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Ketones: potential to achieve brain energy rescue and sustain cognitive health during ageing

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Abstract

Alzheimer's disease (AD) is the most common major neurocognitive disorder of ageing. Although largely ignored until about a decade ago, accumulating evidence suggests that deteriorating brain energy metabolism plays a key role in the development and/or progression of AD-associated cognitive decline. Brain glucose hypometabolism is a well-established biomarker in AD but was mostly assumed to be a consequence of neuronal dysfunction and death. However, its presence in cognitively asymptomatic populations at higher risk of AD strongly suggests that it is actually a pre-symptomatic component in the development of AD. The question then arises as to whether progressive AD-related cognitive decline could be prevented or slowed down by correcting or bypassing this progressive 'brain energy gap'. In this review, we provide an overview of research on brain glucose and ketone metabolism in AD and its prodromal condition – mild cognitive impairment (MCI) – to provide a clearer basis for proposing keto-therapeutics as a strategy for brain energy rescue in AD. We also discuss studies using ketogenic interventions and their impact on plasma ketone levels, brain energetics and cognitive performance in MCI and AD. Given that exercise has several overlapping metabolic effects with ketones, we propose that in combination these two approaches might be synergistic for brain health during ageing. As cause-and-effect relationships between the different hallmarks of AD are emerging, further research efforts should focus on optimising the efficacy, acceptability and accessibility of keto-therapeutics in AD and populations at risk of AD.

Key words: Exercise: Brain glucose metabolism: Mitochondrial function: Brain function: Alzheimer: β-hydroxybutyrate: Mild cognitive impairment

Alzheimer's disease aetiology and treatments

Neurodegenerative diseases of ageing are a cluster of conditions characterised by deteriorating brain function associated with the gradual and regionally selective loss of brain cells that have become a major concern for society[1]. The most common neurodegenerative disease of ageing is Alzheimer's disease (AD), a chronic syndrome in which progressive cognitive decline ultimately threatens the individuals' capacity to reason clearly and perform basic activities of daily living[2]. Despite the broad documentation of multiple factors affecting the development of AD pathogenesis, the exact aetiology underlying AD remains unclear[3,4]. Normal ageing is accompanied by some decrease in certain cognitive abilities, but a large proportion of the population remains cognitively healthy during their lifetime, indicating that advanced cognitive dysfunction is not an inevitable consequence of old age[5]. Thus, the progression of brain neuropathology leading to AD is not related to ageing *per se*, but to environmental and genetic factors[6]. To date, the quest for disease-modifying therapies addressing the amyloid, tau and neurotransmitters hypotheses[7] has failed to produce an approved drug in over 20 years, highlighting the difficulty in determining the right target, type of intervention and/or timing to intervene[8]. At present, only two neurotransmitter-based therapies – cholinesterase inhibitors and an N-methyl-D-aspartate antagonist – have been approved for the management of cognitive symptoms, but they remain ineffective for reversing underlying AD pathology[9].

Abbreviations: AcAc, acetoacetate; AD, Alzheimer's disease; BGH, brain glucose hypometabolism; CMR, cerebral metabolic rate; FDG, fluorodeoxyglucose; IR, insulin resistance; KD, ketogenic diet; kMCT, ketogenic medium chain TAG; MCI, mild cognitive impairment; PET, positron emission tomography; RCT, randomised controlled trials; βHB, β-hydroxybutyrate.

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Over the last decade, considerable interest has emerged in the role of brain energy metabolism in the natural history of AD-related cognitive decline[10]. Long considered as a simple biomarker of neuronal death in the progression and manifestation of clinical symptoms of AD, altered brain glucose utilisation is now believed to have more of a causal or aggravating role in the development of AD[11]. Furthermore, regional brain glucose hypometabolism (BGH) assessed by positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (FDG) is a reliable marker to predict the conversion from cognitively normal adults to mild cognitive impairment (MCI) and MCI to AD[12,13]. Longitudinal studies in late-onset (sporadic) and autosomal dominant AD have demonstrated that regional BGH may develop secondarily to amyloid plaque deposition, but it can also develop prior to the neuropathology in at least a quarter of sporadic AD[14–18]. The pattern of regional cerebral amyloid deposition was previously reported to not be correlated with brain glucose BGH[19,20], but recent studies challenged these findings by reporting positive associations with amyloid and local or distant AD-related brain regions displaying hypometabolism[21,22]. Regardless of whether impairment in energy metabolism constitutes a primary or secondary event in AD, it is of great interest to better understand its role in the onset of the disease and determine whether correcting it could be an effective treatment or preventive strategy. AD pathologies can be present over 20 years before the onset of clinical symptoms[23] which offers a critical window of opportunity to initiate treatments and hopefully change the course of the disease after which reversing neurological damage and functional decline might prove to be more difficult[24].

Lifestyle improvement including dietary modifications is recommended as the first-line treatment for most chronic diseases. Observational studies show that increased consumption of single nutrient classes (*n*-3[25], antioxidants[26]), certain food groups (vegetables[27], fish[28]) as well as energetic restriction[29] offer some protection against AD, but results from adequately powered randomised controlled trials (RCT) in humans have yielded mixed results or are simply lacking[30,31]. In healthy adults[32] and adults with MCI[33], adherence to nutrient-rich dietary patterns (Mediterranean, Dietary approaches to stop hypertension (DASH), Mediterranean-DASH intervention for neurodegenerative delay (MIND)) has been shown to improve cognitive function and reduce the risk of AD but, again, most of these findings are based on epidemiological studies and do not establish a causal relationship. Diets with high glycaemic load and sugar content are associated with increased levels of cerebral amyloid and lower global cognitive performance, respectively, in older adults, potentially highlighting a link between diet composition and brain health[34]. At the other end of the dietary spectrum, very-low-carbohydrate ketogenic diets (KD), which have a marked effect on brain energy metabolism[35], have yielded encouraging preliminary results in populations with cognitive deficits[36].

