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Review

Aging, lifestyle and dementia

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ABSTRACT

Aging is the greatest risk factor for most diseases including cancer, cardiovascular disorders, and neurodegenerative disease. There is emerging evidence that interventions that improve metabolic health with aging may also be effective for brain health. The most robust interventions are non-pharmacological and include limiting calorie or protein intake, increasing aerobic exercise, or environmental enrichment. In humans, dietary patterns including the Mediterranean, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) and Okinawan diets are associated with improved age-related health and may reduce neurodegenerative disease including dementia. Rapamycin, metformin and resveratrol act on nutrient sensing pathways that improve cardiometabolic health and decrease the risk for age-associated disease. There is some evidence that they may reduce the risk for dementia in rodents. There is a growing recognition that improving metabolic function may be an effective way to optimize brain health during aging.

1. Introduction

The world's population is aging rapidly. By 2050, it is expected that the global population will total nearly 9.8 billion people and strikingly, the fastest growing population are people over the age of 60; the number of people in this age group will reach 2.1 billion or 25% of the total global population (United Nations Department of Economic and Social Affairs/Population Division, 2017). Furthermore, aging is the greatest risk factor for most chronic diseases including cardiovascular disease, cancers, osteoporosis, arthritis, diabetes, and neurodegenerative disorders such as dementia (de Cabo and Le Couteur, 2015).

Neurodegenerative diseases are characterised by cellular and metabolic processes which accelerate during advanced age (Mattson and Arumugam, 2018). Mattson and Arumugam outlined the common characteristics of brain aging which include: (1) reduced DNA repair; (2) abnormal molecular waste disposal; (3) mitochondrial dysfunction; (4) oxidative damage; (5) neuronal calcium dysregulation; (6) impaired adaptive stress response; (7) inflammation; (8) stem cell exhaustion; and (9) abnormal neuronal network activity (Fig. 1). The authors attributed these characteristics to dysregulated brain energy metabolism which occurs during aging (Mattson and Arumugam, 2018).

The observation that the aging process and dementia share common characteristics suggests that the two processes are linked on cellular and molecular levels (Xia et al., 2018). The number of people worldwide with dementia numbered 47 million in 2015, and this number is set to triple by 2050 (Livingston et al., 2017). There is an urgent need to understand the factors that contribute to dementia in order to develop interventions that delay the onset of the disease or improve symptoms during aging. One concept in the field of aging biology is that lifestyle modifications can directly influence the rate of aging and may reduce the burden of age-associated disease, including dementia, in humans (Fontana et al., 2014; Fontana and Partridge, 2015). Many of these pharmacological and non-pharmacological interventions act on nutrient sensing pathways to influence systemic metabolic health, suggesting a key role for metabolic health in the pathogenesis of age-related diseases.

2. The spectrum of normal brain aging

There is a continuum in the molecular, microscopic and gross

Abbreviations: ACh, Acetylcholine; AD, Alzheimer's disease; PFC, Prefrontal cortex; MCI, Mild cognitive impairment; LOAD, Late-onset Alzheimer's disease; BDNF, Brain-derived neurotropic factor; PET, Positron emission tomography; MRI, Magnetic resonance imaging; LBD, Lewy body dementia; VD, Vascular dementia; FTD, Frontal temporal dementia; EE, Enriched Environment; MET, Metformin; NAFLD, Non-alcoholic fatty liver disease; Trp, Tryptophan; RAPA, Rapamycin; HFD, High fat diet; SIRT1, Sirtuin 1; RAS, Renin-angiotensin system; LPHC, Low-protein, high carbohydrate

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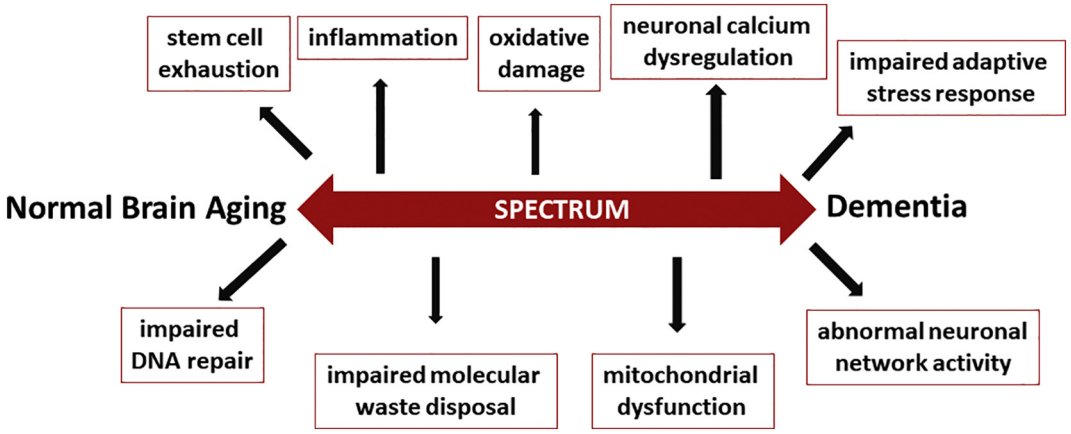

Fig. 1. The main hallmarks of normal brain aging are also present in dementia. These include: Reduced DNA repair, impaired molecular waste disposal, mitochondrial dysfunction, oxidative damage, neuronal calcium dysregulation, abnormal neuronal network activity, impaired adaptive stress response, inflammation, and stem cell exhaustion.

morphological characteristics of normal aging and many cases of late onset dementia (Wahl et al., 2016). The 'Hallmarks of Aging' (biological processes that underlie aging) inevitably occur in dementia, while many pathological features of dementia occur in older people without cognitive impairment. Therefore, it is often the degree of neuropathology (eg plaques and tangles in the case of Alzheimer's disease) that differentiates normal brain aging and dementia, rather than any specific pathological features (Anderton, 1997).

With old age there is an overall reduction in brain volume with the majority of grey matter shrinkage occurring in the hippocampus and prefrontal cortex (PFC) (Anderton, 2002). Aging brains also exhibit neuroinflammation (Barrientos et al., 2015) and disruption of calcium homeostasis (Nikoletopoulou and Tavernarakis, 2012; Verkhratsky and Toescu, 1998) which coincides with a decrease in brain-derived neurotrophic factor (BNDF). The cognitive changes associated with aging may be associated with slight alterations in synaptic physiology in the hippocampus and PFC (Morrison and Baxter, 2012). This can lead to reduced dendritic branching and spine counts in PFC neurons (Dumitriu et al., 2010). Aβ plaques and neurofibrillary tangles occur to some degree in many older people, and is not exclusive to neurodegenerative disease (Xekardaki et al., 2015).

Minor cognitive changes during normal aging are common (Fletcher et al., 2018). Declines in working memory (Stanley et al., 2015) and executive function (Kirova et al., 2015) are the most common functions to decline with aging. Spatial memory also commonly deteriorates during normal aging and is likely due to shrinkage of the hippocampus and surrounding entorhinal cortex (Coughlan et al., 2018; Epstein et al., 2017). Although less common, some additional changes may be seen in processing speed and attention (Harada et al., 2013). Problems with decision making and reasoning are common in older age, and linked with decline in cardiovascular function (Roberts et al., 2013). Importantly, these changes in brain function do not warrant the criteria for a diagnosis of dementia.

3. Defining dementia

Dementia is generally defined as a neurodegenerative condition that is progressive, influences a range of cognitive domains (Dening and Sandilyan, 2015) and impairs function. Dementia is associated with deterioration of memory, thinking, learning, comprehension, decision making and behaviour. By definition, dementia causes a loss of the ability to perform everyday tasks (World Health Organization, 2015). There are several subtypes of dementia which have distinct genetic and molecular aetiologies. The spectrum of dementia includes late-onset Alzheimer's disease (LOAD), vascular dementia (VD), Lewy body dementia (LBD), and frontotemporal dementia (FTD) (Table 1). Mild cognitive impairment (MCI) is considered to be the mid-point between normal cognition and dementia, and may share several molecular and pathological hallmarks with dementia (Petersen, 2016a).

Various imaging technologies are used to aid in the diagnosis of dementia in clinical practice and to determine the subtypes of dementia (Fig. 2) (Petersen, 2011; Petersen, 2016b). Magnetic resonance imaging (MRI) usually shows overall shrinkage in superficial cortical grey and underlying white matter, with further atrophy of the temporal lobes, frontal cortex, and hippocampi, regardless of the dementia subtype (Fig. 2a). There is reduction in neuronal glucose uptake as measured by fluorodeoxyglucose uptake on PET scans and this may be region-specific depending on the type of dementia (Fig. 2b). Positron emission tomography (PET) scans can identify amyloid aggregates (Fig. 2c) and Tau protein aggregation, which largely occurs in the temporal lobes and hippocampus particularly in LOAD (Fig. 2d) (Petersen, 2011).

3.1. Mild cognitive impairment

It is estimated that approximately 15% of older people are affected by MCI, but this percentage varies substantially depending upon diagnostic criteria (Roberts et al., 2008). Although patients with MCI do not meet the criteria for a dementia diagnosis, they are at increased risk of developing dementia, particularly if they have amnestic MCI (Petersen, 2016b) MCI is considered to represent early dementia, but many people with MCI do not develop dementia or may return to normal. The neuropathology of MCI is mixed, but amyloid plaques and neurofibrillary tangles may be detected, in association with atrophy on MRI and deposition of amyloid and tau on PET scans (Fig. 2). MCI may be linked to the Ɛ4 allele of *APOE* which increases the risk of Alzheimer's disease (Tervo et al., 2004). No pharmacological intervention has yet been shown to influence MCI or its progression to dementia (Tervo et al., 2004).

3.2. Late onset Alzheimer's disease

Early onset AD (before the age of 65 years) has a strong genetic component, and increasing age is not its major risk factor (Mendez, 2017) therefore, it is not discussed here. Although old age is the main risk factor for LOAD, it should be noted that there are several genes that increase the risk of LOAD. The main gene associated with LOAD is the Ɛ4 allele of Apolipoprotein E (*APOE*) (Goate et al., 1991; Guerreiro and Hardy, 2014; Saunders et al., 1993), which increases the risk of AD (unlike the genetic polymorphisms associated with EOAD which are directly causative). Other genetic studies have shown that as many as 20 genes or more (Rezazadeh et al., 2019) are associated with LOAD although their role in LOAD remains uncertain.

Table 1
Summary of the most prevalent forms of dementia and mild-cognitive impairment, prevalence, links to cardiometabolic health and lifestyle, molecular aetiologies, and most commonly used treatments. Aβ = amyloid beta; MAP = microtubule associated protein; NMDA = *N*-methyl-D-aspartate.

Neurodegenerative disorder	Prevalence	Suggested cardiometabolic and lifestyle links	Suggested molecular links	Most commonly used treatments	Selected references
Mild Cognitive Impairment	8.4% (65–69); 10.1% (70–74); 14.8% (75–79); 25.2% (80–84).	Obesity; metabolic syndrome; no physical activity; smoking	Aβ; Tau. ε4 allele of the *APOE* gene	No effective pharmaceutical treatments	(Petersen et al., 2018; Tervo et al., 2004)
Late onset Alzheimer's Disease	~50–56% as determined by autopsy	Obesity; diabetes; smoking; no physical activity; low social engagement; stroke; lack of cognitive stimulation	Aβ and Tau; loss of white and grey matter; oxidative damage; inflammation; synaptic failure; mitochondrial dysfunction; calcium dysregulation. ε4 allele of the *APOE* gene	NMDA receptor antagonists and acetylcholinesterase inhibitors	(Biessels and Despa, 2018; Bloom, 2014; Flicker, 2010; McGleenon et al., 1999; Querfurth and LaFerla, 2010)
Vascular dementia	4.1% 80–89 years; 6.1% > 90 years; oftentimes coexists with Alzheimer's	Stroke; hypertension; diabetes; heart disease; stroke; raised cholesterol; smoking; metabolic syndrome; obesity; no physical activity	Atherosclerosis; cortical lesions; cerebral haemorrhages. Possible links with mutations in the *APOE* gene	NMDA receptor antagonists and acetylcholinesterase inhibitors; Cholesterol lowering medications	(Biessels and Despa, 2018; Hebert and Brayne, 1995; Iadecola, 2013; O'Brien and Thomas, 2015; Smith, 2017; Zonneveld et al., 2018)
Lewy body dementia	~ 3.2% to 7.1% depending on stage of diagnosis	Stroke; obesity; no physical activity	Alpha-synuclein protein (Lewy bodies); amyloid β accumulation; mutations in the *SNCA* and *LRRK2* genes	Cholinesterase inhibitors; NMDA receptor antagonists; antidepressants	(Boot et al., 2013; Capouch et al., 2018; Emre et al., 2004; Hogan et al., 2016; Hyun et al., 2013; Mayo and Bordelon, 2014; Spillantini et al., 1997; Walker et al., 2015; Yang et al., 2018)
Frontotemporal dementia	~3-26% (< 65 years)	Diabetes; heart disease; bradycardia	Gliosis; microvascular changes; MAP misfolding and *tau* misfolding (Pick bodies). Mutations in *C9orf72, MAPT,* and *GRN* genes	Focused on behavioural issues associated with the disease	(Bang et al., 2015; Ferrari et al., 2014; Golimstok et al., 2014; Le Ber, 2013; Robles Bayon et al., 2014)

LOAD is the most prevalent form of dementia, responsible for about half of all cases of dementia (Querfurth and LaFerla, 2010). It has generally been accepted that LOAD is caused by aggregation of cortical amyloid plaques and tau protein tangles which lead to neuronal dysfunction and/or death (Lippens et al., 2007). Morphological changes include a reduction in dendritic branching in the PFC, a decrease in dendritic spine density, hippocampal and subcortical grey and white matter atrophy (Cummings, 2004). Another key feature of LOAD is a decrease in cerebral blood flow, which may also contribute to neuronal death, and suggests a cardiometabolic role in the pathogenesis of LOAD (Sweeney et al., 2018). Further cellular changes include mitochondrial dysfunction, increased oxidative stress, calcium dysregulation, and abnormal insulin signalling (Querfurth and LaFerla, 2010; Sanabria-Castro et al., 2017) which are also key 'Hallmarks of Aging'.

3.3. Vascular dementia

The human brain uses approximately 25% of total oxygen and glucose ingested, despite accounting for only 2–3% of the total body weight (Dekaban, 1978; Ozturk and Tan, 2018). Adequate blood supply to the brain is highly dependent on optimal cardiovascular function and cerebral vasculature. There is a close association between cardiovascular disease and dementia, including LOAD and VD. Cardiovascular risk factors in midlife are associated with subcortical white matter lesions, impaired vascular microstructure of the brain, and disrupted neuronal network activity, and contribute to the deterioration of higher cortical function during aging (Iadecola, 2013).

