not uncommon.<sup>235</sup> Addressing such limitations<sup>235,236</sup> in future larger and prospective studies in appropriate middle aged or elderly populations may considerably enhance our understanding

of the effects of nutrition in brain energy metabolism. While imaging brain glucose uptake provided insights on the reduced glucose uptake that associate with neurodegeneration, imaging ketone, and fatty acid uptake<sup>121,237</sup> may provide insights into early change in brain lipid remodeling occurring decades before the onset of cognitive decline and likely influenced by the diet. As improved MR spectroscopy techniques are being developed nutritional neuroimaging may help us better comprehend the effects of diet in a variety of additional neurotransmitters. As new PET radiotracers are developed, nutritional effects in additional mechanisms affecting brain bioenergetics including inflammation, oxidative stress, etc., will be better understood. At the same time, different imaging modalities may have a unique explanatory power relative to each other and the prospect of the simultaneous inclusion of multiple imaging outcome measures may provide us with deeper understanding of nutritional effects in brain metabolism. We are in an era of impressive expansion of the list of biological specimens derived nutrient biomarkers and of impressive technological advances of all neuroimaging techniques. A parallel progress of analytical methods could bring us closer to a more precision medicine, personalized-type understanding<sup>153</sup> of the nutrition-cerebral metabolism relation.

### 4.4 | Microbiota sampling in human studies

The need for novel alternatives for early diagnosis, prevention, and treatment aimed to restore cerebral bioenergetic dysfunction in aging and AD cannot be overstated. Microbiome-based treatments to reverse mitochondrial dysfunction are likely to be validated for use in the near foreseeable future. Although it is important to recognize the need for further investigation of microbiome-based interventions, current evidence-based assessments demonstrate an efficacious and promising outcome post-treatment in other disease conditions in addition to AD. However, longitudinal clinical studies on human blood and stool metabolites and their link to neuropsychiatric disorders and cognitive function would further establish the benefits of this novel mode of treatment regime. Stool sampling, which is a non-invasive, cost-effective biomarker assessment method, when combined with in depth target-based, bioenergetic pathway screening is likely to provide data on selective biomarkers to consider for future clinical trials. For example, delineating homo- and heterofermentative *Lactobacillus* spp and their synergistic association with other probiotics like *Bifidobacterium* spp may offer a better understanding of the probiotic mutualism for effective drug design. This is particularly important in deciphering and identifying the right prebiotics, probiotics and postbiotics that positively influence cerebral bioenergetics. Preclinical studies have established SCFAs as important contributors to cerebral bioenergetics. Therefore, future studies involving screening and validation of multitudes of pre- and probiotic co-culture combinations that produce postbiotics with the greatest potential to restore bioenergetic homeostasis are likely to yield best-in-class microbiome-based treatments.



## 5 | CONCLUSIONS

AD represents a complex disease with cell-specific energy failure affected by nutrient availability early in the preclinical disease phases and impacting nutrient brain delivery and metabolism later as the disease progresses. Many questions remain on the individual cell-specific metabolic changes that contribute to neuronal bioenergetics failures. Such mechanistic studies are important to design targeted therapeutics. One can speculate that drugs or supplements that can better support astroglial mitochondria FAO and spare neuronal mitochondria might be advantageous. Basic research into mechanisms of impaired FAO could lead to novel drugs that shift metabolism away for oxidative or glycolytic stress. The integrated bioenergetic system of astrocytes, pericytes and endothelial cells has direct effects on vascular blood flow and BBB functions. Maintaining BBB integrity is a highly regulated and metabolically demanding task that appears to fail early in AD, particularly among *APOE4* carriers. Since BBB function has a major impact on nutrient brain delivery, understanding the mechanisms that restore cerebral bioenergetics promise to enhance the role of nutritional interventions on brain functions. As the nutrition field moves further toward personalized medicine, single or a combination of a few nutrients may still have a role in AD prevention when targeted to vulnerable populations and guided by validated biomarkers including the microbiome. Current efforts are ongoing to explore potential effects of dietary pattern interventions such as the MIND trial,<sup>173</sup> the BEAT-AD trial of a modified ketogenic diet (NCT03472664), the Multicultural Health Diet (MHD) an anti-inflammatory diet (NCT03240406) and multiple World Wide FINGER initiatives (where dietary patterns are considered within the framework of multidomain lifestyle interventions). Such efforts need to be expanded and supplemented by parallel biomarker investigations toward aiding in better understanding of dietary pattern effects in brain bioenergetics. It will also be important to design and implement these nutritional interventions in ethno-rationally diverse populations to fully explore cerebral bioenergetics as a viable target for the prevention of cognitive decline and dementia.

### AUTHOR CONTRIBUTIONS

Hussein N. Yassine, Gene L. Bowman designed the study. All other authors significantly contributed to the discussions and study materials and critically participated in writing and reviewing certain sections of the manuscript.