Since the brain possesses very limited glycogen storage capacity, sufficient and continuous substrate and oxygen delivery from the periphery is critical to ensure optimal brain health and resilience throughout the lifespan. Under normal circumstances, glucose is the main fuel for the brain and accesses the intracellular space via specific glucose transporters GLUT-1 and GLUT-3, and to a lesser extent insulin-stimulated GLUT-4[37]. When glucose availability is severely limited for a prolonged period such as during fasting or a KD, the ketones – acetoacetate (AcAc) and *β*-hydroxybutyrate (*β*HB) – are synthesised by the liver at an increased rate and contribute significantly to the energetic demands of the brain[38]. The recent advent of exogenous ketones now allows individuals to similarly increase circulating ketones without having to make dietary changes. In this review, we will present evidence supporting the use of ketogenic interventions as a principal component of 'brain energy rescue' strategies to bypass BGH, maintain brain fuel supply and improve cognitive health during ageing[39].

Regional brain glucose hypometabolism in individuals with or at risk of Alzheimer's disease

Starting in 1963, a series of arteriovenous difference studies were conducted in individuals at different stages of AD and reported significant reductions of 22–55 % in global brain glucose utilisation as compared with age-matched controls[40–44], whereas cerebral blood flow and oxygen consumption were far less impaired[42,43]. Using PET with the glucose tracer ^{18}FDG, BGH has been widely confirmed in AD on many occasions[45–50]. As with cognitive performance, the magnitude of the whole-brain decline in cerebral metabolic rate (CMR) of glucose worsens with advancing AD and is usually on the order of ~10–20 % in mild AD, with specific regional deficits of 10–50 %. In AD, the regional pattern seems to affect initially the medial temporal lobe including the hippocampus as well as the parietal cortex, and posterior cingulate[50,51]. Along these lines, accumulation in the posterior cingulate and precuneus regions of certain metabolites including glucose has been previously reported in AD and likely reflects their under-utilisation as an energy source[52].

MCI is a condition characterised by cognitive decline greater than what is expected during normal ageing but that does not yet interfere with activities of daily life. It is usually defined by a combination of: (i) subjective concern regarding a change in cognition, (ii) objective evidence of lower performance in one or more cognitive domains and (iii) preservation of independence in functional abilities in daily life[53]. Individuals with MCI, particularly the amnestic subtype which affects memory, are at higher risk of developing AD[54]. In this population, regional BGH starts in the posterior cingulate cortex[55], progresses to the temporal and parietal cortices and is considered to be a sensitive marker of AD risk and progression[56]. Since 2000, several studies in MCI using PET-FDG have reported significant reductions in glucose utilisation of up to 20 % in AD-vulnerable brain regions[50,57–60]. These findings suggest that MCI represents an intermediary state of metabolic decline in which BGH is more pronounced compared with healthy older adults but in which the decline is still lower in magnitude and spatial distribution than in AD. Recently, the longest PET-FDG study in MCI (median follow-up of 72 months) clearly demonstrated the progressive decline in glucose utilisation potentially leading to AD-onset and observed a significantly higher rate of decline in ApoE *ε*4 carriers as compared with non-carriers in several brain regions[61]. Taken together, these reports clearly indicate that BGH is already present in individuals with various levels of cognitive deficit,

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but they do not provide information as to the chronological sequence of cognitive, pathological and brain energetic impairment over time.

In cognitively healthy older people, mild BGH is observed almost exclusively in the frontal cortex[62]. Hence, BGH changes qualitatively and quantitatively from normal ageing to MCI and AD; the qualitative change is in the brain regions affected, while the quantitative change is that the magnitude of BGH increases as objective signs of cognitive decline become apparent. Less decline in glucose utilisation in the anterior cingulate cortex and the anterior temporal lobes of older adults (80+ years old) has recently been associated with both cognitive resilience and vascular health and proposed as a disease-targeting, modifiable risk factor for AD[63]. Hence, the cognitively healthy older person is an important reference to set the baseline for the energy deficit in MCI and AD but, equally, is also a target for brain energy modifying interventions aiming to reduce the risk of progression to MCI or AD.

For decades, BGH in AD was considered to result from advanced neuronal dysfunction, which correlates well with the degree of cognitive impairment[64], but emerging evidence reporting its occurrence years prior to the onset of AD clinical symptoms challenges this interpretation[39,65]. Indeed, populations at high risk for AD including the ones carrying genetic mutations presenilin-1[66], young adults carrying the APOE 4 gene[67] or with a family history of AD[68] display reduced regional PET-FDG uptake in the brain decades *before the onset of the cognitive deficit*. Individuals with risk factors for AD such as age > 65 years[69], IR[70] and subjective memory complaints[71] also present impairments in brain glucose utilisation. The reported reduction in regional brain glucose utilisation in these populations ranged from 8 to up to 25 % and, as in AD, affected the parietal cortex, posterior cingulate and temporal cortex. Clearly, BGH can develop pre-symptomatically so it is conceivable that it plays a contributing role in the development of brain energy deficit and AD-associated cognitive decline. This does not exclude the possibility that neuronal dysfunction and death further exacerbate BGH as part of a vicious cycle. BGH may not be the first detectable form of dysfunction in the ageing brain, but it has an upstream place in the cascade of events leading to AD.

Underlying mechanisms of impaired brain glucose utilisation

The disruption of glucose utilisation in the brain of individuals with cognitive decline is widely observed, but its underlying causes are still not fully understood. In AD, numerous abnormalities in brain glucose transport (e.g. cerebral perfusion, blood–brain barrier, cerebral blood flow and GLUT1 and GLUT3 expression) and metabolism (e.g. glycolysis, pentose phosphate pathway, tricarboxylic acid cycle, oxidative phosphorylation) have been reported[72–76]. Normally, brain glucose delivery largely exceeds local consumption thereby almost always avoiding a potential brain energy shortage[77]. Brain regions vulnerable to AD can display glucose accumulation, suggesting that glucose transport might not be the initial limiting factor in brain glucose utilisation[73].

In AD, mitochondrial dysfunction is part of a vicious cycle contributing to amyloid beta and tau pathology, both closely associated with oxidative damage which promotes further mitochondrial dysfunction, proteotoxicity, cell dysfunction and death[74,78]. Mitochondrial structure and function differ significantly between AD and healthy older adults including total number, protein expression, antioxidant capacity and enzymatic activity in the tricarboxylic acid cycle and oxidative phosphorylation complexes I, III and IV [96]. Such pathological changes reduce ATP production from glucose by 20–50 % in sporadic AD[41]. Thus, mitochondrial dysfunction is a major and early defect responsible for the reduction in brain glucose utilisation in AD[79]. However, glycolysis is up-regulated during brain activation[77] and glycolytic impairment in specific brain regions has also been proposed as a fundamental feature contributing to AD symptoms[73]. In addition to limiting ATP production, dysregulation in glycolysis would also reduce the amount of anaplerotic intermediates entering the citric acid cycle which in turn would limit oxidative phosphorylation and the synthesis of acetylcholine and γ-aminobutyric acid.