3.4. Lewy body dementia

LBD occurs mainly in people older than 65 years and is differentiated from other dementia mostly by the presence of parkinsonian features (Walker et al., 2015), and like Parkinson's disease, is associated with deposition of alpha-synuclein (Yang et al., 2018). In LBD, there may also be aggregation of amyloid and tau, suggesting some overlap with AD (Jellinger, 2018). There is a rare genetic link to LBD with mutations in the *SNCA* and *LRRK2* genes; *APOE* may also contribute to disease progression (Keogh et al., 2016).

3.5. Frontotemporal dementia

FTD often occurs in younger patients (45–64 years) and presents with behavioural disturbances (apathy, decline in socially appropriate behavior) and speech impairment which precede the onset of other dementia symptoms (Faber, 1999). Imaging shows pronounced atrophy of the frontal and temporal lobes (Bang et al., 2015). The risk of FTD is increased in people with diabetes, heart disease, and bradycardia (Golimstok et al., 2014; Robles Bayon et al., 2014). However, there is a strong genetic component to the disease. Mutations in the *C9orf72*, *MAPT,* and *GRN* genes account for about 60% of all cases of inherited early-onset frontotemporal lobar degeneration (Le Ber, 2013).

4. Therapeutic approaches for the treatment of dementia

Table 1 outlines the most common forms of dementia and the standard therapeutic approaches for their treatment, which are primarily pharmacological and usually prescribed after the disease has progressed to a moderate clinical severity (Jeschke et al., 2011). All pharmacological treatments are symptomatic with modest effects on measures of cognitive function, and no pharmaceutical intervention influences progression of dementia. These treatments were developed for LOAD and include acetylcholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor antagonists (Agatonovic-Kustrin et al., 2018). Acetylcholinesterase inhibitors counteract the low levels of the neurotransmitter acetylcholine (ACh) that contribute to memory impairment in dementia.

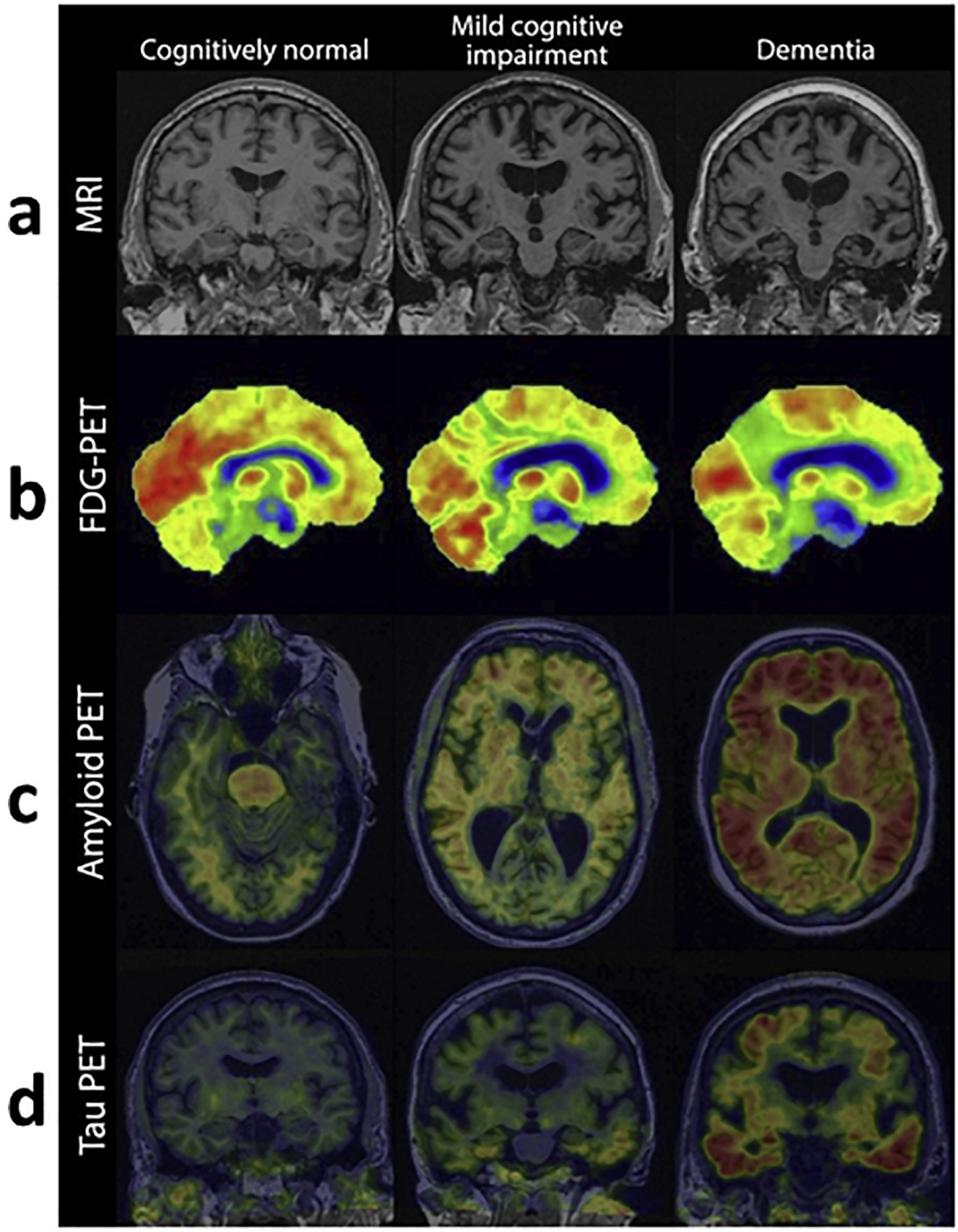

Fig. 2. The spectrum of dementia including the key markers for disease diagnosis as determined from imaging technology. MRI = magnetic resonance imaging; PET = positron emission tomography; FDG-PET = fluorodeoxyglucose positron emission tomography. Reproduced with permission from Wolters Kluwer Health, Inc. and Ronald C. Petersen, M.D., PhD from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5390929/figure/F4/. Magnetic Resonance Imaging: MRI; Fluorodeoxyglucose-positron emission tomography: FDG-PET; Positron emission tomography: PET.

The amyloid cascade hypothesis is at the forefront of research into new therapies for the treatment and prevention of AD (Gallardo and Holtzman, 2017; Hardy, 2006). This hypothesis proposes that aggregation of amyloid plaques and tau tangles is the main mechanism leading to neuronal death (Gomperts et al., 2008; Querfurth and LaFerla, 2010). There has been success with targeting amyloid using antibodies, vaccines and medications in animal models of dementia and AD (Sevigny et al., 2016), but this has not yet been translated into any successful phase III clinical trials in established dementia in humans (Le Couteur et al., 2016). Amyloid accumulation predates the onset of symptoms by decades, therefore there is continued hope that treatments that target amyloid may prevent AD if commenced early enough (Asih et al., 2014).

However, the failure of anti-amyloid therapies has led to reconsideration of other mechanisms for AD that might generate new therapeutic approaches or opportunities. Dementia may be the consequence of genetic and lifestyle risk factors impacting on the brain over the entire lifespan and the pathogenesis of dementia is likely to be multifactorial, requiring multifaceted therapies (Canter et al., 2016). Old age is the greatest risk factor for the development of dementia, while the deposition of amyloid and tau may be part of normal aging even in the absence of cognitive impairment. Post-mortem studies from

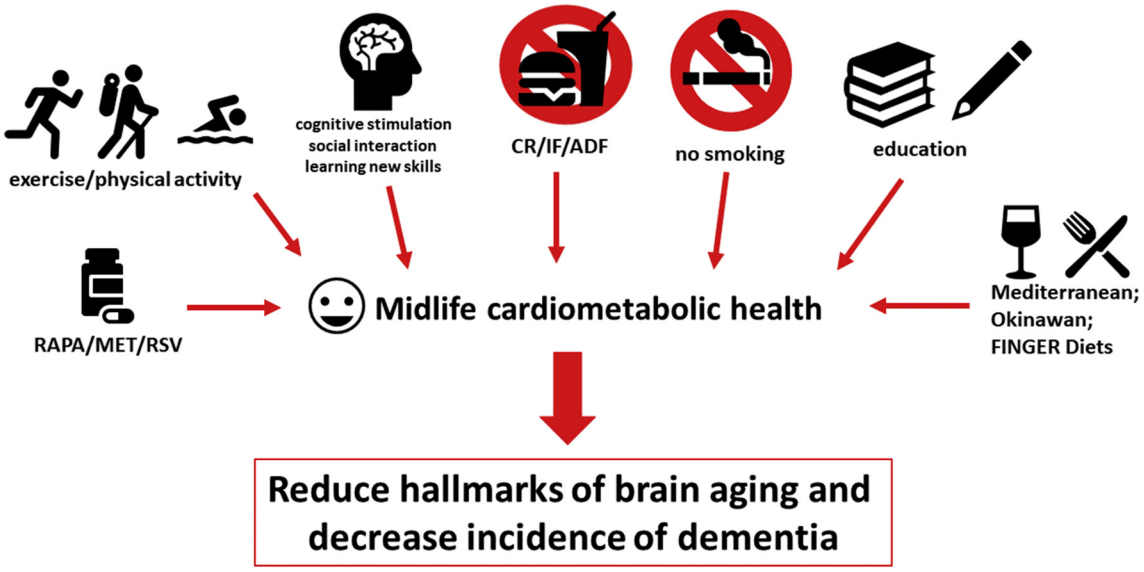

Fig. 3. Lifestyle factors, dietary intake, and pharmaceuticals that are associated with improved midlife cardiometabolic health. There is a strong link between midlife cardiometabolic health and dementia in later life. Applying lifestyle changes in midlife can reduce the incidence and burden of dementia in later life. Rapamycin: RAPA; Resveratrol: RSV; Metformin: MET; Caloric restriction: CR; Intermittent fasting: IF; Alternative day fasting: ADF.

several large cohorts (Savva et al., 2009) have revealed similar degrees of Alzheimer's neuropathology in cognitively normal older people compared to older people with dementia diagnoses. On one hand, these results might suggest that some people have a biological resilience to the neurotoxic effects of plaques and tangles, while on the other hand the results may also indicate that plaques and tangles are not solely responsible for AD (Ganz et al., 2018; Mufson et al., 2016). Therefore, a multidimensional approach for dementia has been proposed including lifestyle factors and pharmaceutical agents (Vina and Sanz-Ros, 2018). Interventions that influence the aging process may prove to be a useful part of this therapeutic armamentarium.

5. Modifiable risk factors and dementia

There is a strong association between midlife cardiometabolic health and the risk for dementia (Fig. 3). Regardless of the subtype of dementia, they share several risk factors which include obesity, metabolic syndrome and diabetes, heart disease and related conditions, smoking, and lack of cognitive interaction or brain stimulation (Topiwala et al., 2018) (Table 1). These type of risk factors suggest that there is an important potential role for lifestyle interventions in reducing the risk of dementia. Many of the lifestyle interventions that improve cardiometabolic health have also been shown to reduce the risk for dementia (at least in animal models) such as reduced calorie or protein intake and physical activity.

5.1. High saturated fat diet

It is well established that a mid-life atherogenic diet negatively affects cardiometabolic health and contributes to the development of neurodegenerative disease. A high fat diet (HFD) leads to insulin resistance, hypertension, inflammation, and vascular alterations (Freeman et al., 2014), all of which may contribute to dementia. Additional detrimental effects of a saturated high-fat diet include loss of blood supply to the brain which can contribute to the loss of white matter and adverse cognitive effects (Anjum et al., 2018). A chronic HFD causes increased microglial activation, increased hippocampus amyloid burden, and reduced memory performance in triple-transgenic mouse models of AD (Barron et al., 2013; Knight et al., 2014). Reversal of a high-fat diet in mice led to a complete amelioration of memory loss, which was partly associated with rescue of cerebral blood flow (Johnson et al., 2016).

The negative effects of a high-fat diet have been documented in humans (Spencer et al., 2017). In middle-aged adults, high saturated fat consumption is associated with poorer memory (Oleson et al., 2017) and may contribute to a reduction in total hippocampus volume (Mestre et al., 2017). A number of studies have demonstrated that both humans and animals consuming a diet high in fat and/or sugar consistently performed worse on memory tasks; the decline in memory function was secondary to atrophy and reduced functioning of the medial temporal lobes and hippocampi (Yeomans, 2017). High-fat diets compromise the hippocampus by sensitizing the immune cells (most likely microglia) thus priming inflammatory responses to subsequent challenging stimuli. Moreover, high saturated fat diets have been linked to elevated pro-inflammatory cytokines (Giugliano et al., 2006) which in the hippocampus can lead to deterioration of many mechanisms that enable synaptic plasticity and in turn long-term memory. A recent meta-analysis reported that intentional weight loss in people with obesity was sufficient to reverse cognitive decline, improve executive function, and heighten memory performance (Siervo et al., 2011).

5.2. Sedentary lifestyle

Sedentary lifestyles are becoming an intrinsic part of modern society, encouraged by technological advances. Older people may be particularly prone to the negative effects of a sedentary lifestyle (Bailey, 2017). It is well established that sedentary lifestyles contribute to chronic illnesses (Byrne et al., 2018) including obesity, diabetes mellitus, non-alcoholic fatty liver disease (NAFLD) and cardiovascular disease (Al-Dayyat et al., 2018). There is emerging evidence that a sedentary lifestyle has adverse effects on the brain. In a recent study, sedentary behaviour was associated with reduced medial temporal lobe thickness in adults which may coincide with reduced memory function during aging (Siddarth et al., 2018). Another study suggested that MCI and subsequent dementia risk are closely associated with sedentary behaviour while exercise reduced the associated risk of MCI and dementia (Falck et al., 2017).

5.3. Lack of social interaction

Social interaction, especially later in life, is important for brain health during aging. An active and socially integrated lifestyle may

protect against dementia (Fratiglioni et al., 2004). Cardiometabolic studies have indicated that remaining socially active has positive effects on reducing stress and improving cardiovascular health in later years, and therefore may provide a mechanism for the effectiveness of cognitive stimulation on delaying the risk for dementia (Fratiglioni et al., 2004). Several longitudinal studies have demonstrated that rich social networks, learning novel activities, and increased information processing (i.e. learning new skills: musical instrument, playing board games, learning a new dance) to which one is not typically accustomed, results in a lower probability of cognitive decline in later life (Hultsch et al., 1999). Measures of cognitive activity, self-improvement, and domestic activity in middle to later life are also inversely correlated with a risk of dementia (Crowe et al., 2003).