### ACKNOWLEDGMENTS

We thank Brianna Liu for helping with the figures and Thomas Ulrich for proofreading the manuscript and assisting with the references. H.N.Y. is supported by R13AG069386, R21AG056518, R01AG055770, R01AG054434, R01AG067063, RF1AG076124 and RF1AG078362 from the National Institute on Aging as well as Alzheimer' Association and receives consulting fees from Huron Consulting Firm. H.N.Y. was the NMD PIA co-chair 2019-2021, and sits on the ISTAART Advisory board 2022–2024. G.G. is supported by 2P01AG014930-15A1,

R01AG043679 from Alzheimer's Drug Discovery Foundation as well as Method for treating neurodegenerating diseases with benfotiamine or derivatives thereof for Patents planned, issued or pending. M.G.H. is supported by 1R01AG054434, 2P01AG052350-06, RO1AG063857, RO1 AG055770 from L.K. Whittier Foundation and W.M. Keck Foundation as well as R01NS072497 for grants or contracts. M.G.H. is also a member of NINDS Study Section ZRG1 BDCN-W, NINDS Headache CDE Working Group, Co-Chair of Biomarkers Committee. R.S. is supported by P30072973 from the National Institute on Aging as well as honoraria for lectures from Nestle Health. S.C. receives funding from Nestlé Health Science SC: Payment to institution—Abitec SC: Research materials. S.C. has License for BrainXpert product. S.C.: Paid to me and institution. S.C. receives consulting fees from Nestlé Health Science, Cargill and Abbott. S.C. receives payment or honoraria from Nestlé Health Science SC: Paid to me. S.C. receives support for attending meetings and/or travel from Nestlé Health Science. S.C. has Patents planned, issued or pending from MCT formulation, co-inventor with Bernard Cuenoud, Nestlé Health Science. S.C. has participation on a Data Safety Monitoring Board or Advisory Board from AB—Nestlé Health Science, AB—Abbott, AB—Cargill SC: Paid to me, and receives equipment, materials, drugs, medical writing, gifts or other services from Abitec, research materials SC: Institution. N.S. receives funding from EISAI—Local Pi of recruiting site for multinational, multicenter industry sponsored phase III treatment trial for Alzheimer's disease NS: Payments to Institution, and EPAD—Local PI of recruiting site for multinational, multicenter Innovative Medicines Initiative (IMI) sponsored observational study of prodromal stages of dementia NS: Payments to Institution, as well as NovoNordisc—Local PI of recruiting site for multinational, multicenter industry sponsored phase III treatment trial for Alzheimer's disease NS: Payments to Institution. N.S. chairs and receives funding from the Albert Einstein College of Medicine Data Safety Monitoring Board- NIH funded study NS. J.G. receives funding from ERC Starting Grant, StG 678832 as well as patents planned, issued or pending on Inventor for European Patent No. 16180434.9 "Methods of Diagnosis Alzheimer's Disease." Co-Inventor for U.S. patent 12/917,402 "The Use of CI-994 and Dinaline for the Treatment of Memory/Cognition and Anxiety Disorders." L.A.J. is supported by R01 AG062550, R01 AG060056 from the National Institute on Aging as well as Cure Alzheimer's Fund. J.L. is supported by Springer for co-editor of the book Diabetes and the Brain. J.L. also receives consulting fees from vTv therapeutics. H.F. receives funding from Annovis (QR Pharma), Vivoryon (Probiodrug), AC immune, and LuMind; service agreements for consulting activities with Genetech (DSMB), Roche/Banner (DMC), Tau Consortium (SAB), Samus Therapeutics, Biosplice Therapeutics, Axon Neurosciences, Novo Nordisk Inc., Janssen Research & Development LLC; and travel funding from World Events Forum (ADDF) with no personal funds received and all payments to UCSD. HF also reports a philanthropic donation from the Epstein Family Alzheimer's Disease Collaboration for therapeutic research in AD. G.L.B. is supported by R01 AG043398 from NIH/NIA as well as R90AT008924 from NIH/NCCIH. G.L.B. is a founder 2015, served as co-chair 2015–2019 and immediate past co-chair

2019–2021. H.Y., G.L.B., B.A., C.S., and W.S. are all members of the NMD PIA, ISTAART. This manuscript was facilitated by the Alzheimer's Association International Society to Advance Alzheimer's Research and Treatment (ISTAART), through the Nutrition, Metabolism and Dementia professional interest area (PIA). The views and opinions expressed by authors in this publication represent those of the authors and do not necessarily reflect those of the PIA membership, ISTAART or the Alzheimer's Association. [Correction added on 12 January 2023, after first online publication: The preceding two sentences were added and the acknowledgment in the byline was removed.]

## CONFLICT OF INTEREST

All other authors report no relevant disclosures. Author disclosures are available in the [supporting information](#).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

**How to cite this article:** Yassine HN, Self W, Kerman BE, et al. Nutritional metabolism and cerebral bioenergetics in Alzheimer's disease and related dementias. *Alzheimer's Dement*. 2022;1-26. <https://doi.org/10.1002/alz.12845>