In the brain, insulin's role goes beyond glucose homoeostasis[80] and impairment in its signalling pathways is now recognised as an important characteristic of AD[81]. Brain insulin resistance (IR) can develop in the absence of systemic IR[82], but epidemiological and neuroimaging studies consistently report a strong association between type 2 diabetes and AD, suggesting that both peripheral and central IR usually co-exist[83,84]. In patients with AD, impaired insulin action may contribute to abnormal brain energetics in several ways including impaired mitochondrial oxidative metabolism and ATP-dependent maintenance processes that are critical to neuronal survival[85]. Moreover, increased production of reactive species and inflammatory cytokines resulting from reduced brain insulin signalling damage brain cell structure and functional integrity[86]. It is also possible that IR down-regulates the utilisation of glucose through the blood–brain barrier and by altering GLUT4 trafficking, though the impact on overall brain glucose homoeostasis remains to be determined[87]. While it is unclear whether IR on its own is enough to cause neuronal damage, it can exacerbate (and be exacerbated by) the pathophysiological mechanisms underlying AD, particularly amyloid β accumulation (via the competitive inhibition of its degradation) or neuronal loss (via apoptosis)[78].

Brain ketone metabolism in health and Alzheimer's disease

The common perception that glucose is the obligatory and preferred fuel for the brain originates from the observations that insulin-induced hypoglycaemia leads to severe sensory and cognitive disturbances that can be reversed by the administration of glucose[88] and that, under normal conditions, glucose is the dominant source of energy for the brain[89]. However, βHB infusion and prolonged fasting attenuate the physiological response to severe hypoglycaemia including autonomic symptoms[90–92], neuronal death[93] and cerebral energy metabolism[94]. Moreover, under circumstances in which the ketone:glucose ratio in the blood is increased allowing for potential substrate competition, brain glucose utilisation is displaced by ketones and its oxidation by the normal brain is reduced[35]. Generally,

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an increase of 0·1 mM in plasma βHB is usually paralleled by an increase of 1·0–1·2 % in the contribution of ketones to total brain energy metabolism[95]. In extreme physiological ketosis (~6–7 mM of βHB) such as a 30–40-d fast, ketones can become the major fuel of the brain and provide up to 2/3 of its total energy needs[89]. Some evidence suggests that the ketone contribution to total brain energy metabolism does not surpass this 2/3 value even when βHB levels are as high as 8 mM in humans[92] and 17 mM in rats[96] unless a high level of insulin is infused simultaneously[92]. One possible explanation is that, like fatty acids, ketones 'burn in the flame of carbohydrates' and thus require the presence of an anaplerotic substrate like glucose to replenish tricarboxylic acid intermediates and ensure the complete oxidation of ketones to ATP[97]. Excessive ketone metabolism in the brain at the expense of glucose could potentially have a detrimental impact on neuronal signalling driven by glutamate[98]. Contrary to brain glucose utilisation, which is mainly dependent on neuronal activity, brain ketone utilisation is directly related to ketone concentrations in circulation over a broad range of concentrations, that is, from 0·1 to at least 6–7 mM of βHB[95], thus ensuring a continuous supply of energy to the brain during glucose scarcity.

Despite the widespread characterisation of lower brain glucose utilisation in AD, few studies have evaluated the capacity of the brain to utilise its main alternative fuel – ketones – in AD. To the best of our knowledge, only four studies have directly evaluated brain glucose and ketone metabolism concomitantly in AD (Table 1). Using the arteriovenous difference method, Lying-Tunell *et al.* and Ogawa *et al.*, reported that while CMR of glucose was impaired in moderate-advanced AD, CMR of AcAc and βHB remained similar to cognitively healthy, age-matched controls[42,44]. Decades later, these findings were confirmed using PET in mild-AD. We have also demonstrated that plasma AcAc concentrations and AcAc utilisation in healthy older adults, MCI and AD were all positively correlated with the same slope indicating a similar capacity of the brain to extract and utilise ketones despite the progression of cognitive decline[47,50]. Using a 4-year longitudinal study in healthy older adults, we later showed that while declining regional brain glucose utilisation (–6 to –12 %) was paralleled by deteriorating cognitive performance, AcAc utilisation remained unchanged over the same period[99]. A study in postmortem AD brains recently supported these *in vivo* observations by showing that while glycolytic gene expression was impaired in all cell types, ketolytic gene expression was normal in neurons, astrocytes and microglia but sub-normal in oligodendrocytes[100]. Overall, the impairment in brain energy metabolism in AD clearly seems to be specific to glucose, which opens the possibility of providing ketones as an alternative substrate to the brain to reduce or bypass the energetic deficit in AD caused by BGH.

Ketogenic interventions

Research into the potential therapeutic applications of ketones has grown exponentially over the past decade and suggests that ketones may be clinically beneficial in several diseases including heart failure, diabetes and AD[101–103]. Nutritional ketosis is usually defined as having a blood concentration of βHB or AcAc higher than 0·5 mM [104]. It should be differentiated from pathological ketoacidosis in which plasma ketones are much higher (often ≥ 10 mM βHB + AcAc) but also because nutritional ketosis occurs without either an underlying disease or metabolic acidosis[105]. Fasting and other dietary modifications resulting in mild endogenous ketosis have been used to treat a variety of diseases for centuries, including epilepsy[106], IR[107], obesity[108] and neurodegenerative diseases[39]. Recently, the development of exogenous sources of ketones such as salts and esters permits plasma ketones to be raised independent of plasma glucose or insulin levels, widening the spectrum of potential therapeutic applications of this form of exogenous nutritional ketosis[109].