Studies in rodents have demonstrated that enriched environment (EE) housing reduces dementia-related neuropathology. When rodents are housed in an EE they are provided with stimulating objects, more space to move about and to sleep, and 5–6 interacting cage mates. It was recently demonstrated that EE housing conditions reduced astroglial degeneration in a mouse model of LOAD (Rodriguez et al., 2013). Exposure to EE reduced the severity of pathology in a mouse model of Alzheimer's, provided long-term protection against cognitive impairment (Verret et al., 2013), and protected against amyloid pathologies and memory deficits in a HFD mouse model (Maesako et al., 2012). Similar results have pointed towards improved memory scores in humans with more social interaction and who remain energetic at home with cognitive and physical training (Hultsch et al., 1999). Interestingly, there is a strong link between early-life education and the risk of dementia, suggesting that people with fewer years of educational schooling may be at a higher risk of dementia (Sharp and Gatz, 2011).

5.4. Insulin resistance

Data from epidemiological studies suggest that obesity, insulin resistance and type 2 diabetes at midlife are key risk factors in the pathogenesis of cognitive impairment and AD (Tolppanen et al., 2014). Peripheral insulin resistance and associated compensatory hyperinsulinemia seem to play a central role in the progression of AD even in the absence of elevated plasma glucose levels. In the Rotterdam study, insulin resistance and elevated baseline insulin levels were associated with a 40% greater risk of conversion to AD over a 3-yr period (Schrijvers et al., 2010) Both excessive adiposity and insulin resistance are associated with systemic inflammation and amyloid deposition in the human brain (Fishel et al., 2005). Peripheral insulin resistance is associated with impaired glucose uptake in the precuneus and prefrontal cortex (Baker et al., 2011) and abnormal brain insulin binding. Brain insulin resistance has recently been shown to occur in AD even in the absence of peripheral insulin resistance (Talbot et al., 2012) while AD-related pathology typically occurs in brain regions with a high density of insulin receptors, such as the hippocampus, the prefrontal cortex, the cingulate cortices, and the precuneus (Craft and Watson, 2004; Henneberg and Hoyer, 1995; Zhao et al., 2004). Interestingly, in nonhuman and human primates (Blalock et al., 2010; Garcia-Casares et al., 2014; Raji et al., 2010; Rasgon et al., 2011; Willette et al., 2012) peripheral insulin resistance predicts neural atrophy in these regions. In summary, insulin resistance affects multiple neurodegenerative processes that are deeply implicated in AD etiopathogenesis.

5.5. Smoking

Chronic tobacco smoking has many adverse health outcomes including diabetes, cardiovascular disease, cancers, lung disease and dementia (Topiwala et al., 2018). Smoking is a major risk factor for cerebrovascular disease which is a major risk factor for dementia (Vijayan and Reddy, 2016). Smoking results in increased cerebral amyloid burden, oxidative stress, and thinning of brain cortical tissue, leading to irreversible memory loss in humans (Durazzo et al., 2014; Karama et al., 2015).

5.6. Dietary protein and branched chained amino acids

In mice, ad-libitum low-protein, high-carbohydrate (LPHC) diets promote cardiometabolic health and longevity (Solon-Biet et al., 2014; Solon-Biet et al., 2015a). Conversely, high-protein, low-carbohydrate diets adversely affected cardiometabolic health parameters. Similar results have been reported in observational studies in humans. It was hypothesised that this may have partly been due to dietary protein particularly branched-chain amino acids (BCAAs) increasing activation of hepatic mechanistic target of rapamycin (MTOR) (Solon-Biet et al., 2015b). A recent study demonstrated that long term consumption of diets high in BCAAs led to hyperphagia and reduced lifespan in male and female mice, which was associated with reduced tryptophan uptake and serotonin synthesis in the brain (Solon-Biet et al., 2019).

The effects of ad-libitum LPHC diets and caloric restriction on hippocampus biology has been reported in mice. LPHC diets conferred positive effects on hippocampus health in male and female mice including increased dendritic spine density in the dentate gyrus, reduced markers of neuroinflammation, increased expression of pro-longevity genes, and improved markers of cognition (Wahl et al., 2018b). Increased dietary BCAAs resulted in a microglia mediated pro-inflammatory cytokine response resulting in neurotoxicity (De Simone et al., 2013) and high protein diets worsened spatial memory in rats (Mendez-Lopez et al., 2015). Another study demonstrated that mice consuming a high-protein diet had lower brain weights and hippocampus neuronal density than their counterparts consuming a standard diet (Pedrini et al., 2009).

The link between a high protein diet and cardiovascular health in humans has been examined with results indicating that increased protein intake is correlated with an increased risk of heart failure and type-2 diabetes (Virtanen et al., 2018). This finding may provide a clue into potential adverse effects of a chronic high protein diet on brain aging. In humans there is limited evidence to suggest that high protein diets negatively affect brain health during aging with one study suggesting that humans consuming a high-protein diet (esp. from animal sources) had a higher risk of MCI (Ding et al., 2018). The source of protein plays an important role in the association between protein intake and cognition. A recent study found that diets high in legumes and/or plant protein sources were associated with improved cognitive performance as opposed to red meat consumption (Mazza et al., 2017). The mechanisms by which plant protein may confer cognitive benefits are still under investigation. However other studies have reported that high protein and fiber diets may be protective against dementia in humans, partly by reducing plasma and brain Aβ levels (Fernando et al., 2018).

5.7. Excessive alcohol consumption

A recent study highlighted the risk for excessive alcohol consumption (> 100 g/week) on cardiometabolic health by showing a positive linear correlation with alcohol consumption and all-cause mortality (Wood et al., 2018). The effects of excessive alcohol consumption on the brain is thought to be detrimental, in part due to increased inflammation (Flores-Bastias and Karahanian, 2018). A recent review pointed to excessive alcohol consumption as one of the main contributors – up to 24% – of cases of dementia. Excessive alcohol consumption is linked to loss of brain tissue (Harper, 1998) and might also affect cognition via cerebrovascular disease related to alcohol-related increases in triglycerides and blood pressure (Gupta and Warner, 2018).

6. Current therapeutic opportunities

There is evidence that lifestyle factors in middle age can influence the development of dementia in later life. Several lifestyle factors, including exercise, cognitive stimulation, and diet are associated with

aging, age-related health and brain aging (Wahl et al., 2017). There is now interventional evidence that these types of approaches are effective in non-human primates and humans (Fontana, 2018; Most et al., 2017). There are other lifestyle interventions that have mostly been studied in relationship to aging, rather than age-related diseases. In particular, these include various types of restricted diets which have been shown to improve health, and there is some evidence they might reduce the risk for dementia as well.

6.1. Restricted diets

One of the most robust nutritional interventions that improves cardiometabolic health and delays aging is caloric restriction (Fontana, 2018; Fontana and Partridge, 2015; Most et al., 2017), which can be accomplished by reducing daily caloric intake, intermittent fasting, or alternative day fasting. Calorie restriction is defined as a total reduction of daily caloric intake by 10% - 50% without malnutrition and with inclusion of all essential dietary vitamins and minerals (Mitchell et al., 2016). Alternatively, dietary restriction can be provided in the form of intermittent fasting or alternative day fasting, whereby an animal is given full access to food for a short period of time but with long fasting periods in between. These periods can range from 8 h (intermittent fasting) to 24 h (alternative day fasting) (Mattson et al., 2017).

These nutritional interventions delay the onset of neurodegeneration in rodents. On an evolutionary scale, it has been suggested that a brain functions at best when moderately challenged with a reduction in food intake so that an animal must 'outwit' competitors in order to eat (Mattson et al., 2003). In addition to reducing stress insults and improving neuronal plasticity, there is evidence that restricting caloric intake prevents most of the major hallmarks of brain aging (Table 2) in non-human primates and humans (Pani, 2015). Moreover, dietary restriction reduces the accumulation of β-amyloid and γ-secretase in mice (Schafer et al., 2015), reduces age-related behaviour deficits in a triple-transgenic model of AD and protects against tau-related pathologies (Halagappa et al., 2007). Caloric restriction may be an effective treatment to reduce dementia pathologies in non-human primates where is reduces amyloid pathologies in the temporal cortex (Qin et al., 2006) and prevents astrogliosis and brain inflammation (Sridharan et al., 2013).

Data from randomized clinical trials in humans show that caloric restriction without malnutrition has a profound effect in improving insulin sensitivity, reducing inflammation and oxidative stress. Results from the multicenter CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) trial show that caloric restriction is a feasible and effective intervention. Over two years, participants in the caloric restricted group achieved 11.7% CR and a sustained 10% weight loss, of which 71% was fat mass loss. Caloric restriction induced major improvements in insulin sensitivity, as reflected in significantly lower HOMA-IR, HOMA-β, insulin response and increased insulin sensitivity index, fasting and AUC-insulin, C-reactive protein, TNFα, F2-isoprostanes, LDL-cholesterol, total cholesterol to HDL-cholesterol ratio, systolic and diastolic blood pressure, which are all factors implicated in the pathogenesis of AD (Il'yasova et al., 2018; Weiss et al., 2006).

The effects of other types of restricted diets on brain pathology have been studied in several animal models. Intermittent fasting prevented cognitive deficits in a transgenic model of AD in mice (Halagappa et al., 2007). Multiple mechanisms by which intermittent fasting protects brains cells have been proposed including increased production of neurotrophic factors (e.g. BDNF and FGF2), protein chaperones (e.g., HSP70 and GRP78) and antioxidant enzymes (e.g. heme oxygenase 1) and suppression of neuro-inflammation (Arumugam et al., 2010; Yu and Mattson, 1999). Recent findings from other animal studies also suggest that alternate day fasting can have similar beneficial effects to caloric restriction, even with relatively modest 10–25% reductions in overall calorie intake (Anson et al., 2003; Wan et al., 2003; Wan et al., 2004).

In addition to reducing overall caloric intake, restricting dietary protein has also shown promise for improving metabolic health and protect the brain during aging. In humans, protein restriction has been associated with improved metabolic health, increased insulin sensitivity and reduced morbidity (Mirzaei et al., 2014). In a mouse model of AD, protein restriction cycles reduced phosphorylated tau and improved behavioural performance (Parrella et al., 2013). There are as yet no studies of protein restriction and dementia in humans.

The restriction of certain amino acids including methionine (Herring et al.) and tryptophan (Trp) improves healthspan and lifespan, and therefore may improve brain health. Met restriction improves lifespan by suppressing the MTOR-nutrient sensing pathway, promoting stress resistance and reducing inflammation. Met restriction also improves insulin sensitivity and mitochondrial function (Ables and Johnson, 2017). Trp restriction is beneficial in modulating thermogenesis and reducing body weight in obese rats (Zapata et al., 2018). These positive effects of specific amino acid restriction on metabolic health warrant further investigation.

7. Dietary patterns

Dietary patterns characterised by high vegetable, legumes, minimally processed whole grains, fruit, fish and unsaturated fat combined with limited meat and saturated fatty acids intakes such as the Mediterranean diet (Bloomfield et al., 2016; Castellani et al., 2010; Cooper et al., 2015; Etgen et al., 2011; Frisardi et al., 2010; Knight et al., 2016; Lourida et al., 2013; Morris, 2016; Petersson and Philippou, 2016; Solfrizzi et al., 2011; Tosti et al., 2018; van de Rest et al., 2015), traditional Japanese diet (Kiyohara, 2014; Tomata et al., 2016), and FINGER diet (Ngandu et al., 2015) have been shown to improve health and may lower the incidence of dementia. A number of mechanisms have been proposed mostly via vascular, antioxidant, and anti-inflammatory pathways (Feart et al., 2013).

7.1. Mediterranean diet

Characterised by high monounsaturated fat, vegetables and fruit and limited animal protein, the Mediterranean dietary pattern has been liked to positive health outcomes such as reduction in cardiometabolic disease (Dai et al., 2008) and improved cognitive health. The high fiber, antioxidant and monounsaturated fat content of this type of dietary pattern has been linked to reduction in inflammation (Chrysohoou et al., 2004). Numerous studies have shown that strict and long-term adherence to the Mediterranean diet protects against cognitive decline and dementia in older humans (Anastasiou et al., 2017; Solfrizzi et al., 2017; Tanaka et al., 2018).

7.2. FINGER diet

The FINGER nutritional study is one of the largest and longest population-based multidomain randomized controlled trials to investigate the effects of several lifestyle factors on health and the brain. Participants in the intervention group were provided with tailored diets with high consumption of fruit, vegetables, fish, wholegrain cereals and reduced intake of simple sugars. Positive effects were seen on overall cognition, executive functioning and processing speed (Ngandu et al., 2015).

7.3. Japanese diet

The traditional Japanese diet contains high amounts of vegetables, fruit, legumes, omega-3 fatty acids and low amounts of meat and dairy products, and has been linked with lower incidence of dementia (Tomata et al., 2016). The Japanese diet is high antioxidants such as green tea and seaweed, which play a protective role against

Table 2
The main hallmarks of brain aging, adapted from (Mattson and Arumugam, 2018), which are linked to dementia. Several interventions have been associated improving the molecular aspects of brain aging in rodents, non-human primates, and humans. Here, the most commonly studied and reproduced interventions are included. Importantly, most of those interventions are also known to improve cardiometabolic health and increase lifespan. A "✓" symbol indicates that the intervention positively influences that particular aspect of brain aging. BBB = blood brain barrier; BDNF = brain-derived neurotropic factor; CRP = C-reactive protein; DR = dietary restriction; EE = environmental enrichment; HFD = high fat diet; PFC = pre-frontal cortex; RAPA = Rapamycin; MET = Metformin; RSV = Resveratrol; CR = Calorie restriction; IF = intermittent fasting; ADF; alternative day fasting; LTP = long-term potentiation; ROS = reactive oxygen species.