Endogenous ketosis

A KD will trigger metabolic and enzymatic adaptations that make the brain less reliant on glucose and favour the utilisation of ketones[35,110]. The blood profile that accompanies endogenous ketosis on KD (or fasting) differs from the one with exogenous ketosis[111]. First, given the low amount of carbohydrates consumed on a KD, glucose and insulin fluctuations are greatly reduced. Second, a KD promotes the release of NEFA from adipocytes through reduced insulin[112], and increased counterregulatory hormones (e.g. glucagon, catecholamines, cortisol, growth hormones)[113,114] while βHB inhibits their mobilisation[115]. The effect of cortisol and glucagon on adipocytes is heavily influenced by insulin; when insulin is low, they promote lipolysis and ketogenesis and when insulin is high, they promote fat storage and lipogenesis[114,116]. In adults, short-term KD (≤ 4 weeks)[35,117,118] and its forms used for epilepsy (with or without MCT)[119] can produce moderate ketosis (βHB 1·5–4·0 mM). Nevertheless, longer-term studies (≥ 6 weeks) in MCI and AD[120–123] and other populations with[124–126] and without[127–129] chronic diseases have usually reported more modest βHB levels (< 1·0 mM). Additionally, since physical fitness, total energy intake, diet composition and metabolic profile influence ketone kinetics, it can be difficult to sustainably achieve a blood ketone target with a diet intervention alone[130]. Achieving endogenous ketosis can take many hours, sometimes days, and adherence to this relatively restrictive dietary pattern can be problematic[131], even more so if cognition and autonomy are already suboptimal. Ketogenic medium chain TAG (kMCT) can be used to supplement a KD to optimise ketone levels and to allow the introduction of some carbohydrates, thereby facilitating long-term adherence[132]. The beneficial effects of a KD in reducing risk factors for AD such as IR, impaired glycaemic control, inflammation, and elevated blood pressure and body weight can outweigh the difficulties of adjusting to a KD[133]. While weight loss is usually beneficial for metabolic health in those who are overweight, it could potentially have deleterious effect in older people who are frail, sarcopenic or cachectic[134]. Similar to reports in populations without cognitive impairment[126,135,136], studies in MCI and AD using KD have reported significant improvements in body weight as well as circulating glucose, insulin and TAG, while both HDL- and LDL-cholesterol were increased[120,122,137].

Not all fat sources are equally efficient in raising blood ketones[138]. In the absence of carbohydrate restriction, among dietary fatty acids only octanoic acid and to a lesser extent, decanoic acid are truly ketogenic[139–142]. Since kMCT are only found at very low levels in adipocytes and in the diet, they need to be repeatedly

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Table 1. Cerebral metabolic rate of ketones but not glucose remains normal in Alzheimer's disease compared with healthy age-matched controls (Mean values and standard deviations)

	Older controls		Alzheimer		
	Mean	SD	Mean	SD	Effect of Alzheimer
Early Alzheimer		CMR-PET (μmol/100 g/min)			
Croteau *et al.* 2018[50]					
Age	73	6	73	5	
AcAc	0·28	0·19	0·30	0·20	↔
βHB + AcAc	0·71	0·51	0·89	0·62	↔
Glucose	29·7	2·5	27·0	3·3	↓*
Castellano *et al.* 2015[47]					
Age	72	5	76	4	
AcAc	0·35	0·16	0·31	0·24	↔
Glucose	38·3	4·9	34·2	5·0	↓*
Advanced Alzheimer		CMR-AVD (μmol/100 g/min)			
Ogawa *et al.* 1996[42]					
Age	63	9	66	8	
AcAc	0·18	0·13	0·09	0·04	↔
βHB	0·11	0·06	0·14	0·08	↔
Glucose	24·9	7·2	11·6	4·0	↓*
	Median	Range	Median	Range	
Lying-Tunell *et al.* 1981[44]					
Age	64	54–71	60	52–67	
AcAc	0·44	−0·6–1·7	0·39	0·0–2·5	↔
βHB	0·62	0·0–1·6	0·45	0·2–1·4	↔
Glucose	24·8	18·8–32·1	18·7	11·9–30·3	↓*

CMR-PET, cerebral metabolic rate measured by positron emission tomography; *βHB*, β-hydroxybutyrate; AcAc, acetoacetate; CMR-AVD, cerebral metabolic rate measured using the arteriovenous difference method.
Data are presented as mean (standard deviation) and as median (range) for as Lying-Tunell *et al.*
Significantly lower *v.* cognitively healthy age-matched older adults
* $P < 0·05$.

ingested to ensure their transformation into ketones within the liver[143]. In cognitively healthy young and older adults, kMCT reduce postprandial glucose[144], have a neutral effect on fasting lipids and glucose and can moderately reduce body weight (−0·5 kg)[145,146]. The consumption of kMCT in MCI and AD for 4–24 weeks is safe and has no significant effects on body weight or plasma cardiometabolic and inflammatory marker profiles[147,148]. Their consumption, especially at high doses, can be associated with mild gastrointestinal issues in some patients, but they are usually transitory and can be tempered by dose titration[139]. Certain dietary patterns including intermittent fasting, time-restricted feeding[149], energetic restriction[29] and even coconut oil[150,151] do not necessarily raise blood ketones, so their clinical and physiological implications fall outside the scope of this report.

Exogenous ketosis

Racemic ketone salts and βHB monoester produce plasma D-βHB of ~1 and ~3 mM for 24 g dose, respectively[152]. In both cases, no dietary carbohydrate restriction is required, but given the transient nature of exogenous ketones, multiple daily ingestions may be necessary for therapeutic efficacy. Most but not all[153] ketone salts are racemic, that is, containing both the D and the L form of βHB (of which only the D form is metabolisable into energy intermediates). Like with the esters, their half-life is too short to achieve a specific, sustained βHB blood level[109]. Nevertheless, ketone esters allow a similar level of blood βHB to be attained within 30 min to those observed after several days of fasting or following a KD[154]. Moreover, they contain only D-βHB and are salt free[155]. Their bitter taste and high price, however, currently limit their utility. The acute consumption of ketone salts and βHB monoesters transiently and mildly raise insulin secretion, an effect unlikely to be of clinical significance[152,154]. While both ketone salts and the βHB monoester raise blood βHB and lower blood glucose, NEFA and blood pressure, they have different metabolic and safety effects[152,154,156,157]: Ketone salts transiently raise urine pH while ketone esters transiently decrease it and, when comparing equimolar doses, the ketone monoester raises chloride more than ketone salts[152,158]. On the other hand, the Na content to achieve therapeutic levels of blood βHB using most commercially available ketone salts exceeds the recommended upper limit. To date, no RCT has investigated the effect of oral ketone supplementation in populations with cognitive decline although one is currently in progress (Clinicaltrials.gov identifier: NCT04466735).

The understanding of the acute and short- to medium-term (1–24 weeks) effect of different ketogenic interventions on cardiometabolic markers has considerably expanded in recent years (summarised in Table 2), but whether there are potential long-term side effects of the non-physiological environment accompanying exogenous ketosis (i.e. elevated glucose, ketones and insulin simultaneously) is still unknown and will need to be determined in order to optimise the safety and efficacy of ketogenic interventions in different therapeutic contexts.

Fuel efficiency: a core feature of ketones

Besides substituting for glucose as a fuel, there are three reasons why ketones are a more efficient source of carbon to fuel the mitochondrial respiratory chain than glucose or NEFA: First, ketones are more reduced than pyruvate (higher hydrogen to carbon ratio), so have a higher redox potential or potential to generate ATP[159].

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Table 2. Characteristics and general effects of ketogenic interventions

	Ketogenic diet	kMCT	Ketone salts	βHB monoester
Doses	CHO < 50 g/d	15–40 g	Racemic βHB: 12–25 g, Pure D-βHB: 12 g	10–50 g
D-βHB (mM)	0·4–4·0	0·4–0·7 mM	Racemic βHB: 0·4–1·0 mM, Pure D-βHB: 0·8 mM	1·5–5·0 mM
βHB : AcAc	2–4:1	2:1	2:1	3–4:1
Time to ketosis	Days to weeks	1–2 h	< 30 min	< 30 min
Insulin	↓↓	↔	↔ ↑	↔ ↑
Glycaemia	↓↓	↔ ↓	↔ ↓	↔ ↓
NEFA	↑	↔	↔ ↓	↔ ↓
LDL-cholesterol	↑	↔	?	?
HDL-cholesterol	↑	↔	?	?
TAG	↓↓	↔	↔ ↓	↔ ↓
CRP	↓	↔	?	↓
Blood pressure	↓	↔	↔ ↓	↔ ↓
Blood pH	↔	↔↔	↔ ↑	↔ ↓
Body weight	↓	↔ ↓	↔	↔
Cost	Low-moderate	Low-moderate	Low-moderate	High
Adherence	Low-moderate	Moderate-high	Moderate	Low-moderate
Taste	Multiple choices	Tasteless	Usually sweet	Very bitter
Potential limitations	Sensitive to dietary transgressions, keto-induction symptoms, adherence, LDL-cholesterol	Gastrointestinal issues, mild and transient ketosis	Cation overload, transient ketosis	Expensive, taste aversion, transient ketosis, adherence

kMCT, ketogenic medium chain TAG (C8 and C8C10 combined); βHB:AcAc, β-hydroxybutyrate:acetoacetate ratio in the blood; BW, body weight; CHO, carbohydrates; IR, insulin resistance; AD, Alzheimer's disease.

Second, in contrast with fatty acid oxidation which promotes the expression of uncoupling proteins (via PPARα transcription regulation), ketone oxidation is electrochemically more efficient to produce ATP. During fatty acid β-oxidation, only half of the reducing equivalents are NADH while the other half are FADH (which has a redox potential above that of the NAD couple) resulting in the synthesis of five instead of the six possible ATP molecules[159]. Third, because of the dual role of succinate dehydrogenase in the Krebs cycle and electron transport chain, half of the reducing equivalents enter the electron transport chain via Complex II during ketone β-oxidation instead of Complex I[159]. Complex II has a smaller reduction potential with the Q-couple (which is near equilibrium) than Complex I (–0·320 mV for the NAD couple[160] *v.* +0·32 mV for the fumarate and succinate couple[161]). This larger gradient results in more electrochemical energy available to fuel ATP production during ketones oxidation[162,163]. Furthermore, most reactive oxygen species in the cell are produced in mitochondria, principally at the electron transfer step between Complex I and the Q-couple. Since ketone oxidation preserves the Q-couple in the oxidised state (as opposed to glucose or fatty acid β-oxidation), fewer reactive oxygen species are produced during ketolysis than during β-oxidation. Ketolysis also expands the citric cycle metabolite pool, despite a lower concentration of glycolysis intermediates.

Keto-therapeutics for brain energetics, cognition and neuroprotection

In healthy humans[35] and rodent models[164], total brain energy levels remain unchanged following a KD because the increase in brain ketone utilisation is paralleled by a compensatory reduction in glucose utilisation. This homoeostatic mechanism is not observed in populations with cognitive impairments in whom ketones help fill in the energetic deficit and increase total energy levels in the brain *without* reducing brain glucose utilisation[122,141,165]. Even at low levels of ketosis (βHB ~0·6 mM), we previously showed using ^{11}C-AcAc- and ^{18}FDG-PET that long-term consumption of 30 g/d of kMCT significantly increased whole-brain CMR of ketones by 230 % in MCI and 144 % in AD without affecting CMR of glucose. The result was a net improvement in total brain energy consumption of 3–4 % in both groups[141,165]. Neth *et al.* also observed increased brain perfusion and ketone body utilisation in individuals with subjective memory complaints or MCI on a KD[122]. Thus, ketones effectively compensate for at least part of the energy deficit in older populations with cognitive decline. Importantly, Neth *et al.*[122] and Fortier *et al.*[107] included cognitive performance as a secondary outcome in their trial. While both studies reported some improvement in cognition following the use of a ketogenic Mediterranean diet[122] or kMCT[141] in subjective memory complaints and MCI, they were not powered to adequately assess cognitive changes post-intervention. Thus, the first phase of the BENEFIC trial reported by Fortier *et al.*[141] was extended by doubling the sample size so as to better evaluate cognitive outcomes. As compared with an energy-matched drink, the consumption of kMCT for 6 months led to clinically meaningful improvements in several cognitive domains related to the risk of progression towards AD including episodic memory, language, executive function and processing speed[166].