Aging brain hallmark	Species	Dietary interventions (CR, IF, ADF)	Exercise/physical activity	Social interaction	Pharmaceutical interventions (RAPA/RSV/MET)
Impaired DNA repair	Rodents	✓ Improves DNA Polymerase β activity in neurons (Swain et al., 2016); reduces 8-hydroxyadenine (Sohal et al., 1994)	✓ Increases mtDNA repair (Bo et al., 2014); and DNA repair (Raefsky and Mattson, 2017)	✓EE decreases hippocampus levels of 5-hydroxymethylcytosine. May reduce DNA damage (Irier et al., 2014)	✓ RSV activates NAD^+ repair mechanisms (Scheibye-Knudsen et al., 2014)
	Non-human primates	✓ Improves mitochondrial DNA repair (Ingram et al., 2007)	Not yet known.	Not yet known.	Not yet known.
	Humans	✓ Increased DNA repair of human blood mononuclear cells (Matt et al., 2016).	✓May reduces DNA damage. More studies needed (Schmidt et al., 2016)	Not yet known.	✓RSV may promote DNA repair. More studies needed (Lopez-Miranda et al., 2012).
Impaired molecular waste disposal	Rodents	✓Inhibits apoptosis (Mattson et al., 2001); promotes autophagy (Liu et al., 2017)	✓ Induces autophagy (He et al., 2012b); also in peripheral tissues (He et al., 2012a)	Not yet known.	✓RAPA increases autophagy (Zhai et al., 2018)
	Non-human primates	✓May improve molecular waste disposal (Madeo et al., 2015).	Not yet known.	Not yet known.	✓RSV reduces markers of apoptosis (Bernier et al., 2016)
	Humans	✓Activates autophagy pathways. More studies needed (Longo and Mattson, 2014).	✓May improve metabolic waste clearance. More studies needed (Gallaway et al., 2017)	Not yet known.	✓RSV improves molecular waste disposal (Kennedy et al., 2010; Sarubbo et al., 2017)
Mitochondrial dysfunction	Rodents	✓Increases mitochondrial respiratory activity (Cerqueira et al., 2012) and health (Mattson, 2010; Nicoletti et al., 2005)	✓ Increase in mitochondrial density and biogenesis (Bernardo et al., 2016; Bo et al., 2014; Steiner et al., 2011)	✓EE protects mitochondria (Lores-Arnaiz et al., 2010)	✓MET and RSV improves mitochondrial function (Jardim et al., 2018; Pintana et al., 2012; Suski et al., 2016)
	Non-human primates	✓ CR may exert positive effects on mitochondrial DNA (Ingram et al., 2007)	✓May improve mitochondrial health but no clear studies to date (Thomas et al., 2012)	Not yet known.	✓RSV improves proteomic markers of mitochondrial health (Swomley et al., 2017)
	Humans	✓Fasting and re-feeding may confer protection for mitochondria by reducing SOD2 activity (Traba et al., 2015)	✓May benefit mitochondrial health (Moreira et al., 2017)	✓Optimal mitochondria function is critical for memory function (Todorova and Blokland, 2017)	✓RSV may improve mitochondria health. More studies needed. (Witte et al., 2014)
Abnormal neuronal network activity	Rodents	✓CR exerts a positive influence on neuronal network activity (Martin et al., 2016)	✓Promotes neurogenesis, improves neurotransmitter concentrations (van Praag, 2008)	✓Positive impacts on neuronal connections (Kramer et al., 2004) and LTP (Davis et al., 2004)	✓RAPA improves LTP in mice (Fu et al., 2017); RAPA improves brain vascular integrity (Lin et al., 2013)
	Non-human primates	✓CR improves white matter integrity (Bendlin et al., 2011)	✓Increases the vascularity of motor cortices (Rhyu et al., 2010)	✓Increases activity of neurons in the PFC (Constantinidis and Klingberg, 2016; Qi and Constantinidis, 2013); Increases neuronal connections (Floeter and Greenough, 1979)	✓RSV improves proteomic markers of neurotransmission (Swomley et al., 2017)
	Humans	✓May enhance neuronal plasticity and synaptic morphology (Mattson, 2010; Mattson et al., 2017)	✓May improve neural network circuitry (Chapman et al., 2015); neurogenesis (Ma et al., 2017); networks (Voss et al., 2016); processing (Gutmann et al., 2018)	✓ Increases activity of PFC (Constantinidis and Klingberg, 2016; Qi and Constantinidis, 2013); Can improve brain integrity (May, 2011)	✓RSV enhances hippocampus connectivity (Witte et al., 2014); MET increases white matter (Huang et al., 2014)
Impaired adaptive stress response	Rodents	✓CR protects against toxicity (Di Biase et al., 2017); promotes adaptive stress response (van de Ven et al., 2006)	✓Reduces brain stress responses and promotes resilience (Pietrelli et al., 2018)	✓EE reduces stress in mice (Hannan, 2014); improves responses to stress (Fernandez et al., 2004)	✓RSV reduces HFD oxidative stress (Bernier et al., 2016); MET reduces stress response (Garg et al., 2017); RAP reduces stress (Kolosova et al., 2013)
	Non-human primates	✓CR reduces oxidative stress (Maswood et al., 2004) and glucoregulatory dysfunction (Willette et al., 2012)	✓Increases BDNF and reduces CRP levels (Mitchell et al., 2010a)	✓Cognitive stimulation enhances cognitive behaviour (Woo et al., 2018)	✓RSV reduces markers of oxidative stress (Swomley et al., 2017)
	Humans	✓Increases cortisol; return to baseline after a short time; adaptation to the		Not yet known.	

(*continued on next page*)

Table 2 (*continued*)

Aging brain hallmark	Species	Dietary interventions (CR, IF, ADF)	Exercise/physical activity	Social interaction	Pharmaceutical interventions (RAPA/RSV/MET)
		stress of fasting (Nakamura et al., 2016)	✓Promotes stress resistance (Fleshner et al., 2011); increases BDNF (Mokhtarzade et al., 2018)		✓RSV supplementation may improve stress responses in the human brain. More studies needed (Sun et al., 2010)
Neuronal calcium dysregulation	Rodents	✓ DR is beneficial for calcium signalling in the brain (Mattson et al., 2001)	✓Promotes calcium homeostasis (Mattson and Magnus, 2006)	✓EE improves neuronal calcium signalling in rat hippocampus (Stein et al., 2016)	✓RSV improves calcium signalling in cortical neurons (Zhang et al., 2013)
	Non-human primates	✓ DR and CR improves brain calcium signalling (Mattson, 2008)	✓May be effective in promoting calcium homeostasis (Stranahan and Mattson, 2012)	Not yet known.	✓RSV affects calcium homeostasis (Swomley et al., 2017)
	Humans	✓DR may improve calcium signalling but not yet a firm consensus (Gleichmann and Mattson, 2011).	✓May be effective in promoting calcium homeostasis. More studies needed. (Stranahan and Mattson, 2012)	Not yet known.	Not yet known.
Inflammation	Rodents	✓CR reduces markers of brain inflammation (Pani, 2015)	✓Reduces markers of brain inflammation (E et al., 2014; Gu et al., 2014)	✓EE reduces inflammation (Chen et al., 2017; Smith et al., 2018)	✓RSV and MET protect against inflammation (Jeong et al., 2016; Okawara et al., 2007; Ou et al., 2018)
	Non-human primates	✓CR reduces inflammation (Mascarucci et al., 2002; Willette et al., 2013)	✓Lowers levels of CRP; increases BDNF (Mitchell et al., 2010b)	✓Reduces brain inflammation (Hennessy et al., 2017)	✓RSV reduces markers of inflammation (Bernier et al., 2016)
	Humans	✓ADF reduces inflammation (Johnson et al., 2007) and inflammatory cytokines (Witte et al., 2009)	✓Reduces BBB permeability and inflammation (Ford, 2002; Mokhtarzade et al., 2018)	✓May reduce inflammation (Sartori et al., 2012); Reduces pro-inflammatory cytokines (Pesce et al., 2017)	✓RSV reduces inflammation (Berman et al., 2017)
Stem cell exhaustion	Rodents	✓CR improves cell division in the hippocampus (Park et al., 2013); enhances neurogenesis (Hornsby et al., 2016)	✓Increases neurogenesis (Jiang et al., 2018; Radak et al., 2016; Yu et al., 2014)	✓EE increases synapses (Anderson et al., 1994); stem cells (Kramer et al., 2004); granule cells (Kempermann et al., 1997)	✓MET enhances neurogenesis (Wang et al., 2012); promotes proliferation of neural precursor cells (Fatt et al., 2015)
	Non-human primates	DR may increase neural stem cell proliferation. More studies needed (Park and Lee, 2011)	Not yet known.	Not yet known.	Not yet known.
	Humans	✓DR may increase neural progenitor cell proliferation (Park and Lee, 2011)	✓Increases stem cell proliferation (Pereira et al., 2007; Xing et al., 2018)	Not yet known.	✓MET enhances neurogenesis (Wang et al., 2012); stimulates stem cells (Fatt et al., 2015)
Oxidative damage	Rodents	✓ DR reduces markers of oxidative damage (Maalouf et al., 2009)	✓Reduces oxidative stress (Goto et al., 2007); and inflammatory damage (de Castro et al., 2017); improves memory (Cui et al., 2018)	✓EE prevents oxidative stress; Improves memory (Cechetti et al., 2012) (Fernandez et al., 2004)	✓ RSV may protect against oxidative stress (Okawara et al., 2007); MET reduces stress (Garg et al., 2017); RAPA decreased ROS (Fu et al., 2017)
	Non-human primates	✓ CR reduces markers of oxidative stress (Colman and Anderson, 2011); More conclusive studies needed.	May protect against oxidative stress; More studies needed (Garcia-Mesa et al., 2016)	✓Working memory is associated with lower markers of oxidative damage (Hara et al., 2014)	✓RSV confers stress protection (Bernier et al., 2016)
	Humans	✓CR protects neuroblastoma cells from lipid peroxidation (Hyun et al., 2006)	✓Reduces markers of oxidative stress (Camiletti-Moiron et al., 2013; Franzke et al., 2018; Roh et al., 2017)	✓Reduces markers of oxidative stress in blood plasma and improves antioxidant potential (Pesce et al., 2018)	✓ RAPA may sensitize glioma cells to hypoxia induced cell death (Thiepold et al., 2017); RSV may protect against oxidative stress (Sun et al., 2010)

cardiovascular disease and cognitive decline (Grant, 2014). Interestingly, recent changes to the Japanese diet towards a more Western diet (animal-based protein, saturated fat, cholesterol and alcohol) has partially contributed to an increase in obesity and dementia rates (Grant, 2014).

7.4. Ketogenic diet

A ketogenic diet, which is high in fat and low in carbohydrate and protein, has improved some aspects of cardiometabolic health. Ketogenic diet reduces obesity and diabetes and may reduce the onset of neurodegenerative disease by decreasing oxidative damage and metabolic stress (Paoli et al., 2014). In mice, a ketogenic diet reduced midlife mortality and improved memory (Newman et al., 2017), rescued hippocampal deficits and increased neurogenesis in a mouse model of Kabuki syndrome (model of intellectual disability) (Benjamin et al., 2017). Additional studies have suggested that a diet supplemented with ketone bodies in middle-age may delay the onset of neurodegenerative disease (Hertz et al., 2015).

8. Exercise and physical activity

Exercise and physical activity are robust, non-pharmacological interventions that improve cardiometabolic health, increase longevity, and reduce most hallmarks of brain aging (DiMenna and Arad, 2018; van Praag et al., 2014). Many studies have investigated the effects of physical activity in rodents, but there is now emerging evidence that physical exercise can reduce the burden of neurodegenerative disease in non-human primates and humans. In addition to reducing most hallmarks of brain aging (Table 2), it has been shown that running reduced amyloid plaques, inflammation and oxidative stress in TgCRND8 (a model of late-onset Alzheimer's) mice (Herring et al., 2016). Physical exercise improved memory by increasing hippocampal neurogenesis and preventing Aβ-related cognitive deficits in a mouse model of Alzheimer's disease (Sun et al., 2018).

Many studies have demonstrated the beneficial effects of exercise and physical activity in humans. Physical (particularly aerobic) exercise interventions are associated with improved memory performance and executive function in humans with neurodegenerative disease (Guitar et al., 2018). Physical exercise in patients with mild Alzheimer's disease resulted in an improvement in VO_2 max and those changes were associated with an improvement in cognitive function (Sobol et al., 2018). Another intervention study showed that 6-months of physical activity (150 min of moderate intensity per week) mildly improved memory scores of participants over the age of 50 years, who had previously reported memory problems (Lautenschlager et al., 2008). Additional studies revealed that physical aerobic exercise benefits global cognitive function in older individuals with MCI and may therefore be protective against dementia (Song et al., 2018).

9. Nutrient sensing metabolic pathways

Diet influences aging via a group of cellular pathways called nutrient sensing pathways, and altered signalling in the nutrient sensing metabolic pathways influences cardiometabolic health and aging (Zemke et al., 2007). There are several compounds that act on these nutrient sensing pathways and improve health. These include rapamycin, metformin, and resveratrol. There is some evidence that these compounds may possibly reduce the risk for dementia. Most of these studies have been investigated in rodents; however, there are now some data in non-human primates and humans (Table 2).

9.1. Rapamycin

Rapamycin inhibits MTOR activity and extends lifespan in male and female mice (Ehninger et al., 2014). In addition to improving cardiometabolic health (Sabatini, 2017), RAPA supplementation may also be effective in attenuating most hallmarks of dementia. MTOR regulates many cell processes, such as autophagy and neuronal proliferation that are involved in dementia (Maiese, 2018). RAPA supplementation reduces specific molecular hallmarks of dementia in most rodent models. For example, RAPA reduced demyelination and tau aggregates in OXYS (an accelerated model of aging) rats (Kolosova et al., 2013). RAPA improved memory performance in mouse models of AD, reduced amyloid plaque loads and restored cerebral blood flow (Richardson et al., 2015). These positive results in rodents warrant translational studies in humans.

9.2. Metformin

Metformin is an agonist of AMPK and is widely prescribed for the management of type-2 diabetes. Metformin has a wide range of effects on aging, including reduction in the rates of cancers, inflammation, and increased lifespan (Novelle et al., 2016). There have been several studies in rodents that demonstrate that metformin improves cardiometabolic health and increases lifespan. Intermittent metformin supplementation reduced body weight and improved markers of cardiometabolic health in mice, without impacting food consumption (Alfaras et al., 2017). Prolonged metformin supplementation improved healthspan and lifespan in mice by increasing antioxidant protection and AMPK activity (Martin-Montalvo et al., 2013). In terms of the brain, metformin improved spatial memory performance and reduced neuron loss and amyloid plaque load in APP/PS1 mice (Ou et al., 2018) and improved markers of hippocampal neurogenesis, even when compared to mice treated only with the cholinesterase inhibitor, donepezil (Ahmed et al., 2017). Metformin protected brains from the detrimental effects of an HFD in rats by reducing amyloid plaque load (Asadbegi et al., 2016).

In humans metformin coupled with donepezil improved memory and cognitive function in patients with vascular cognitive impairment (Lin et al., 2018) and improved memory performance in older adults with MCI (Luchsinger et al., 2016). Another human study revealed that metformin supplementation for > 6 years was associated with a lower risk of cognitive decline and the authors partially attributed these findings to improved insulin sensitivity (Ng et al., 2014).

9.3. Resveratrol

Resveratrol (RSV) is a naturally occurring polyphenol compound that is commonly found in red wines and the skin of berries. RSV allosterically activates the enzyme Sirtuin 1 (SIRT1) which is a key nutrient sensing pathway. It is one of the most widely studied compounds in aging research. RSV improves cardiometabolic health and promotes longevity in organisms ranging from yeast to humans (Novelle et al., 2015; Wahl et al., 2018a). RSV led to improved cognitive function, increased synaptic plasticity and reduced brain inflammation (Cao et al., 2018). RSV reduces fibrillary amyloid deposition (Ge et al., 2012), clears Aβ peptides, and reduces the burden of plaques and tangles in rodents (Jia et al., 2017). RSV supplementation may also reduce oxidative stress, improve neuronal energy homeostasis and promote neuronal autophagy (Bastianetto et al., 2015).