Several other trials as well as a few case studies using ketogenic interventions in MCI and AD have reported benefits on global cognition (ADAS-CoG) and memory[120,121,123,140,142,148,167–169] or quality-of-life and activities of daily living[137] as compared with placebo or pre-intervention status (Table 3). Two systematic

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Table 3. Nutritional studies using keto-therapeutics in populations with cognitive impairment linked to Alzheimer's disease

	Design	Population	Interventions	Duration	Therapy	Ketone level	Domains/tests showing cognitive improvement
Krikorian *et al.* 2012[120]	RCT – parallel	MCI	KD (34 (SD 18) g CHO/d) (*n* 12, 68 (SD 3) years) or HCLF (*n* 11, 71 (SD 8) years)	6 weeks	Diet	Blood βHB: 0·3 mM	Verbal memory
Brandt *et al.* 2019[121]	RCT – parallel	MCI, AD	KD (30–50 g CHO/d) (*n* 9, 74 (SD 6) or HCLF (*n* 5, 69 (SD 5) years)	12 weeks	Diet	Urine: 7·5–10 mg/dl	Memory composite score (at week 6)
Neth *et al.* 2020[122]	RCT – cross-over	SMC, MCI	KD (40 (SD 99) g CHO/d) or HCLF (*n* 20, 64 (SD 6) years)	6 weeks	Diet	Capillary βHB: 0·9 mM	Improved memory performance (*v.* baseline)
Phillips *et al.* 2021[137]	RCT – cross-over	AD	KD (6 % net CHO) or HCLF (*n* 13, 70 (SD 6) years)	12 weeks	Diet	Capillary βHB: 0·95 mM	None (under-powered)
Taylor *et al.* 2018[123]	One arm trial	AD	KD (46 (SD 27) g CHO/d) + MCT (C8C10), 21–42 g/d (*n* 10, 73 (SD 9) years)	12 weeks	Diet + MCT	Blood βHB: 0·3–0·5 mM	ADAS-Cog (–4·1 points *v.* baseline)
Reger *et al.* 2003[142]	RCT – cross-over	MCI, AD	C8, 40 ml (*n* 20, 75 (SD 7) years)	1 dose	MCT	Blood βHB: 0·5–0·7 mM	ADAS-Cog (–1·7 points in ApoE4-)
Henderson *et al.* 2009[140]	RCT – parallel	AD	C8, 20 g/d (*n* 77, 77 (SD 9) years) or placebo (*n* 63, 77 (SD 7) years)	12 weeks	MCT	Blood βHB: 0·4 mM	ADAS-Cog (–1·9 ITT, –2·6 DC at day 45) (–3·4 ITT, –5·3 DC at day 90 in ApoE4-)
Ohnuma *et al.* 2016[139]	One arm trial	AD	C8, 20 g/d (*n* 22, 64 (SD 9) years)	12 weeks	MCT	Blood βHB: 0·3 mM	None (under-powered)
Xu *et al.* 2019[148]	RCT – cross-over	AD (APOE4 -/-)	C8C10, 17 g/d or placebo (*n* 46, 75 (SD 8) years)	4 weeks	MCT	Not reported	ADAS-Cog (–5·2 points)
Ota *et al.* 2019[167]	One arm trial	AD	C8C10, 20 g/d (*n* 16, 73 (SD 6) years)	12 weeks	MCT	Blood BHB: 0·5 mM	Verbal memory and processing speed (*v.* baseline)
Fortier *et al.* 2019[141]	RCT – parallel	MCI	C8C10, 30 g/d (*n* 19, 74 (SD 6) years) or placebo (*n* 20, 75 (SD 7) years)	24 weeks	MCT	Blood BHB: 0·5 mM	Episodic memory, language, executive function and processing speed
Fortier *et al.* 2021[166]*	RCT – parallel	MCI	C8C10, 30 g/d (*n* 44, 71 (SD 7) years) or placebo (*n* 39, 73 (SD 7) years)	24 weeks	MCT	Blood BHB: 0·5 mM	Episodic memory, language, executive function and processing speed

ADAS-Cog, Alzheimer's disease assessment scale-cognitive subscale; AD, Alzheimer's disease; βHB, β-hydroxybutyrate; C8, caprylic acid; C10, capric acid; CHO, carbohydrates; DC, dosage compliant; HCLF, high-carbohydrate low-fat diet; ITT, intention-to-treat; KD, ketogenic diet; MCI, mild cognitive impairment; MCT, medium chain TAG; MEC-WOLF, mini examen cognoscitivo (Spanish adaptation of the MMSE); RCT, randomised controlled trial; SMS, subjective memory complaints.

* Fortier *et al.* (2021) extended the recruitment from Fortier *et al.* (2019) by adding forty more participants.

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Table 4. Potential mechanisms involved in the improvement of cognitive impairment and neuroprotection by ketogenic interventions in AD

Potential mechanisms
Increase total brain energy metabolism by bypassing the issues with glycolysis and brain glucose metabolism
Provide a more efficient metabolic fuel for brain cells in terms of ATP delivered/g
Increase cytoplasmic NAD+:NADH redox state
Reduce the risk of neuroinflammation by increased scavenging of reactive oxygen species
Attenuate the intracellular accumulation and toxicity of amyloid beta and tau protein on brain cells
Attenuate inflammation through HCAR2, NLRP3 inflammasome, $PPAR_{\gamma}$ and sirtuins
Increase antioxidant capacity and resistance to oxidative stress through HDAC inhibition
Inhibit apoptosis and promote mitochondrial function and biogenesis by up-regulating sirtuins, $PPAR_{\gamma}$ and PGC1-α activities
Increase neurotrophic factors expression such as BDNF
Improve TCA cycle activity thereby stimulating acetylcholine and GABA synthesis
Attenuate hyperglycaemia and hyperinsulinaemia leading to diminished insulin signalling pathways

Based on references[174–177].NAD, nicotinamide adenine dinucleotide; NADH, nicotinamide adenine dinucleotide hydrogen; HCAR2, hydroxycarboxylic acid receptor 2; NLRP3, nucleotide oligomerisation domain-like receptor family pyrin domain containing 3; HDAC, histone deacetylase; PGC1-α, peroxisome proliferator-activated receptor gamma co-activator-1 alpha; BDNF, brain-derived neurotrophic factor; TCA, tricarboxylic acid; GABA, neurotransmitter γ-aminobutyric acid.

reviews and meta-analyses recently concluded that, though preliminary, available evidence suggests that ketogenic interventions constitute an effective and feasible approach to improve cognition in older populations with cognitive impairment[170,171]. While it is possible that the APOE4 allele induces a lower change in blood βHB, brain blood flow and cognition in response to a ketogenic supplement[140,142,172], other studies reported no difference between APOE phenotypes[121,141]. Given the existing heterogeneity in the ketogenic interventions, small sample size, and different populations and duration of the studies (see Table 3), it remains to be determined how best to optimise ketones to improve cognitive performance in older people.