In humans, RSV is well tolerated, and possibly influences AD biomarker trajectories (Sawda et al., 2017). A number of small human studies in humans have indicated that RSV supplementation might improve cerebrovascular function, cognition, and reduces the risk of developing dementia (Evans et al., 2016) while others have reported no effects (Huhn et al., 2018). Additional studies in humans have indicated that RSV reduces markers of neuroinflammation, improves immunity, and reduces the burden of neurodegenerative disease (Moussa et al., 2017). However, overall the evidence for the effects of resveratrol in humans is weak, with several clinical trials showing the RSV supplementation does not substantially change insulin sensitivity, blood

lipids, inflammation or gene expression (Pediatria et al., 2018; Haghighatdoost and Hariri, 2018).

10. Anti-hypertensive therapy

Medications prescribed for hypertension may reduce the risk of dementia in people with hypertension (Petek et al., 2018). Aberrant activity of the renin-angiotensin system may play an important role in dementia due to its role in the regulation of blood pressure (Kehoe, 2018). It has been concluded that the use of antihypertensive drugs is associated with a reduced risk of dementia (Xu et al., 2017), while a meta-analysis showed that diuretic antihypertensive medications were associated with a reduction in dementia risk (Tully et al., 2016).

11. Conclusions

Numerous clinical trials targeting amyloid and tau to treat and prevent AD have to date been negative and have led to pessimism about the possibilities of preventing dementia. On the other, there is evidence that lifestyle factors that impact on cardiometabolic health and insulin resistance also influence brain health and the risk of dementia. Emerging evidence suggests that drugs such as RAPA, metformin, and RSV which improve health may also have a positive effect on reducing hallmarks of dementia. Aging is the greatest risk factor for dementia, and therefore, slowing the aging process may be an effective way to reduce the burden of neurodegenerative disease. Such multifaceted approaches that target lifestyle and aging show therapeutic promise for improving brain health in old age and potentially delaying dementia.

Conflicts of interests

The authors declare no competing interests.

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References

Ables, G.P., Johnson, J.E., 2017. Pleiotropic responses to methionine restriction. Exp. Gerontol. 94, 83–88.
Agatonovic-Kustrin, S., et al., 2018. A molecular approach in drug development for Alzheimer's disease. Biomed. Pharmacother. 106, 553–565.
Ahmed, S., et al., 2017. Effect of metformin on adult hippocampal neurogenesis: comparison with donepezil and links to cognition. J. Mol. Neurosci. 62, 88–98.
Al-Dayyat, H.M., et al., 2018. Non-alcoholic fatty liver disease and associated dietary and lifestyle risk factors. Diabet. Metab. Syndr. 12, 569–575.
Alfaras, I., et al., 2017. Health benefits of late-onset metformin treatment every other week in mice. NPJ Aging Mech. Dis. 3, 16.
Anastasiou, C.A., et al., 2017. Mediterranean diet and cognitive health: Initial results from the Hellenic Longitudinal Investigation of Ageing and Diet. PLoS One 12, e0182048.
Anderson, B.J., et al., 1994. Glial hypertrophy is associated with synaptogenesis following motor-skill learning, but not with angiogenesis following exercise. Glia 11, 73–80.
Anderton, B.H., 1997. Changes in the ageing brain in health and disease. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 352, 1781–1792.
Anderton, B.H., 2002. Ageing of the brain. Mech. Ageing Dev. 123, 811–817.
Anjum, I., et al., 2018. Does obesity increase the risk of dementia: a literature review. Cureus 10, e2660.
Anson, R.M., et al., 2003. Intermittent fasting dissociates beneficial effects of dietary restriction on glucose metabolism and neuronal resistance to injury from calorie intake. Proc. Natl. Acad. Sci. U. S. A. 100, 6216–6220.
Arumugam, T.V., et al., 2010. Age and energy intake interact to modify cell stress pathways and stroke outcome. Ann. Neurol. 67, 41–52.
Asadbegi, M., et al., 2016. Neuroprotective effects of metformin against Abeta-mediated inhibition of long-term potentiation in rats fed a high-fat diet. Brain Res. Bull. 121, 178–185.
Asih, P.R., et al., 2014. Clearing the amyloid in Alzheimer's: progress towards earlier diagnosis and effective treatments - an update for clinicians. Neurodegener. Dis. Manag. 4, 363–378.
Bailey, D.P., 2017. Editorial: sedentary behavior in human health and disease. Front. Physiol. 8, 901.
Baker, L.D., et al., 2011. Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes. Arch. Neurol. 68, 51–57.
Bang, J., et al., 2015. Frontotemporal dementia. Lancet 386, 1672–1682.
Barrientos, R.M., et al., 2015. Neuroinflammation in the normal aging hippocampus. Neuroscience 309, 84–99.
Barron, A.M., et al., 2013. Sex-specific effects of high fat diet on indices of metabolic syndrome in 3xTg-AD mice: implications for Alzheimer's disease. PLoS One 8, e78554.
Bastianetto, S., et al., 2015. Neuroprotective action of resveratrol. Biochim. Biophys. Acta 1852, 1195–1201.
Bendlin, B.B., et al., 2011. Effects of aging and calorie restriction on white matter in rhesus macaques. Neurobiol. Aging 32 (2319.e1-11).
Benjamin, J.S., et al., 2017. A ketogenic diet rescues hippocampal memory defects in a mouse model of Kabuki syndrome. Proc. Natl. Acad. Sci. U. S. A. 114, 125–130.
Berman, A.Y., et al., 2017. The therapeutic potential of resveratrol: a review of clinical trials. NPJ Precis. Oncol. 1, 35.
Bernardo, T.C., et al., 2016. Physical exercise and brain mitochondrial fitness: the possible role against Alzheimer's disease. Brain Pathol. 26, 648–663.
Bernier, M., et al., 2016. Resveratrol supplementation confers neuroprotection in cortical brain tissue of nonhuman primates fed a high-fat/sucrose diet. Aging (Albany N. Y.) 8, 899–916.
Biessels, G.J., Despa, F., 2018. Cognitive decline and dementia in diabetes mellitus: mechanisms and clinical implications. Nat. Rev. Endocrinol. 14, 591–604.
Blalock, E.M., et al., 2010. Aging-related gene expression in hippocampus proper compared with dentate gyrus is selectively associated with metabolic syndrome variables in rhesus monkeys. J. Neurosci. 30, 6058–6071.
Bloom, G.S., 2014. Amyloid-beta and tau: the trigger and bullet in Alzheimer disease pathogenesis. JAMA Neurol. 71, 505–508.
Bloomfield, H.E., et al., 2016. Effects on health outcomes of a mediterranean diet with no restriction on fat intake: a systematic review and meta-analysis. Ann. Intern. Med. 165, 491–500.
Bo, H., et al., 2014. Exercise-induced neuroprotection of hippocampus in APP/PS1 transgenic mice via upregulation of mitochondrial 8-oxoguanine DNA glycosylase. Oxidative Med. Cell. Longev. 2014, 834502.
Boot, B.P., et al., 2013. Risk factors for dementia with Lewy bodies: a case-control study. Neurology 81, 833–840.
Byrne, H., et al., 2018. Self-directed exercise programmes in sedentary middle-aged individuals in good overall health; a systematic review. Prev. Med. 114, 156–163.
Camiletti-Moiron, D., et al., 2013. Does exercise reduce brain oxidative stress? A systematic review. Scand. J. Med. Sci. Sports 23, e202–e212.
Canter, R.G., et al., 2016. The road to restoring neural circuits for the treatment of Alzheimer's disease. Nature 539, 187–196.
Cao, W., et al., 2018. Resveratrol boosts cognitive function by targeting SIRT1. Neurochem. Res. 43, 1705–1713.
Capouch, S.D., et al., 2018. A review of dementia with Lewy bodies' impact, diagnostic criteria and treatment. Neurol. Ther. 7, 249–263.
Castellani, R.J., et al., 2010. Alzheimer disease. Dis. Mon. 56, 484–546.
Cechetti, F., et al., 2012. Environmental enrichment prevents behavioral deficits and oxidative stress caused by chronic cerebral hypoperfusion in the rat. Life Sci. 91, 29–36.
Cerqueira, F.M., et al., 2012. Calorie restriction increases cerebral mitochondrial respiratory capacity in a NO*-mediated mechanism: impact on neuronal survival. Free Radic. Biol. Med. 52, 1236–1241.
Chapman, S.B., et al., 2015. Neural mechanisms of brain plasticity with complex cognitive training in healthy seniors. Cereb. Cortex 25, 396–405.
Chen, X., et al., 2017. Treatment with enriched environment reduces neuronal apoptosis in the periinfarct cortex after cerebral ischemia/reperfusion injury. Cell. Physiol. Biochem. 41, 1445–1456.
Chrysohoou, C., et al., 2004. Adherence to the Mediterranean diet attenuates inflammation and coagulation process in healthy adults: the Attica study. J. Am. Coll. Cardiol. 44, 152–158.
Colman, R.J., Anderson, R.M., 2011. Nonhuman primate calorie restriction. Antioxid. Redox Signal. 14, 229–239.
Constantinidis, C., Klingberg, T., 2016. The neuroscience of working memory capacity and training. Nat. Rev. Neurosci. 17 (438-49).
Cooper, C., et al., 2015. Modifiable predictors of dementia in mild cognitive impairment: a systematic review and meta-analysis. Am. J. Psychiatry 172, 323–334.
Coughlan, G., et al., 2018. Spatial navigation deficits - overlooked cognitive marker for preclinical Alzheimer disease? Nat. Rev. Neurol. 14, 496–506.
Craft, S., Watson, G.S., 2004. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol. 3, 169–178.
Crowe, M., et al., 2003. Does participation in leisure activities lead to reduced risk of Alzheimer's disease? A prospective study of swedish twins. J. Gerontol. 58, P249–P255.
Cui, J., et al., 2018. Effects of exercise on learning and memory, oxidative stress and nNOS expression in marginal division of striatum of ovariectomized rats. J. Sports Med. Phys. Fitness 58, 356–365.
Cummings, J.L., 2004. Alzheimer's disease. N. Engl. J. Med. 351, 56–67.
Dai, J., et al., 2008. Association between adherence to the Mediterranean diet and oxidative stress. Am. J. Clin. Nutr. 88, 1364–1370.

Davis, C.D., et al., 2004. Novel environments enhance the induction and maintenance of long-term potentiation in the dentate gyrus. J. Neurosci. 24, 6497–6506.
de Cabo, R., Le Couteur, D.G., 2015. The biology of aging. In: Kasper, D. (Ed.), Harrison's Principles of Internal Medicine. McGraw-Hill Education, New York, NY, pp. 19e.
de Castro, M.R.T., et al., 2017. Previous physical exercise alters the hepatic profile of oxidative-inflammatory status and limits the secondary brain damage induced by severe traumatic brain injury in rats. J. Physiol. 595, 6023–6044.
De Simone, R., et al., 2013. Branched-chain amino acids influence the immune properties of microglial cells and their responsiveness to pro-inflammatory signals. Biochim. Biophys. Acta (BBA) - Mol. Basis Dis. 1832, 650–659.
Dekaban, A.S., 1978. Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. Ann. Neurol. 4, 345–356.
Dening, T., Sandilyan, M.B., 2015. Dementia: definitions and types. Nurs. Stand. 29, 37–42.
Di Biase, S., et al., 2017. Fasting regulates EGR1 and protects from glucose- and dex-amethasone-dependent sensitization to chemotherapy. PLoS Biol. 15, e2001951.
DiMenna, F.J., Arad, A.D., 2018. Exercise as 'precision medicine' for insulin resistance and its progression to type 2 diabetes: a research review. BMC Sports Sci. Med. Rehabil. 10, 21.
Ding, B., et al., 2018. The association between macronutrient intake and cognition in individuals aged under 65 in China: a cross-sectional study. BMJ Open 8, e018573.
Dumitriu, D., et al., 2010. Selective changes in thin spine density and morphology in monkey prefrontal cortex correlate with aging-related cognitive impairment. J. Neurosci. 30, 7507–7515.
Durazzo, T.C., et al., 2014. Smoking and increased Alzheimer's disease risk: a review of potential mechanisms. Alzheimers Dement. 10, S122–S145.
E, L., et al., 2014. Effect of high-intensity exercise on aged mouse brain mitochondria, neurogenesis, and inflammation. Neurobiol. Aging 35, 2574–2583.
Ehninger, D., et al., 2014. Longevity, aging and rapamycin. Cell. Mol. Life Sci. 71, 4325–4346.
Emre, M., et al., 2004. Rivastigmine for dementia associated with Parkinson's disease. N. Engl. J. Med. 351, 2509–2518.
Epstein, R.A., et al., 2017. The cognitive map in humans: spatial navigation and beyond. Nat. Neurosci. 20, 1504–1513.
Etgen, T., et al., 2011. Mild cognitive impairment and dementia: the importance of modifiable risk factors. Deutsches Arzteblatt Int. 108, 743–750.
Evans, H.M., et al., 2016. Clinical evaluation of effects of chronic resveratrol supple-mentation on cerebrovascular function, cognition, mood, physical function and general well-being in postmenopausal women-rationale and study design. Nutrients 8, 150.
Faber, R., 1999. Frontotemporal lobar degeneration: a consensus on clinical diagnostic criteria. Neurology 53, 1159.
Falck, R.S., et al., 2017. Cross-sectional relationships of physical activity and sedentary behavior with cognitive function in older adults with probable mild cognitive im-pairment. Phys. Ther. 97, 975–984.
Fatt, M., et al., 2015. Metformin acts on two different molecular pathways to enhance adult neural precursor proliferation/self-renewal and differentiation. Stem Cell Rep. 5, 988–995.
Feart, C., et al., 2013. Potential benefits of adherence to the Mediterranean diet on cognitive health. Proc. Nutr. Soc. 72, 140–152.
Fernandez, C.I., et al., 2004. Environmental enrichment-behavior-oxidative stress inter-actions in the aged rat: issues for a therapeutic approach in human aging. Ann. N. Y. Acad. Sci. 1019, 53–57.
Fernando, W., et al., 2018. Associations of dietary protein and fiber intake with brain and blood amyloid-beta. J. Alzheimers Dis. 61, 1589–1598.
Ferrari, R., et al., 2014. Frontotemporal dementia and its subtypes: a genome-wide as-sociation study. Lancet Neurol. 13, 686–699.
Fishel, M.A., et al., 2005. Hyperinsulinemia provokes synchronous increases in central inflammation and beta-amyloid in normal adults. Arch. Neurol. 62, 1539–1544.
Fleshner, M., et al., 2011. The neurobiology of the stress-resistant brain. Stress 14, 498–502.
Fletcher, E., et al., 2018. Brain volume change and cognitive trajectories in aging. Neuropsychology 32, 436–449.
Flicker, L., 2010. Modifiable lifestyle risk factors for Alzheimer's disease. J. Alzheimers Dis. 20, 803–811.
Floeter, M.K., Greenough, W.T., 1979. Cerebellar plasticity: modification of Purkinje cell structure by differential rearing in monkeys. Science 206, 227–229.
Flores-Bastias, O., Karahanian, E., 2018. Neuroinflammation produced by heavy alcohol intake is due to loops of interactions between Toll-like 4 and TNF receptors, per-oxisome proliferator-activated receptors and the central melanocortin system: a novel hypothesis and new therapeutic avenues. Neuropharmacology 128, 401–407.
Fontana, L., 2018. Interventions to promote cardiometabolic health and slow cardio-vascular ageing. Nat. Rev. Cardiol. 15, 566–577.
Fontana, L., Partridge, L., 2015. Promoting health and longevity through diet: from model organisms to humans. Cell 161, 106–118.
Fontana, L., et al., 2014. Medical research: treat ageing. Nature 511, 405–407.
Ford, E.S., 2002. Does exercise reduce inflammation? Physical activity and C-reactive protein among U.S. adults. Epidemiology 13, 561–568.
Franzke, B., et al., 2018. Age and the effect of exercise, nutrition and cognitive training on oxidative stress - the Vienna Active Aging Study (VAAS), a randomized controlled trial. Free Radic. Biol. Med. 121, 69–77.
Fratiglioni, L., et al., 2004. An active and socially integrated lifestyle in late life might protect against dementia. Lancet Neurol. 3, 343–353.
Freeman, L.R., et al., 2014. Damaging effects of a high-fat diet to the brain and cognition: a review of proposed mechanisms. Nutr. Neurosci. 17, 241–251.
Frisardi, V., et al., 2010. Nutraceutical properties of Mediterranean diet and cognitive decline: possible underlying mechanisms. J. Alzheimers Dis. 22, 715–740.
Fu, J., et al., 2017. Rapamycin effectively impedes melamine-induced impairments of cognition and synaptic plasticity in Wistar rats. Mol. Neurobiol. 54, 819–832.
Gallardo, G., Holtzman, D.M., 2017. Antibody therapeutics targeting abeta and tau. Cold Spring Harb. Perspect. Med. 6.
Gallaway, P.J., et al., 2017. Physical activity: a viable way to reduce the risks of mild cognitive impairment, Alzheimer's disease, and vascular dementia in older adults. Brain Sci. 7, 22.
Ganz, A.B., et al., 2018. Neuropathology and cognitive performance in self-reported cognitively healthy centenarians. Acta Neuropathol. Commun. 6, 64.
Garcia-Casares, N., et al., 2014. Structural and functional brain changes in middle-aged type 2 diabetic patients: a cross-sectional study. J. Alzheimers Dis. 40, 375–386.
Garcia-Mesa, Y., et al., 2016. Oxidative stress is a central target for physical exercise neuroprotection against pathological brain aging. J. Gerontol. A Biol. Sci. Med. Sci. 71, 40–49.
Garg, G., et al., 2017. Antiaging effect of metformin on brain in naturally aged and ac-celerated senescence model of rat. Rejuvenation Res. 20, 173–182.
Ge, J.F., et al., 2012. The binding of resveratrol to monomer and fibril amyloid beta. Neurochem. Int. 61, 1192–1201.
Giugliano, D., et al., 2006. The Effects of Diet on Inflammation. Emphasis on the Metabolic Syndrome. vol. 48. pp. 677–685.
Gleichmann, M., Mattson, M.P., 2011. Neuronal calcium homeostasis and dysregulation. Antioxid. Redox Signal. 14, 1261–1273.
Goate, A., et al., 1991. Segregation of a missense mutation in the amyloid precursor protein gene with familial Alzheimer's disease. Nature 349, 704–706.
Golimstok, A., et al., 2014. Cardiovascular risk factors and frontotemporal dementia: a case–control study. Transl. Neurodegen. 3, 13.
Gomperts, S.N., et al., 2008. Imaging amyloid deposition in Lewy body diseases. Neurology 71, 903–910.
Goto, S., et al., 2007. Hormetic effects of regular exercise in aging: correlation with oxidative stress. Appl. Physiol. Nutr. Metab. 32, 948–953.
Grant, W.B., 2014. Trends in diet and Alzheimer's disease during the nutrition transition in Japan and developing countries. J. Alzheimers Dis. 38, 611–620.
Gu, Y.L., et al., 2014. Cognitive improvement of mice induced by exercise prior to traumatic brain injury is associated with cytochrome c oxidase. Neurosci. Lett. 570, 86–91.
Guerreiro, R., Hardy, J., 2014. Genetics of Alzheimer's disease. Neurotherapeutics 11, 732–737.
Guitar, N.A., et al., 2018. The effects of physical exercise on executive function in com-munity-dwelling older adults living with Alzheimer's-type dementia: a systematic review. Ageing Res. Rev. 47, 159–167.
Gupta, S., Warner, J., 2018. Alcohol-related dementia: a 21st-century silent epidemic? Br. J. Psychiatry 193, 351–353.
Gutmann, B., et al., 2018. The effects of exercise intensity and post-exercise recovery time on cortical activation as revealed by EEG alpha peak frequency. Neurosci. Lett. 668, 159–163.
Haghighatdoost, F., Hariri, M., 2018. Effect of resveratrol on lipid profile: an updated systematic review and meta-analysis on randomized clinical trials. Pharmacol. Res. 129, 141–150.
Halagappa, V.K., et al., 2007. Intermittent fasting and caloric restriction ameliorate age-related behavioral deficits in the triple-transgenic mouse model of Alzheimer's dis-ease. Neurobiol. Dis. 26, 212–220.
Hannan, A.J., 2014. Environmental enrichment and brain repair: harnessing the ther-apeutic effects of cognitive stimulation and physical activity to enhance experience-dependent plasticity. Neuropathol. Appl. Neurobiol. 40, 13–25.
Hara, Y., et al., 2014. Presynaptic mitochondrial morphology in monkey prefrontal cortex correlates with working memory and is improved with estrogen treatment. Proc. Natl. Acad. Sci. U. S. A. 111, 486–491.
Harada, C.N., et al., 2013. Normal cognitive aging. Clin. Geriatr. Med. 29, 737–752.
Hardy, J., 2006. Alzheimer's disease: the amyloid cascade hypothesis: an update and reappraisal. J. Alzheimers Dis. 9, 151–153.
Harper, C., 1998. The neuropathology of alcohol-specific brain damage, or does alcohol damage the brain? J. Neuropathol. Exp. Neurol. 57, 101–110.
He, C., et al., 2012a. Exercise induces autophagy in peripheral tissues and in the brain. Autophagy 8, 1548–1551.
He, C., et al., 2012b. Exercise induces autophagy in peripheral tissues and in the brain. Autophagy 8, 1548–1551.
Hebert, R., Brayne, C., 1995. Epidemiology of vascular dementia. Neuroepidemiology 14, 240–257.
Henneberg, N., Hoyer, S., 1995. Desensitization of the neuronal insulin receptor: a new approach in the etiopathogenesis of late-onset sporadic dementia of the Alzheimer type (SDAT)? Arch. Gerontol. Geriatr. 21, 63–74.
Hennessy, M.B., et al., 2017. Depressive-like behavior, its sensitization, social buffering and altered cytokine responses in rhesus macaques moved from outdoor social groups to indoor housing. Soc. Neurosci. 12, 65–75.
Herring, A., et al., 2016. Late running is not too late against Alzheimer's pathology. Neurobiol. Dis. 94, 44–54.
Hertz, L., et al., 2015. Effects of ketone bodies in Alzheimer's disease in relation to neural hypometabolism, beta-amyloid toxicity, and astrocyte function. J. Neurochem. 134, 7–20.
Hogan, D.B., et al., 2016. The prevalence and incidence of dementia with lewy bodies: a systematic review. Can. J. Neurol. Sci. 43 (Suppl. 1), S83–S95.
Hornsby, A.K.E., et al., 2016. Short-term calorie restriction enhances adult hippocampal neurogenesis and remote fear memory in a Ghsr-dependent manner. Psychoneuroendocrinology 63, 198–207.
Huang, Y.C., et al., 2014. Effects of metformin on the cerebral metabolic changes in type 2