Our work over the last two decades suggests that ketogenic interventions improve cognitive performance principally by reducing the existing brain energy deficit through the provision of an insulin-independent alternative fuel to glucose, that is, ketones. However, using keto-therapeutics in rodent models, several other signalling, metabolic and epigenetic actions that may confer neuroprotection and improve cognitive impairment have been suggested (reviewed here[173–177]) (Table 4). So far, only one human study evaluating the effect of ketogenic interventions on traditional neuropathological hallmarks of AD has been reported. In this 6-week pilot study in older adults at risk for AD, a ketogenic Mediterranean diet increasing βHB levels to ~1·0 mM increased β-amyloid 42 and reduced tau levels in cerebrospinal fluid, both of which are considered as positive changes[122]. In mouse models of AD, substantial evidence depicting a reduction in intracellular accumulation and toxicity of amyloid beta and tau protein on brain cells as well as neuroinflammation using both KD and exogenous ketones has been published[178–182]. Given that very different ketogenic interventions (i.e. KD *v.* ketone ester) seem to provide some cognitive benefits and potentially very rapidly (within 2 h), it is likely that the role of ketones themselves as an efficient fuel is directly involved in the observed benefit, at least in the short term. The optimal therapeutic levels of ketones to achieve long-term neuroprotection and cognitive benefits in humans remain unknown, which could be an order of magnitude lower than the levels tested so far in most rodent models of AD (3–5 mM). Importantly, part of the clinical benefits attributed to some ketogenic interventions in populations with cognitive decline may not be due to the actions of ketones as fuels but rather to other effects of specific kMCT. For example, as compared with other medium-chain TAG, decanoic acid may offer superior neuroprotection through mechanisms that might include increased peroxisomal proliferator-activated receptor-γ activation, mitochondrial biogenesis and inhibition of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (reviewed here[174]). Given the distinctions that exist between traditional KD, modified medium-chain TAG KD and kMCT supplementation (i.e. kMCT and carbohydrate contents), future studies should investigate whether the effect on cognition in MCI and AD differs between these two ketogenic strategies.

Physical activity as an adjunct to keto-therapeutics in populations with cognitive deficits

Physical inactivity is thought to contribute to ~8·0 % of dementia cases globally[183]. Nevertheless, there are currently no official physical activity guidelines specifically for individuals with AD who need to defer to those for healthy older adults and/or for other health conditions[184]. In older adults without cognitive dysfunction, physical activity is inversely associated with the risk of AD, with the APOE4 allele potentially diminishing[185] or strengthening[186] the relationship. Importantly, home-based and group-based exercise interventions have been shown to be feasible and improve quality of life, physical performance and the ability to perform daily activities in both older adults with and without cognitive deficit[187–189]. Though controversial, several recent meta-analyses in MCI and AD patients themselves support the idea that exercise interventions, especially the aerobic type, might slow down the decline of global cognition[190–193]. However, most of the evidence remains of low to moderate quality and has a low effect sizes, so definitive conclusions would be premature. The regular practice of physical activity improves several major risk factors for AD including blood lipids, hypertension, cardiorespiratory fitness[194] and peripheral IR[195], the latter being inversely associated with regional BGH[84]. It is likely that exercise treatment should be initiated as early as possible in the AD process to minimise the effect of the patients' potential physical and mental health decline on their capacity to sustain an exercise dose

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sufficient to yield health benefits. In rodent experiments, exercise restores mitochondrial ATP production, lowers reactive oxygen species emission and improves tau pathology through improved insulin action in the insulin-resistant brain[196]. Exercise also reduces brain amyloid in transgenic AD mice[197,198], but so far interventional studies assessing cerebrospinal fluid A β_{1-42} have failed to see similar results in AD[199], though some interesting trends were observed in older adults at risk of AD[200,201]. Determining whether exercise improves cognition by correcting brain IR will provide important information for future AD therapy.

Multidomain lifestyle interventions including exercise and cognitive training with and without diet improve and maintain cognitive function in older adults at risk for AD[202,203], potentially more than exercise alone[204]. While both physical activity[205] and nutritional ketogenic interventions[171] independently improve brain health and cognition, no RCT have evaluated their combined effect on cognitive function in populations at risk of or living with cognitive decline. To the best of our knowledge, only a single case study using high-intensity interval training and KD along with cognitive training for 12 weeks in a 57-year-old woman with MCI has been published and reported a significant improvement in cognition (+8 points; MoCA) and biomarkers of the metabolic syndrome[206]. Although cognition was not assessed in their studies, Miller *et al.* did look at the combined effect of exercise and KD in healthy young individuals and reported significant improvements in skeletal muscle mitochondrial function and efficiency[207]. Myette-Côté *et al.* reported better glucose control and endothelial function following a 4-d KD combined with exercise as compared with both KD alone and a low-fat low-glycaemic index diet in type 2 diabetes[208,209].

Prolonged glycogen-depleting exercise has long been known to stimulate ketone turnover and induce a marked rise in blood ketone concentrations especially during the recovery period when fatty acid oxidation is elevated[210,211]. In normoglycaemic but not in mildly hyperglycaemic individuals, aerobic exercise potentiates the plasma ketone response (+69 %) to kMCT supplementation; whether the same would apply in AD has not been assessed[212]. Along these lines, one study in both mice and older adults reported that aerobic exercise but not resistance training was effective at raising blood βHB levels and improving cognition which might help guide the optimal exercise modality to select in AD[213].

Factors such as fitness level, pre-exercise ketone levels, exercise intensity and metabolic status can influence muscle ketone disposal by as much as 2–5-fold[214]. Unfortunately, studies on brain ketones utilisation during exercise are scarce with one showing no change in brain substrate utilisation (ketones, lactate, glycerol) in young adults during prolonged exercise when βHB levels remained relatively low ~0·4 mM[215]. More recently, we showed that in AD, exercise increases ketone *transport* into the brain, thereby translating into a higher contribution of ketones to total brain energy. Indeed, mild to moderate exercise bouts (50 % VO_{2max} for 40 min) performed over 3 months significantly increased both plasma ketones (+0·3 mM) and tripled CMR of AcAc (from 0·2 (SD 0·1) μmol/100 g/min to 0·6 (SD 0·4)) without affecting CMR of glucose[216]. Thus, combining a ketogenic intervention and exercise would be expected to have a more pronounced benefit for brain energy metabolism and would potentially be associated with better cognitive performance. While moderate physical activity level has previously been associated with higher CMR of glucose in older adults at risk of AD[217], Gaitan *et al.* failed to observe a significant change in CMR of glucose following a 26-week exercise intervention in the same population[218]. Interestingly, Porto *et al.*[219] and Shah *et al.*[220] reported that exercise interventions did improve regional brain glucose utilisation in MCI and older adults, respectively. Though the reason for this discrepancy remains uncertain, these interventions all led to some cognitive benefits that were correlated with changes in regional ^{18}FDG metabolism which highlights the potential of exercise to improve AD-related symptoms through a mechanism linked to improved brain energy metabolism.