diabetic patients. Sci. World J. 2014, 694326.
Huhn, S., et al., 2018. Effects of resveratrol on memory performance, hippocampus connectivity and microstructure in older adults - a randomized controlled trial. Neuroimage 174, 177–190.
Hultsch, D.F., et al., 1999. Use it or lose it: engaged lifestyle as a buffer of cognitive decline in aging? Psychol. Aging 14, 245–263.
Hyun, D.H., et al., 2006. Calorie restriction up-regulates the plasma membrane redox system in brain cells and suppresses oxidative stress during aging. Proc. Natl. Acad. Sci. U. S. A. 103, 19908–19912.
Hyun, C.H., et al., 2013. LRRK2 as a potential genetic modifier of synucleinopathies: interlacing the two major genetic factors of Parkinson's disease. Exp. Neurobiol. 22, 249–257.
Iadecola, C., 2013. The pathobiology of vascular dementia. Neuron 80, 844–866.
Il'yasova, D., et al., 2018. Effects of 2 years of caloric restriction on oxidative status assessed by urinary F2-isoprostanes: the CALERIE 2 randomized clinical trial. Aging Cell 17.
Ingram, D.K., et al., 2007. Calorie restriction in nonhuman primates: assessing effects on brain and behavioral aging. Neuroscience 145, 1359–1364.
Irier, H., et al., 2014. Environmental enrichment modulates 5-hydroxymethylcytosine dynamics in hippocampus. Genomics 104, 376–382.
Jardim, F.R., et al., 2018. Resveratrol and brain mitochondria: a review. Mol. Neurobiol. 55, 2085–2101.
Jellinger, K.A., 2018. Dementia with Lewy bodies and Parkinson's disease-dementia: current concepts and controversies. J. Neural Transm. (Vienna) 125, 615–650.
Jeong, S.I., et al., 2016. Resveratrol attenuates peripheral and brain inflammation and reduces ischemic brain injury in aged female mice. Neurobiol. Aging 44, 74–84.
Jeschke, E., et al., 2011. Prescribing patterns in dementia: a multicentre observational study in a German network of CAM physicians. BMC Neurol. 11, 99.
Jia, Y., et al., 2017. Resveratrol and amyloid-beta: mechanistic insights. Nutrients 9.
Jiang, L., et al., 2018. Effect of running exercise on the number of the neurons in the hippocampus of young transgenic APP/PS1 mice. Brain Res. 1692, 56–65.
Johnson, J.B., et al., 2007. Alternate day calorie restriction improves clinical findings and reduces markers of oxidative stress and inflammation in overweight adults with moderate asthma. Free Radic. Biol. Med. 42, 665–674.
Johnson, L.A., et al., 2016. Amelioration of metabolic syndrome-associated cognitive impairments in mice via a reduction in dietary fat content or infusion of non-diabetic plasma. EBioMedicine 3, 26–42.
Karama, S., et al., 2015. Cigarette smoking and thinning of the brain's cortex. Mol. Psychiatry 20, 778–785.
Kehoe, P.G., 2018. The coming of age of the angiotensin hypothesis in Alzheimer's disease: progress toward disease prevention and treatment? J. Alzheimers Dis. 62, 1443–1466.
Kempermann, G., et al., 1997. More hippocampal neurons in adult mice living in an enriched environment. Nature 386, 493.
Kennedy, D.O., et al., 2010. Effects of resveratrol on cerebral blood flow variables and cognitive performance in humans: a double-blind, placebo-controlled, crossover investigation. Am. J. Clin. Nutr. 91 (1590–7).
Keogh, M.J., et al., 2016. Exome sequencing in dementia with Lewy bodies. Transl. Psychiatry 6, e728.
Kirova, A.M., et al., 2015. Working memory and executive function decline across normal aging, mild cognitive impairment, and Alzheimer's disease. Biomed. Res. Int. 2015, 748212.
Kiyohara, Y., 2014. Epidemiology of dementia: the Hisayama study. Nippon Rinsho Jpn. J. Clin. Med. 72, 601–606.
Knight, E.M., et al., 2014. High-fat diet-induced memory impairment in triple-transgenic Alzheimer's disease (3xTgAD) mice is independent of changes in amyloid and tau pathology. Neurobiol. Aging 35, 1821–1832.
Knight, A., et al., 2016. Is the Mediterranean diet a feasible approach to preserving cognitive function and reducing risk of dementia for older adults in Western countries? New insights and future directions. Ageing Res. Rev. 25, 85–101.
Kolosova, N.G., et al., 2013. Rapamycin suppresses brain aging in senescence-accelerated OXYS rats. Aging (Albany N. Y.) 5, 474–484.
Kramer, A.F., et al., 2004. Environmental influences on cognitive and brain plasticity during aging. J. Gerontol. A Biol. Sci. Med. Sci. 59, M940–M957.
Lautenschlager, N.T., et al., 2008. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. JAMA 300, 1027–1037.
Le Ber, I., 2013. Genetics of frontotemporal lobar degeneration: an up-date and diagnosis algorithm. Rev. Neurol. (Paris) 169, 811–819.
Le Couteur, D.G., et al., 2016 Dec 29. Solanezumab and the amyloid hypothesis for Alzheimer's disease. BMJ 355, i6771. https://doi.org/10.1136/bmj.i6771.
Lin, A.L., et al., 2013. Chronic rapamycin restores brain vascular integrity and function through NO synthase activation and improves memory in symptomatic mice modeling Alzheimer's disease. J. Cereb. Blood Flow Metab. 33, 1412–1421.
Lin, Y., et al., 2018. Evaluation of metformin on cognitive improvement in patients with non-dementia vascular cognitive impairment and abnormal glucose metabolism. Front. Aging Neurosci. 10, 227.
Lippens, G., et al., 2007. Tau aggregation in Alzheimer's disease: what role for phosphorylation? Prion 1, 21–25.
Liu, Y., et al., 2017. Short-term caloric restriction exerts neuroprotective effects following mild traumatic brain injury by promoting autophagy and inhibiting astrocyte activation. Behav. Brain Res. 331, 135–142.
Livingston, G., et al., 2017. Dementia prevention, intervention, and care. Lancet 390, 2673–2734.
Longo, Valter D., Mattson, Mark P., 2014. Fasting: molecular mechanisms and clinical applications. Cell Metab. 19, 181–192.
Lopez-Miranda, V., et al., 2012. Resveratrol: a neuroprotective polyphenol in the Mediterranean diet. Rev. Neurol. 54, 349–356.
Lores-Arnaiz, S., et al., 2010. Mitochondrial function and nitric oxide production in hippocampus and cerebral cortex of rats exposed to enriched environment. Brain Res. 1319, 44–53.
Lourida, I., et al., 2013. Mediterranean diet, cognitive function, and dementia: a systematic review. Epidemiology 24, 479–489.
Luchsinger, J.A., et al., 2016. Metformin in amnestic mild cognitive impairment: results of a pilot randomized placebo controlled clinical trial. J. Alzheimers Dis. 51, 501–514.
Ma, C.L., et al., 2017. Physical exercise induces hippocampal neurogenesis and prevents cognitive decline. Behav. Brain Res. 317, 332–339.
Maalouf, M., et al., 2009. The neuroprotective properties of calorie restriction, the ketogenic diet, and ketone bodies. Brain Res. Rev. 59, 293–315.
Madeo, F., et al., 2015. Essential role for autophagy in life span extension. J. Clin. Invest. 125, 85–93.
Maesako, M., et al., 2012. Environmental enrichment ameliorated high-fat diet-induced Abeta deposition and memory deficit in APP transgenic mice. Neurobiol. Aging 33 (1011.e1123).
Maiese, K., 2018. The mechanistic target of rapamycin (mTOR) and the silent mating-type information regulation 2 homolog 1 (SIRT1): oversight for neurodegenerative disorders. Biochem. Soc. Trans. 46, 351–360.
Martin, S.A., et al., 2016. Regional metabolic heterogeneity of the hippocampus is nonuniformly impacted by age and caloric restriction. Aging Cell 15, 100–110.
Martin-Montalvo, A., et al., 2013. Metformin improves healthspan and lifespan in mice. Nat. Commun. 4, 2192.
Mascarucci, P., et al., 2002. Cytokine responses in young and old rhesus monkeys: effect of caloric restriction. J. Interf. Cytokine Res. 22 (56571).
Maswood, N., et al., 2004. Caloric restriction increases neurotrophic factor levels and attenuates neurochemical and behavioral deficits in a primate model of Parkinson's disease. Proc. Natl. Acad. Sci. U. S. A. 101 (181716).
Matt, K., et al., 2016. Influence of calorie reduction on DNA repair capacity of human peripheral blood mononuclear cells. Mech. Ageing Dev. 154 (24-9).
Mattson, M.P., 2008. Dietary factors, hormesis and health. Ageing Res. Rev. 7 (438).
Mattson, M.P., 2010. The impact of dietary energy intake on cognitive aging. Front. Aging Neurosci. 2, 5.
Mattson, M.P., Arumugam, T.V., 2018. Hallmarks of brain aging: adaptive and pathological modification by metabolic states. Cell Metab. 27, 1176–1199.
Mattson, M.P., Magnus, T., 2006. Ageing and neuronal vulnerability. Nat. Rev. Neurosci. 7, 278.
Mattson, M.P., et al., 2001. Suppression of brain aging and neurodegenerative disorders by dietary restriction and environmental enrichment: molecular mechanisms. Mech. Ageing Dev. 122 (757-78).
Mattson, M.P., et al., 2003. Meal size and frequency affect neuronal plasticity and vulnerability to disease: cellular and molecular mechanisms. J. Neurochem. 84 (417-31).
Mattson, M.P., et al., 2017. Impact of intermittent fasting on health and disease processes. Ageing Res. Rev. 39, 46–58.
May, A., 2011. Experience-dependent structural plasticity in the adult human brain. Trends Cogn. Sci. 15, 475–482.
Mayo, M.C., Bordelon, Y., 2014. Dementia with Lewy bodies. Semin. Neurol. 34 (182-8).
Mazza, E., et al., 2017. Impact of legumes and plant proteins consumption on cognitive performances in the elderly. J. Transl. Med. 15 109-109.
McGleenon, B.M., et al., 1999. Acetylcholinesterase inhibitors in Alzheimer's disease. Br. J. Clin. Pharmacol. 48, 471–480.
Mendez, M.F., 2017. Early-Onset Alzheimer Disease. Neurol. Clin. 35, 263–281.
Mendez-Lopez, M., et al., 2015. Effects of a high protein diet on cognition and brain metabolism in cirrhotic rats. Physiol. Behav. 149 (220-8).
Mestre, Z.L., et al., 2017. Hippocampal atrophy and altered brain responses to pleasant tastes among obese compared with healthy weight children. Int. J. Obes. 41, 1496–1502.
Mirzaei, H., et al., 2014. Protein and amino acid restriction, aging and disease: from yeast to humans. Trends Endocrinol. Metab. 25 (558-66).
Mitchell, A.C., et al., 2010a. Molecular correlates of spontaneous activity in non-human primates. J. Neural Transm. (Vienna, Austria) 1996 (117), 1353–1358.
Mitchell, A.C., et al., 2010b. Molecular correlates of spontaneous activity in non-human primates. J. Neural Transm. (Vienna) 117 (1353-8).
Mitchell, S.J., et al., 2016. Effects of Sex, Strain, and Energy Intake on Hallmarks of Aging in Mice. Cell Metab. 23, 1093–1112.
Mokhtarzade, M., et al., 2018. Exercise-induced changes in neurotrophic factors and markers of blood-brain barrier permeability are moderated by weight status in multiple sclerosis. Neuropeptides 70, 93–100.
Moreira, O.C., et al., 2017. Mitochondrial function and mitophagy in the elderly: effects of exercise. Oxidative Med. Cell. Longev. 2017, 2012798.
Morris, M.C., 2016. Nutrition and risk of dementia: overview and methodological issues. Ann. N. Y. Acad. Sci. 1367, 31–37.
Morrison, J.H., Baxter, M.G., 2012. The ageing cortical synapse: hallmarks and implications for cognitive decline. Nat. Rev. Neurosci. 13, 240–250.
Most, J., et al., 2017. Calorie restriction in humans: an update. Ageing Res. Rev. 39, 36–45.
Moussa, C., et al., 2017. Resveratrol regulates neuro-inflammation and induces adaptive immunity in Alzheimer's disease. J. Neuroinflammation 14 (1).
Mufson, E.J., et al., 2016. Braak staging, plaque pathology, and APOE status in elderly persons without cognitive impairment. Neurobiol. Aging 37 (147-53).
Nakamura, Y., et al., 2016. Systematic review and meta-analysis reveals acutely elevated plasma cortisol following fasting but not less severe calorie restriction. Stress 19 (151-7).
Newman, J.C., et al., 2017. Ketogenic diet reduces midlife mortality and improves memory in aging mice. Cell Metab. 26, 547–557 (e8).

Ng, T.P., et al., 2014. Long-term metformin usage and cognitive function among older adults with diabetes. J. Alzheimers Dis. 41 (61-8).
Ngandu, T., et al., 2015. A 2 year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): a randomised controlled trial. Lancet 385 (2255-63).
Nicoletti, V.G., et al., 2005. Effect of antioxidant diets on mitochondrial gene expression in rat brain during aging. Neurochem. Res. 30 (737-52).
Nikoletopoulou, V., Tavernarakis, N., 2012. Calcium homeostasis in aging neurons. Front. Genet. 3, 200.
Novelle, M.G., et al., 2015. Resveratrol supplementation: where are we now and where should we go? Ageing Res. Rev. 21, 1–15.
Novelle, M.G., et al., 2016. Metformin: a hopeful promise in aging research. Cold Spring Harb. Perspect. Med. 6, a025932.
O'Brien, J.T., Thomas, A., 2015. Vascular dementia. Lancet 386 (1698-706).
Okawara, M., et al., 2007. Resveratrol protects dopaminergic neurons in midbrain slice culture from multiple insults. Biochem. Pharmacol. 73 (550-60).
Oleson, S., et al., 2017. Nutrient intake and cerebral metabolism in healthy middle-aged adults: implications for cognitive aging. Nutr. Neurosci. 20, 489–496.
Ou, Z., et al., 2018. Metformin treatment prevents amyloid plaque deposition and memory impairment in APP/PS1 mice. Brain Behav. Immun. 69, 351–363.
Ozturk, E.D., Tan, C.O., 2018. Human cerebrovascular function in health and disease: insights from integrative approaches. J. Physiol. Anthropol. 37, 4.
Pani, G., 2015. Neuroprotective effects of dietary restriction: evidence and mechanisms. Semin. Cell Dev. Biol. 40 (106-14).
Paoli, A., et al., 2014. Ketogenic diet in neuromuscular and neurodegenerative diseases. Biomed. Res. Int. 2014, 474296.
Park, H.R., Lee, J., 2011. Neurogenic contributions made by dietary regulation to hippocampal neurogenesis. Ann. N. Y. Acad. Sci. 1229, 23–28.
Park, J.H., et al., 2013. Calorie restriction alleviates the age-related decrease in neural progenitor cell division in the aging brain. Eur. J. Neurosci. 37, 1987–1993.
Parrella, E., et al., 2013. Protein restriction cycles reduce IGF-1 and phosphorylated Tau, and improve behavioral performance in an Alzheimer's disease mouse model. Aging Cell 12, 257–268.
Pediatria, A., Kantartzis, K., et al., 2018. Effects of resveratrol supplementation on liver fat content in overweight and insulin-resistant subjects: a randomized, double-blind, placebo-controlled clinical trial. Diabetes Obes. Metab. 20, 1793–1797.
Pedrini, S., et al., 2009. Dietary composition modulates brain mass and solubilizable Aβ levels in a mouse model of aggressive Alzheimer's amyloid pathology. Mol. Neurodegener. 4, 40.
Pereira, A.C., et al., 2007. An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus. Proc. Natl. Acad. Sci. U. S. A. 104, 5638–5643.
Pesce, M., et al., 2017. Memory training program decreases the circulating level of cortisol and pro-inflammatory cytokines in healthy older adults. Front. Mol. Neurosci. 10, 233.
Pesce, M., et al., 2018. Aging-related oxidative stress: positive effect of memory training. Neuroscience 370, 246–255.
Petek, B., et al., 2018. Connecting the brain cholesterol and renin-angiotensin (RAS) systems. Potential role of statins and RAS-modifying medications in dementia. J. Intern. Med. 284, 620–642.
Petersen, R.C., 2011. Clinical practice. Mild cognitive impairment. N. Engl. J. Med. 364 (2227-34).
Petersen, R.C., 2016a. Mild cognitive impairment. Continuum 22, 404–418.
Petersen, R.C., 2016b. Mild cognitive impairment. Continuum (Minneap Minn). 22, 404–418.
Petersen, R.C., et al., 2018. Practice guideline update summary: mild cognitive impairment: report of the guideline development, dissemination, and implementation subcommittee of the american academy of neurology. Neurology 90, 126–135.
Petersson, S.D., Philippou, E., 2016. Mediterranean diet, cognitive function, and dementia: a systematic review of the evidence. Adv. Nutr. 7, 889–904.
Pietrelli, A., et al., 2018. Lifelong aerobic exercise reduces the stress response in rats. Neuroscience 376, 94–107.
Pintana, H., et al., 2012. Effects of metformin on learning and memory behaviors and brain mitochondrial functions in high fat diet induced insulin resistant rats. Life Sci. 91, 409–414.
Qi, X.L., Constantinidis, C., 2013. Neural changes after training to perform cognitive tasks. Behav. Brain Res. 241, 235–243.
Qin, W., et al., 2006. Calorie restriction attenuates Alzheimer's disease type brain amyloidosis in Squirrel monkeys (Saimiri sciureus). J. Alzheimers Dis. 10, 417–422.
Querfurth, H.W., LaFerla, F.M., 2010. Alzheimer's disease. N. Engl. J. Med. 362, 329–344.
Radak, Z., et al., 2016. Physical exercise, reactive oxygen species and neuroprotection. Free Radic. Biol. Med. 98, 187–196.
Raefsky, S.M., Mattson, M.P., 2017. Adaptive responses of neuronal mitochondria to bioenergetic challenges: roles in neuroplasticity and disease resistance. Free Radic. Biol. Med. 102, 203–216.
Raji, C.A., et al., 2010. Brain structure and obesity. Hum. Brain Mapp. 31 (353-64).
Rasgon, N.L., et al., 2011. Insulin resistance and hippocampal volume in women at risk for Alzheimer's disease. Neurobiol. Aging 32 (1942-8).
Rezazadeh, M., et al., 2019. Genetic discoveries and advances in late-onset Alzheimer's disease. J. Cell. Physiol. https://doi.org/10.1002/jcp.28372. (Epub ahead of print).
Rhyu, I.J., et al., 2010. Effects of aerobic exercise training on cognitive function and cortical vascularity in monkeys. Neuroscience 167 (1239-48).
Richardson, A., et al., 2015. How longevity research can lead to therapies for Alzheimer's disease: the rapamycin story. Exp. Gerontol. 68 (51-8).
Roberts, R.O., et al., 2008. The mayo clinic study of aging: design and sampling, participation, baseline measures and sample characteristics. Neuroepidemiology 30, 58–69.
Roberts, R.O., et al., 2013. Cardiac disease associated with increased risk of nonamnestic cognitive impairment: stronger effect on women. JAMA Neurol. 70, 374–382.
Robles Bayon, A., et al., 2014. Bradycardia in frontotemporal dementia. Neurologia 29, 76–85.
Rodriguez, J.J., et al., 2013. Enriched environment and physical activity reverse astrogliodegeneration in the hippocampus of AD transgenic mice. Cell Death Dis. 4, e678.
Roh, H.T., et al., 2017. Effect of exercise intensity on neurotrophic factors and blood-brain barrier permeability induced by oxidative-nitrosative stress in male college students. Int. J. Sport Nutr. Exerc. Metab. 27, 239–246.
Sabatini, D.M., 2017. Twenty-five years of mTOR: Uncovering the link from nutrients to growth. Proc. Natl. Acad. Sci. U. S. A. 114, 11818–11825.
Sanabria-Castro, A., et al., 2017. Molecular pathogenesis of Alzheimer's disease: an update. Ann. Neurosci. 24, 46–54.
Sartori, A.C., et al., 2012. The impact of inflammation on cognitive function in older adults: implications for health care practice and research. J. Neurosci. Nurs. 44, 206–217.
Sarubbo, F., et al., 2017. Effects of resveratrol and other polyphenols on the most common brain age-related diseases. Curr. Med. Chem. 24, 4245–4266.
Saunders, A.M., et al., 1993. Association of apolipoprotein E allele epsilon 4 with late-onset familial and sporadic Alzheimer's disease. Neurology 43, 1467–1472.
Savva, G.M., et al., 2009. Age, neuropathology, and dementia. The New England Journal of Medicine 360, 2302–2309.
Sawda, C., et al., 2017. Resveratrol for Alzheimer's disease. Ann. N. Y. Acad. Sci. 1403, 142–149.
Schafer, M.J., et al., 2015. Reduction of beta-amyloid and gamma-secretase by calorie restriction in female Tg2576 mice. Neurobiol. Aging 36 (1293-302).
Scheibye-Knudsen, M., et al., 2014. A high-fat diet and NAD(+) activate Sirt1 to rescue premature aging in cockayne syndrome. Cell Metab. 20, 840–855.
Schmidt, R.H., et al., 2016. Exercise as gene therapy: BDNF and DNA damage repair. Asia Pac. J. Ophthalmol. (Phila). 5 (309-11).
Schrijvers, E.M., et al., 2010. Insulin metabolism and the risk of Alzheimer disease: the Rotterdam study. Neurology 75 (1982-7).
Sevigny, J., et al., 2016. The antibody aducanumab reduces Abeta plaques in Alzheimer's disease. Nature 537, 50–56.
Sharp, E.S., Gatz, M., 2011. The relationship between education and dementia an updated systematic review. Alzheimer Dis. Assoc. Disord. 25, 289–304.
Siddarth, P., et al., 2018. Sedentary behavior associated with reduced medial temporal lobe thickness in middle-aged and older adults. PLoS One 13, e0195549.
Siervo, M., et al., 2011. Intentional weight loss in overweight and obese individuals and cognitive function: a systematic review and meta-analysis. Obes. Rev. 12, 968–983.
Smith, E.E., 2017. Clinical presentations and epidemiology of vascular dementia. Clin. Sci. (Lond.). 131, 1059–1068.
Smith, B.M., et al., 2018. A larger social network enhances novel object location memory and reduces hippocampal microgliosis in aged mice. Front. Aging Neurosci. 10, 142.
Sobol, N.A., et al., 2018. Change in fitness and the relation to change in cognition and neuropsychiatric symptoms after aerobic exercise in patients with mild Alzheimer's disease. J. Alzheimers Dis. 65, 137–145.
Sohal, R.S., et al., 1994. Effect of age and caloric restriction on DNA oxidative damage in different tissues of C57BL/6 mice. Mech. Ageing Dev. 76, 215–224.
Solfrizzi, V., et al., 2011. Mediterranean diet in predementia and dementia syndromes. Curr. Alzheimer Res. 8 (520-42).
Solfrizzi, V., et al., 2017. Relationships of dietary patterns, foods, and micro- and macronutrients with Alzheimer's disease and late-life cognitive disorders: a systematic review. J. Alzheimers Dis. 59, 815–849.
Solon-Biet, S.M., et al., 2014. The ratio of macronutrients, not caloric intake, dictates cardiometabolic health, aging, and longevity in ad libitum-fed mice. Cell Metab. 19 (418-30).
Solon-Biet, S.M., et al., 2015a. Dietary protein to carbohydrate ratio and caloric restriction: comparing metabolic outcomes in mice. Cell Rep. 11 (1529-34).
Solon-Biet, S.M., et al., 2015b. Macronutrients and caloric intake in health and longevity. J. Endocrinol. 226, R17–R28.
Solon-Biet, S.M., et al., 2019. Branched-chain amino acids impact health and lifespan indirectly via amino acid balance and appetite control. Nature Metabolism. 1, 532–545.
Song, D., et al., 2018. The effectiveness of physical exercise on cognitive and psychological outcomes in individuals with mild cognitive impairment: a systematic review and meta-analysis. Int. J. Nurs. Stud. 79, 155–164.
Spencer, S.J., et al., 2017. Food for thought: how nutrition impacts cognition and emotion. Npj Sci. Food. 1, 7.
Spillantini, M.G., et al., 1997. Alpha-synuclein in Lewy bodies. Nature 388 (839-40).
Sridharan, A., et al., 2013. Calorie restriction attenuates astrogliosis but not amyloid plaque load in aged rhesus macaques: a preliminary quantitative imaging study. Brain Res. 1508, 1–8.
Stanley, M.L., et al., 2015. Changes in brain network efficiency and working memory performance in aging. PLoS One 10, e0123950.
Stein, L.R., et al., 2016. Short-term environmental enrichment enhances synaptic plasticity in hippocampal slices from aged rats. Neuroscience 329, 294–305.
Steiner, J.L., et al., 2011. Exercise training increases mitochondrial biogenesis in the brain. J. Appl. Physiol. (1985) 111 (1066-71).
Stranahan, A.M., Mattson, M.P., 2012. Recruiting adaptive cellular stress responses for successful brain ageing. Nat. Rev. Neurosci. 13, 209.
Sun, A.Y., et al., 2010. Resveratrol as a therapeutic agent for neurodegenerative diseases. Mol. Neurobiol. 41 (375-83).
Sun, L.N., et al., 2018. Physical exercise reserved amyloid-beta induced brain dysfunctions by regulating hippocampal neurogenesis and inflammatory response via MAPK signaling. Brain Res. 1697, 1–9.

Suski, M., et al., 2016. Influence of metformin on mitochondrial subproteome in the brain of apoE knockout mice. Eur. J. Pharmacol. 772, 99–107.
Swain, U., et al., 2016. Dietary calorie restriction from adulthood through old age in rats: improved DNA polymerase beta and DNA gap repair activity in cortical neurons. Neurochem. Res. 41, 270–277.
Sweeney, M.D., et al., 2018. The role of brain vasculature in neurodegenerative disorders. Nat. Neurosci. 21, 1318–1331.
Swomley, A.M., et al., 2017. Comparative proteomic analyses of the parietal lobe from rhesus monkeys fed a high-fat/sugar diet with and without resveratrol supplementation, relative to a healthy diet: insights into the roles of unhealthy diets and resveratrol on function. J. Nutr. Biochem. 39, 169–179.
Talbot, K., et al., 2012. Demonstrated brain insulin resistance in Alzheimer's disease patients is associated with IGF-1 resistance, IRS-1 dysregulation, and cognitive decline. J. Clin. Invest. 122 (1316-38).
Tanaka, T., et al., 2018. Adherence to a mediterranean diet protects from cognitive decline in the invecchiare in chianti study of aging. Nutrients 10.
Tervo, S., et al., 2004. Incidence and risk factors for mild cognitive impairment: a population-based three-year follow-up study of cognitively healthy elderly subjects. Dement. Geriatr. Cogn. Disord. 17, 196–203.
Thiepold, A.L., et al., 2017. Mammalian target of rapamycin complex 1 activation sensitizes human glioma cells to hypoxia-induced cell death. Brain 140, 2623–2638.
Thomas, A., et al., 2012. The effects of aerobic activity on brain structure. Front. Psychol. 3.
Todorova, V., Blokland, A., 2017. Mitochondria and synaptic plasticity in the mature and aging nervous system. Curr. Neuropharmacol. 15, 166–173.
Tolppanen, A.M., et al., 2014. Midlife and late-life body mass index and late-life dementia: results from a prospective population-based cohort. J. Alzheimers Dis. 38, 201–209.
Tomata, Y., et al., 2016. Dietary patterns and incident dementia in elderly Japanese: the Ohsaki cohort 2006 study. J. Gerontol. Ser. A-Biol. Sci. Med. Sci. 71 (1322-8).
Topiwala, H., et al., 2018. Lifestyle and neurodegeneration in midlife as expressed on functional magnetic resonance imaging: a systematic review. Alzheimers Dement (N Y). 4, 182–194.
Tosti, V., et al., 2018. Health benefits of the Mediterranean diet: metabolic and molecular mechanisms. J. Gerontol. A Biol. Sci. Med. Sci. 73, 318–326.
Traba, J., et al., 2015. Fasting and refeeding differentially regulate NLRP3 inflammasome activation in human subjects. J. Clin. Invest. 125, 4592–4600.
Tully, P.J., et al., 2016. Diuretic antihypertensive drugs and incident dementia risk: a systematic review, meta-analysis and meta-regression of prospective studies. J. Hypertens. 34 (1027-35).
United Nations, Department of Economic and Social Affairs, Population Division, 2017. World Population Ageing 2017 - Highlights (ST/ESA/SER.A/397).
van de Rest, O., et al., 2015. Dietary patterns, cognitive decline, and dementia: a systematic review. Adv. Nutr. 6 (154-68).
van de Ven, M., et al., 2006. Adaptive stress response in segmental progeria resembles long-lived dwarfism and calorie restriction in mice. PLoS Genet. 2, e192.
van Praag, H., 2008. Neurogenesis and exercise: past and future directions. NeuroMolecular Med. 10 (128-40).
van Praag, H., et al., 2014. Exercise, energy intake, glucose homeostasis, and the brain. J. Neurosci. 34 (15139-49).
Verkhratsky, A., Toescu, E.C., 1998. Calcium and neuronal ageing. Trends Neurosci. 21, 2–7.
Verret, L., et al., 2013. Transient enriched housing before amyloidosis onset sustains cognitive improvement in Tg2576 mice. Neurobiol. Aging 34 (211-25).
Vijayan, M., Reddy, P.H., 2016. Stroke, Vascular Dementia, and Alzheimer's Disease: Molecular Links. J. Alzheimers Dis. 54 (427-43).
Vina, J., Sanz-Ros, J., 2018. Alzheimer's disease: only prevention makes sense. Eur. J. Clin. Investig. 48, e13005.
Virtanen, H.E.K., et al., 2018. Intake of different dietary proteins and risk of heart failure in men: the Kuopio Ischaemic heart disease risk factor study. Circ. Heart Fail. 11, e004531.
Voss, M.W., et al., 2016. Fitness, but not physical activity, is related to functional integrity of brain networks associated with aging. Neuroimage. 131, 113–125.
Wahl, D., et al., 2016. Nutritional strategies to optimise cognitive function in the aging brain. Ageing Res. Rev. 31, 80–92.
Wahl, D., et al., 2017. Cognitive and behavioral evaluation of nutritional interventions in rodent models of brain aging and dementia. Clin. Interv. Aging 12, 1419–1428.
Wahl, D., et al., 2018a. Future directions of resveratrol research. Nutr. Healthy Aging. 4, 287–290.
Wahl, D., et al., 2018b. Comparing the Effects of Low-Protein and High-Carbohydrate Diets and Caloric Restriction on Brain Aging in Mice. Cell Rep. 25, 2234–2243 (e6).
Walker, Z., et al., 2015. Lewy body dementias. Lancet 386 (1683-97).
Wan, R., et al., 2003. Intermittent fasting and dietary supplementation with 2-deoxy-D-glucose improve functional and metabolic cardiovascular risk factors in rats. FASEB J. 17 (1133-4).
Wan, R., et al., 2004. Dietary supplementation with 2-deoxy-D-glucose improves cardiovascular and neuroendocrine stress adaptation in rats. Am. J. Physiol. Heart Circ. Physiol. 287 (H1186-93).
Wang, J., et al., 2012. Metformin activates an atypical PKC-CBP pathway to promote neurogenesis and enhance spatial memory formation. Cell Stem Cell 11, 23–35.
Weiss, E.P., et al., 2006. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Am. J. Clin. Nutr. 84 (1033-42).
Willette, A.A., et al., 2012. Calorie restriction reduces the influence of glucoregulatory dysfunction on regional brain volume in aged Rhesus monkeys. Diabetes 61, 1036–1042.
Willette, A.A., et al., 2013. Interleukin-8 and interleukin-10, brain volume and microstructure, and the influence of calorie restriction in old rhesus macaques. Age (Dordr.) 35 (2215-27).
Witte, A.V., et al., 2009. Caloric restriction improves memory in elderly humans. Proc. Natl. Acad. Sci. 106, 1255.
Witte, A.V., et al., 2014. Effects of resveratrol on memory performance, hippocampal functional connectivity, and glucose metabolism in healthy older adults. J. Neurosci. 34 (7862-70).
Woo, D.H., et al., 2018. Visual stimulation-induced mild stress enhances cognitive behavior in cynomolgus monkey. Sci. Rep. 8, 3809.
Wood, A.M., et al., 2018. Risk thresholds for alcohol consumption: combined analysis of individual-participant data for 599 912 current drinkers in 83 prospective studies. Lancet 391, 1513–1523.
Xekardaki, A., et al., 2015. Neuropathological changes in aging brain. Adv. Exp. Med. Biol. 821 (11-7).
Xia, X., et al., 2018. Aging and Alzheimer's disease: comparison and associations from molecular to system level. Aging Cell 284, 620–642 (e12802).
Xing, Y., et al., 2018. The beneficial role of early exercise training following stroke and possible mechanisms. Life Sci. 198, 32–37.
Xu, G., et al., 2017. Association between antihypertensive drug use and the incidence of cognitive decline and dementia: a meta-analysis of prospective cohort studies. Biomed. Res. Int. 2017, 4368474.
Yang, S.K., et al., 2018. Incidence and comorbidity of dementia with lewy bodies: a population-based cohort study. Behav. Neurol. 2018, 7631951.
Yeomans, M.R., 2017. Adverse effects of consuming high fat-sugar diets on cognition: implications for understanding obesity. Proc. Nutr. Soc. 76, 455–465.
Yu, Z.F., Mattson, M.P., 1999. Dietary restriction and 2-deoxyglucose administration reduce focal ischemic brain damage and improve behavioral outcome: evidence for a preconditioning mechanism. J. Neurosci. Res. 57 (830-9).
Yu, J.L., et al., 2014. Voluntary wheel running enhances cell proliferation and expression levels of BDNF, IGF1 and WNT4 in dentate gyrus of adult mice. Sheng Li Xue Bao 66 (559-68).
Zapata, R.C., et al., 2018. Dietary tryptophan restriction dose-dependently modulates energy balance, gut hormones, and microbiota in obesity-prone rats. Obesity (Silver Spring) 26, 730–739.
Zemke, D., et al., 2007. The mTOR pathway as a potential target for the development of therapies against neurological disease. Drug News Perspect. 20 (495-9).
Zhai, B., et al., 2018. Rapamycin relieves anxious emotion and synaptic plasticity deficits induced by hindlimb unloading in mice. Neurosci. Lett. 677, 44–48.
Zhang, J.Q., et al., 2013. Resveratrol promotes cellular glucose utilization in primary cultured cortical neurons via calcium-dependent signaling pathway. J. Nutr. Biochem. 24 (629-37).
Zhao, W.Q., et al., 2004. Insulin and the insulin receptor in experimental models of learning and memory. Eur. J. Pharmacol. 490, 71–81.
Zonneveld, T.P., et al., 2018. Blood pressure-lowering treatment for preventing recurrent stroke, major vascular events, and dementia in patients with a history of stroke or transient ischaemic attack. Cochrane Database Syst. Rev. 7, Cd007858.