While this has not been evaluated in AD, a recent study showed that exogenous ketosis improved exercise tolerance in patients living with Parkinson's disease suggesting that ketogenic interventions could improve adherence and, consequently, facilitate access to exercise-induced cognitive improvements[221]. Moreover, βHB produced during exercise or with ketogenic interventions promoted the expression of brain-derived neurotrophic factor in healthy humans[222,223], and in AD, a state characterised by low levels of brain and circulating brain-derived neurotrophic factor [224,225]. Increased brain-derived neurotrophic factor has been proposed as one potential mechanism to explain the observed cognitive improvement in AD with ketogenic interventions as it is involved in numerous neurophysiological processes that contribute to neuronal growth and survival as well as synaptic plasticity[175]. Importantly, ketogenic interventions and exercise stimulate mitochondrial biogenesis and ATP generation through oxidative metabolism in neurons[226,227]. Mitochondrial dysfunction and aberrant energy metabolism constitute critical factors in the pathogenesis of AD that could potentially be prevented or slowed down by combining these two therapeutic approaches. In addition to their effect on energy metabolism, exercise and ketogenic interventions share different adaptive responses in the brain that could contribute to cognitive health and resilience including neurogenesis, synaptic plasticity as well as protection against neuroinflammation, reactive oxygen species and potentially proteotoxicity[205,228,229]. KD and exercise are also potent stimulators of monocarboxylate transporter expression, which are responsible for the passage of ketones across the blood–brain barrier[230,231]. Taken together, exercise has several overlapping and synergistic effects with keto-therapeutics that could potentially play a key role in the treatment and maybe prevention of AD. Thus, it is of great interest to further investigate the practical limits of combining exercise as an adjunct to ketogenic interventions, bearing in mind that their joint feasibility and effectiveness will likely depend on factors such as physical capacity, motivation and disease stage.

Current challenges and future directions

The aetiology of AD is complex and will most likely require early initiation of a multi-target treatment to significantly improve clinical outcomes[16]. Ketogenic interventions reduce not only the

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brain energy deficit but also oxidative stress and neuroinflammation, while improving mitochondrial function. BGH alone is probably not sufficient to cause AD-related cognitive impairment, but it certainly aggravates the deleterious effects of neuropathophysiological processes and worsens clinical prognosis[78]. Equally, the clinical studies reviewed here show that BGH can be bypassed by a ketogenic intervention and in so doing improve cognitive outcomes, at least in MCI[141,166]. Hence, brain energy rescue is part of the solution; pharmaceutical or non-pharmaceutical interventions in MCI and AD would therefore be predicted to have a better chance of success if they include some form of brain energy rescue.

As to future directions for the field, we have a few suggestions: First, the majority of studies using ketogenic interventions in MCI and AD have been pilot, safety or feasibility trials and were underpowered to detect differences in cognitive outcomes. Thus, it will be critical for future trials to include larger sample sizes to draw more valid conclusions regarding the effectiveness of such treatments to delay cognitive decline associated with AD. Second, although a KD induces higher overall ketosis than exogenous ketones, poor long-term compliance to such a strict diet is an important barrier to its long-term application. The utilisation of exogenous ketones alone or with KD might help alleviate this barrier by allowing a more permissive diet. In type 2 diabetes, the use of continuous remote care during KD interventions that provides patients with access to a healthcare team and biomarkers tracking tools through a web-based application recently showed great diet compliance after 2 years[232]. This novel system will hopefully be applied to populations with AD and MCI attempting to manage their conditions using KD. As clinical experience with ketogenic interventions grows, it is becoming clearer that cardiometabolic markers do not change adversely during studies of up to 6 months, thereby indicating a good margin for safety.

So far, most ketogenic interventions in MCI and AD have resulted in relatively low plasma βHB concentrations (0·3–0·9 mM, see Table 2). Since neurocognitive test performance in MCI is directly related to overcoming BGH by brain ketone utilisation in a dose–response relationship[120,140–142], it is likely that further increasing ketone levels to reduce the brain energy gap as much as possible might yield additional cognitive or functional benefits. To achieve a somewhat higher plasma ketone response and better compliance than with a kMCT or KD, we recently launched the BREAK-AD RCT in MCI using a ketone salt (25 g/d of D-βHB) (ClinicalTrials.gov Identifier: NCT04466735). Third, ketones are part of an effective strategy to delay AD but much work needs to be done to optimise their use in people at risk of AD because even the simplest option of taking 20–30 g/d of a ketogenic supplement for the rest of one's life is still a significant lifestyle change. Exercise is important for well-being and cardiometabolic health and improves ketone delivery to the brain in AD, so should always be encouraged in moderation. More broadly, improving sleep and reducing anxiety and depression will also be beneficial. Correcting impairing hearing is also important as is social engagement. Existing drugs (or those in development) for AD could well be more effective with concomitant brain energy rescue using a ketogenic intervention. This is quite plausible because ketones may not improve neurotransmitter status or reduce amyloid or P-tau load but remains to be assessed. Fourth, with a large proportion of the older population in nursing homes or homes for assisted living, a concerted effort to run RCT in such a setting will be important in the near future. Logistical advantages of such a setting include the proximity of the participants to one another and group meals and other activities. Finally, we now have a solid rationale for a multi-modal AD prevention trial starting no later than in MCI; core components would include a ketogenic intervention, moderate exercise and a MIND-type diet including carbohydrate reduction. The Worldwide Fingers network[233] is a solid foundation for a new era of prevention trials in AD and will hopefully include a trial site using a keto-therapeutic intervention in the years to come.

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